NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Mosunetuzumab for treating relapsed or refractory follicular lymphoma [ID3931]

Committee Papers

© National Institute for Health and Care Excellence 2023. All rights reserved. See Notice of Rights. The content in this publication is owned by multiple parties and may not be re-used without the permission of the relevant copyright owner.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Mosunetuzumab for treating relapsed or refractory follicular lymphoma [ID3931]

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 **Comments on the Draft Guidance** from Roche Products

3. **Consultee and commentator comments on the Draft Guidance Document** from:
   a. Association of Cancer Physicians

4. **Comments on the Draft Guidance Document received through the NICE website**

5. **External Assessment Group critique of company response to the DG**

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

© National Institute for Health and Care Excellence 2023. All rights reserved. See Notice of Rights. The content in this publication is owned by multiple parties and may not be re-used without the permission of the relevant copyright owner.

Mosunetuzumab for treating relapsed or refractory follicular lymphoma

Single Technology Appraisal

Response to consultee, commentator and public comments on the draft guidance (DG)

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 Consultees can make a submission and participate in the consultation on the draft guidance (DG; if produced).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 draft guidance (FDG).

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 DG (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 FDG 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 DG 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	Patient & Professional	Association of Cancer Physicians	Comparing cost effectiveness against R-bendamustine and R-lenalidomide is of limited value for patients that have already received these treatments previously. Patients who have had multiple lines of R-chemotherapy and R-lenalidomide essentially have no further treatment options available to them, so mosunetuzumab so may be a life changing treatment for them.	Thank you for your comments. The committee took these comments into consideration (see points below) along with the company's updated model. 1. The committee understood that the treatment landscape of relapsed and refractory follicular lymphoma is complicated and changing (see final draft guidance [FDG] section 3.2). It is noted that at third line and beyond, treatment choice will be influenced by previous therapy. It is also noted that obinutuzumab plus bendamustine is rarely used third line, so it is not a relevant comparator for this appraisal. 2. In the company's approach, the comparator rituximab plus bendamustine was also used to represent other types of rituximab plus chemotherapy (FDG section 3.5). The committee concluded that whether it is representative of other types of rituximab plus chemotherapy is highly uncertain. 3. The FDG has been updated following stakeholder comments (section 3.1), noting that mosunetuzumab could provide an extra line of treatment.
2	Patient & Professional	Association of Cancer Physicians	Retreatment with the same form of chemotherapy on relapse is not often used due to cumulative toxicities and is not recommended if the patient has demonstrated prior refractoriness to the regime. RCHOP has also been cited as an R-chemo treatment option in the guidance documentation however at our centre it is not frequently used as it usually reserved for treatment of high grade transformation and furthermore is also avoided in patients with cardiac co-morbidity. Therefore the number of suitable alternative treatments may have been over estimated.	Thank you for your comments. The committee took these comments into consideration (see points below) along with the company's updated model. 1. As above, the committee noted that at third line and beyond, treatment choice will be influenced by previous therapy (see FDG section 3.2). In considering subsequent therapies, it was also noted that in the

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
				company's updated model for the rituximab plus lenalidomide arm, it was assumed that people would not have rituximab plus lenalidomide as their subsequent therapy (section 3.14). 2. Clinical experts noted that rituximab plus chemotherapy may include R-CHOP, R-CVP or rituximab plus bendamustine, and that after first line treatment, R CHOP and R CVP may be favoured over rituximab plus bendamustine because rituximab plus bendamustine can be associated with greater toxicity (FDG section 3.2). 3. Clinical experts explained that there is no current standard care and a lack of treatment options (FDG section 3.1). This creates difficult treatment choices from a mixed basket of options for relapsed or refractory follicular lymphoma.
1	Company	Roche	**Underlying challenges of appraisals based on single arm evidence packages (DG, Section 3.16)** The company acknowledges that in its base case mosunetuzumab is not cost-effective against either rituximab-lenalidomide (R-len) or rituximab-bendamustine (RB) when Commercial Medicine Unit prices and confidential discounts are applied to rituximab and lenalidomide. The company has explored alternative scenarios within the model to improve the cost-effectiveness estimates (see response point 4 regarding source of utilities and Appendix A), while also including the EAG's revised assumption on subsequent treatment use since this was verified by clinical experts to be clinically relevant (see response point 3). In this revised base case (including estimated discounts for the comparators), there is no level of additional discount that can be applied to the price of mosunetuzumab that would demonstrate it to be cost-effective vs R-len. Specifically, it is not possible to set any price (even £0) at which mosunetuzumab could generate sufficient cost-savings that would enable it to be considered cost-effective by net monetary benefit at a willingness-to-pay threshold of £30,000. For the comparison with RB, the company believes that additional discount would be needed to be cost-effective in the revised base case, however whatever level of discount is needed to be cost-effective against RB would not be sufficient to be cost-effective against R-len. The company is very disappointed to be in this situation but feels that this raises serious questions regarding the suitability of the current NICE methods to appraise evidence from single arm studies, as no scenario exists that	Thank you for your comments. The committee took these comments into consideration (see points below) along with the company's updated model. 1. The committee discussed that during the consultation the company changed its source of utility values (FDG section 3.13) and updated its subsequent therapy assumptions (section 3.14) in its base case. 2. The committee also noted that in the company's survival modelling, people in the mosunetuzumab arm had lower life-years gained than those in the rituximab plus lenalidomide arm, and that this did not reflect the potential benefit of mosunetuzumab on tumour response suggested by the single-arm study data (FDG section 3.12). 3. The committee concluded that the results of the indirect treatment comparisons were highly uncertain. It also concluded that the inconsistencies within them made them very unreliable (FDG section 3.8). 4. Clinical experts noted that in follicular

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
			mosunetuzumab can demonstrate cost-effectiveness vs R-len. It is important to acknowledge that there is no standard of care for the treatment of relapsed/refractory follicular lymphoma in the third-line+ setting. Mosunetuzumab offers patients and clinicians an innovative and much needed non-rituximab, non-chemotherapy based treatment option in a population that is increasingly refractory to immunochemotherapy. Moreover, clinical experts informed the company that mosunetuzumab would provide an additional line of active therapy, i.e. patients could receive mosunetuzumab in the third-line setting before receiving R-len or another R-chemotherapy, or mosunetuzumab could be given beyond third-line after other regimens, delaying the need for palliative care or clinical trial enrolment. As such, mosunetuzumab is not intended to replace anything in the current treatment pathway. Clinical experts recognise the innovation of mosunetuzumab, stating that the complete response rate observed in the GO29781 trial of 60% hugely exceeds what is currently seen with current available treatments for 3L+ FL (estimated at 30-40%). Moreover, the latest available data cut (academic in confidence information removed) demonstrates that patients continue to derive a benefit from mosunetuzumab (academic in confidence information removed). Consequently, the company strongly feels that further evidence is required to perform a robust comparison vs R-len, particularly given the uncertainty associated with the outcomes from this indirect treatment comparison (ITC) (see response point 6). While the model currently demonstrates a QALY loss for mosunetuzumab vs R-len, it is important to note that the committee concluded in the DG that: • *"the lower life-years gained by people in the model with mosunetuzumab compared with rituximab plus lenalidomide did not reflect the potential benefit of mosunetuzumab on tumour response suggested by the single-arm study data"* • *"in the comparison with rituximab plus lenalidomide, the company's modelling of mosunetuzumab overall survival [which is deemed to be worse than that of R-len] was unlikely to be plausible".* Ultimately, the comparison of mosunetuzumab vs R-len is limited by the available evidence base for mosunetuzumab and the restrictions of comparing against a population from the R-len AUGMENT study that does not truly reflect 3L+ FL patients (mainly 2L and non-refractory to rituximab). As such, the comparative effectiveness results are uncertain and likely underestimate the benefit of mosunetuzumab given the potential for bias towards R-len. These limitations are reflected by the committee's feedback highlighted above. The company acknowledges the challenges of appraising evidence based on single arm studies, and would like to clarify that a randomised phase III trial comparing mosunetuzumab with the PI3 kinase inhibitor idelalisib was planned but did not go ahead due to safety concerns with this class and the withdrawal of FL indications for these treatments in the US. However, the reality is that many treatments are obtaining regulatory approval on the basis on single arm, phase II	lymphoma, if you can achieve a durable complete response then you tend to see good progression-free survival, but that in this cancer type, progression-free survival may not impact overall survival. They also noted it is that unlikely that improved progression-free survival leads to a loss of overall survival. The committee concluded that in the indirect comparison with rituximab plus lenalidomide, the company's modelling of mosunetuzumab overall survival was unlikely to be plausible (section 3.12). 5. It is recognised in the FDG that clinical experts explained that there is no current standard care and a lack of treatment options (FDG section 3.1). It is also acknowledged that that mosunetuzumab could provide an extra line of treatment and that new treatment options would be welcomed by patients and clinicians. 6. The FDG has been updated to note that the committee heard from the company that a phase 3 trial was planned, but this did not go ahead because of emerging safety findings for the comparator drug class (FDG section 3.4). 7. As noted in the company's response point 2 (below), evidence packages involving single arm studies have led to NICE recommendations in haematological indications. In the present appraisal of mosunetuzumab however, taking account of the company's patient access scheme discount (FDG section 3.15), mosunetuzumab was more costly and less effective than rituximab plus lenalidomide in the company's updated base case. For both comparisons, the committee concluded that mosunetuzumab did not represent a cost-effective use of NHS resources so could not be recommended for routine commissioning (FDG section 3.17).

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
			data, particularly since large, phase III randomised controlled trials may not be feasible or ethical in indications with small patient numbers, such as relapsed/refractory FL. It is noteworthy that some treatments in this setting with evidence based on single arm studies either did not achieve reimbursement (e.g. idelalisib [TA604][1]), or NICE appraisals were terminated as no evidence was submitted (duvelisib [TA717][2], tisagenlecleucel [TA842][3]). Mosunetuzumab was granted accelerated assessment by the EMA and Orphan Drug Designation by the EMA and MHRA, based on the same single arm pivotal study presented in this Submission. This illustrates that there is a sizable disconnect between what evidence is acceptable for marketing authorisation versus what is required to demonstrate cost-effectiveness and achieve reimbursement. Consequently, despite medicines being granted regulatory approval, patients are not getting access to much needed innovative treatment options. The company is very keen to engage further with NICE on this matter to understand what can be done to facilitate appraisals of evidence based on single arm studies, with small patient numbers and with no clear standard of care.	
2	Company	Roche	**Criteria for managed access (DG, Section 3.17)** The DG notes that uncertainties in the cost-effectiveness estimates would not be sufficiently resolved with further data collection in a managed access period. The company disagrees with this assessment and cites examples below where treatments in analogous disease areas have achieved access via the CDF on the basis of similar evidence packages and data collection agreements. **Mosunetuzumab data from GO29781** Further analyses providing more robust, long-term data for mosunetuzumab from the GO29781 pivotal cohort is planned, with annual outcomes analyses conducted until at least 2024. In the context of the available evidence to date, in which there is currently (academic in confidence information removed) months follow up, an additional 2–3 years follow up of the GO29781 pivotal cohort would provide valuable data to inform and validate the long term survival extrapolations incorporated in the economic model. This additional data will certainly help to address the current level of uncertainty in the degree of benefit derived from mosunetuzumab. In addition, the company is planning a multi-national, prospective non-interventional study of mosunetuzumab monotherapy in real world clinical practice in the submitted indication for countries where the medicine is accessible. Inclusion of mosunetuzumab in the CDF would allow for local real-world data collection, with an anticipated data cut of (commercial in confidence information removed). The proposed non-interventional study will also allow for the collection of progression-free survival data, something that cannot be captured via SACT. **Comparator data** As highlighted in its Technical Engagement response, the company plans to generate more robust comparator data for the control arms of the ITC through	Thank you for your comments. The committee took these comments into consideration (see points below) along with the company's updated model. 1. The committee noted that the company had submitted a proposal for managed access, which included additional data collection from the GO29781 study cohort until at least June 2024 and a confidential prospective study collecting real-world evidence on mosunetuzumab (FDG section 3.18). The committee noted that longer-term data from the GO29781 study cohort would be helpful to inform the survival modelling. It also noted that the timeframe for data collection with managed access may not be long enough to show an overall survival benefit, which is one of the key uncertainties. As noted in response to the company previous comment (point 1), in the company's survival modelling, people in the mosunetuzumab arm had lower life-years gained than those in the rituximab plus lenalidomide arm (FDG section 3.12). 2. The committee noted that it was unlikely Systemic Anti-Cancer Dataset (SACT) data would sufficiently resolve the high

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
			sponsored projects and supporting investigator-initiated analyses of real world data. (Commercial in confidence information removed). These initiatives could also help address the uncertainty concerning whether RB is representative of all R-chemotherapy regimens by facilitating a retrospective cohort of patients receiving individual chemotherapy regimens. During Technical Engagement, the company submitted a comparative analysis of the GO29781 data set with US real-world data from Flatiron. This demonstrated a significantly higher CR rate and longer OS for mosunetuzumab compared to commonly available treatments for 3L+ FL in the US. With (commercial in confidence information removed) and the company sponsored non-interventional study, the company intends to collect similar real world data based on UK clinical practice to demonstrate the clinical benefit of mosunetuzumab in a population representative of UK patients. Obviously, this evidence is only obtainable if access in the UK is granted. **Precedence from recent CDF reviews** The company believes that the proposed data collection methods are consistent with the evidence package submitted and appraised in recent NICE CDF reviews in haematological indications. For instance, daratumumab monotherapy was recommended as an option for multiple myeloma (TA783) following a period in the CDF[4]. This decision was based on further follow up of the single arm MMY2002 study, with comparator data sourced from the SACT dataset since this represented patients in UK clinical practice. Furthermore, venetoclax was recently recommended for the treatment of CLL (an indolent condition like FL) following its CDF review in TA796, with this reappraisal conducted on the basis of data collected in SACT[5]. The data collection plan proposed by the company aligns with evidence packages that have supported routine commissioning for treatments coming out of the CDF. The company therefore considers the proposed data collection to be robust enough to go some way to addressing the key uncertainties in this appraisal.	uncertainty associated with the indirect treatment comparisons (section 3.18). It would also be unlikely to provide any overall survival data with a long enough duration to reduce uncertainty by very much. 3. Considering other sources of data on comparators (section 3.18), the committee noted these may provide useful information, but any comparison with mosunetuzumab would still be unanchored. Also, when adjusting for prognostic factors and effective modifiers the effective sample size may be small. It also noted that comparator studies cannot form part of a managed access agreement. 4. As noted in the company's response to this point, evidence packages involving single arm studies have led to NICE recommendations with managed access in haematological indications. The committee appreciated that managed access is designed to resolve uncertainties, but it did not think that it would sufficiently resolve the high level of uncertainty in the present submission (section 3.18). Also, it had not seen evidence that mosunetuzumab had plausible potential to be cost effective. It concluded that mosunetuzumab did not meet the criteria to be considered for a recommendation with managed access.
3	Company	Roche	**Subsequent treatment assumption (DG, Section 3.13)** The company accepts that the EAG's preferred assumption regarding subsequent treatment use following treatment on R-len (which excludes R-len given that patients would not be retreated with this regimen) is a fair reflection of clinical practice. The company base case now excludes R-len within the pool of subsequent treatments following 3L R-len. The pool of subsequent treatments (and associated proportion of patients receiving each treatment) for this comparator are modelled as the EAG suggested – R-chemo (50%), non R-chemo (20%), palliative care (10%) and trials (20%). However, the company wishes to express its disappointment regarding the timing of when this change was introduced to the appraisal. The change to this assumption should have been flagged as part of the EAG's report or at a	Thank you for your comments. The committee took these comments into consideration (see below) along with the company's updated model. 1. The committee discussed that during the consultation the company updated its subsequent therapy assumptions (section 3.14) in its base case. It concluded that the company's subsequent treatment assumptions are likely to reflect clinical practice.

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
			minimum during the Technical Engagement period. In fact, the Company was first informed of the EAG's preference on this issue when it received the committee papers before the meeting. Consequently, there was no opportunity to explore this assumption with clinical experts or respond to this revision prior to the committee meeting.	
4	Company	Roche	**Post-progression utility values (DG, Section 3.12)** The DG notes that the company's approach to use utility values derived from the GO29781 trial was *"acceptable but associated with some uncertainty",* due to the number of observations in the post-progression health state (63 observations in total, 19 made after 1 year) and the EAG's comment that utility values in early post-progression are extrapolated forward many years in the model. To address this uncertainty, in the updated analysis provided in Appendix A, the company has changed the source of utilities in its base case to that from the literature, specifically Wild et al. Utility values in this publication were elicited from 222 UK patients and have been used in previous NICE appraisals in relapsed/refractory FL (TA604 and TA627)[1,6]. The company considers this to be a more robust source of utilities, than the values derived from the pivotal trial. This revision should help address the Committee's reservations on this issue.	Thank you for your comments. The committee took these comments into consideration (see below) along with the company's updated model. 1. The committee discussed that during the consultation the company changed its source of utility values, preferring to use Wild et al. in its base case (FDG section 3.13). The committee noted that it was not known whether the utility value for post-progression from the Wild et al. abstract represented people on subsequent treatment or not. It concluded that it preferred the GO29781 study cohort values because they were from a clinical study of people having mosunetuzumab, while Wild et al. may not be a robust source and could not be validated.
5	Company	Roche	**R-bendamustine as a representation of R-chemotherapy in the 3L+ relapsed/refractory FL setting (DG, Sections 3.5, and 3.7)** The DG notes that the committee concluded that *"rituximab plus bendamustine is a reasonable comparator in itself, but whether it is representative of other types of rituximab plus chemotherapy is highly uncertain".* The company acknowledges that there is a paucity of trial evidence for rituximab-based chemotherapy regimens in later lines of FL, therefore there is no available evidence to demonstrate whether RB is representative of rituximab based chemotherapy regimens as a whole. Similar challenges with comparing against rituximab-chemotherapy regimens have been experienced in previous relapsed/refractory FL appraisals, specifically TA604 and TA627, in which idelalisib and R-len respectively were limited to comparisons against treatments from registry data only[1,6]. In the current appraisal, the company has been able to benefit from having access to individual patient data from the CONTRALTO and GO29365 studies to facilitate a propensity score analysis with patients who received RB. The company accepts there are limitations to this ITC due to the differences in populations resulting from varying eligibility criteria between the studies. However the company maintains that methods taken to account for differences in covariates believed to be prognostic factors or treatment-effect modifiers aligned with best practices in observational research methods[7,8] and recommendations	Thank you for your comments. The committee took these comments into consideration (see points below) along with the company's updated model. 1. In considering the suitability of the comparators for mosunetuzumab in the indirect treatment comparisons, the committee concluded that rituximab plus bendamustine is a reasonable comparator, but whether it is representative of other types of rituximab plus chemotherapy is highly uncertain (FDG section 3.5). 2. The FDG notes that the company used the CONTRALTO and GO29365 studies of rituximab plus bendamustine, which had individual patient data, and therefore, propensity score analyses were done (section 3.6). The committee concluded that there was some uncertainty associated with the indirect comparison of mosunetuzumab with rituximab plus bendamustine.

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
			in NICE TSD 17[9]. Despite the absence of trial evidence for different rituximab-chemotherapy regimens, the company feels this corroborates the clinical experts' view stated in the DG that *"there is limited data to challenge whether rituximab plus bendamustine is representative of rituximab plus chemotherapy had by people at third line or later".* Furthermore, the company highlights that clinical experts also said that patients receiving RB would typically be *"younger and fitter"* than patients receiving other rituximab-chemotherapy regimens. The company believes the committee should take this into consideration when reviewing the cost-effectiveness estimate for mosunetuzumab vs RB, particularly if there are reservations that this regimen may not be representative of rituximab-chemotherapy, as this may mean the observed treatment effect of mosunetuzumab vs R-chemotherapy is underestimated.	3. The committee heard from clinical experts that if rituximab plus bendamustine is representative, it sets the bar high for the indirect treatment comparison because people having treatment will be younger and fitter (FDG section 3.5 and 3.8). It also heard from the company that in the propensity score analysis, there were also important differences between the study populations. This suggests that people who had treatment with mosunetuzumab had a poorer prognosis than those in the pooled studies of rituximab plus bendamustine (section 3.8). The committee concluded that the results of the indirect treatment comparisons were highly uncertain. It also noted that issues with the indirect treatment comparisons, including the representativeness of rituximab plus bendamustine for other types of rituximab plus chemotherapy, contributed to the high level of uncertainty in the cost effectiveness estimate (section 3.16). 4. Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will specifically consider the degree of certainty and uncertainty around the ICER (section 3.16). For the comparison with rituximab plus bendamustine, mosunetuzumab was not plausibly cost effective because both the company's updated and EAG's base cases were greater than £30,000 per QALY gained (FDG section 3.15). The estimates are also associated with considerable uncertainty. Therefore, the committee concluded that mosunetuzumab did not represent a cost-effective use of NHS resources so could not be recommended.
6	Company	Roche	**ITC vs R-lenalidomide (DG, Section 3.6)** The ACD notes that the ITC vs R-len *"excluded some important variables".* The company wishes to clarify the reasons why the following important prognostic	Thank you for your comments. The committee took these comments into consideration (see points below) along with the company's updated model.

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
			factors and effect modifiers were excluded from the comparison: • Number of previous therapies: This data is not available from the FL cohort of the R-len AUGMENT study • Refractory status to previous anti-CD20 inhibitor: patients were non-rituximab refractory in AUGMENT so it was not possible to match for this variable • Previous stem cell transplant: No data were reported in AUGMENT but this is not expected to be relevant as stem cell transplant is uncommon in this setting (as mentioned in DG) • Size of largest lymph node: This was not reported in AUGMENT but is controlled for by matching for bulky disease (which is derived from size of largest lymph node) Controlling for all prognostic factors (high and low priority) was included within the original ITC analysis as an alternative scenario, however this reduced the effective sample size to 20.9 (compared to 32.9 in the base case analysis). Therefore, this scenario was not pursued for the economic evaluation since reducing the sample size by 36.5% would serve to increase the overall uncertainty associated with the ITC, rather than reduce it. Furthermore, the DG also states that the analysis has the potential for bias, but the amount and direction of this bias is unclear. To mitigate concerns about residual imbalances, during Technical Engagement the company provided baseline characteristics with all priority factors reported before and after weighting. This analysis demonstrated that there is an important residual bias against mosunetuzumab for all factors that weren't included in the adjustment. Therefore, the comparative effectiveness of mosunetuzumab vs R-len is likely to be underestimated given this high potential for bias towards R-len. The DG also states that low haemoglobin should have been excluded from the analysis as this was imputed from the full GO29781 population. The company wishes to clarify that excluding low haemoglobin as a variable does marginally increase the effective sample size to 35.3 and improves the hazard ratio for overall survival. However, clinical expert opinion obtained at the time of conducting the ITC stated that low haemoglobin was an important prognostic variable to control for, therefore the company prioritised controlling for as many high priority variables as possible in this analysis, even though the overall survival hazard ratio was worse. The company would like to reiterate that it has conducted this ITC in line standard methodology as per NICE Technical Support Documents. It is also noteworthy that the EAG did not conduct alternative analyses to improve the ITC in its base case. The company acknowledges the limitations with the analysis, which is a result of absence of robust data for R-len in the 3L+ setting for FL. Given the differences between study populations compared, with the mosunetuzumab population reflecting a poorer prognosis, the relative effectiveness of mosunetuzumab in the ITC vs R-len is likely to be underestimated.	1. The FDG has been updated to note that the company was not able to match some variables in the matching-adjusted indirect comparison of mosunetuzumab with rituximab plus lenalidomide, because data was not available from AUGMENT (section 3.6). The committee conclusion has also been reworded to state that the indirect comparison of mosunetuzumab with rituximab plus lenalidomide 'was not matched for' some important variables, making it highly uncertain with a potential for bias. 2. The committee noted that the mosunetuzumab study cohort had more relapses and greater treatment refractoriness than people having rituximab plus lenalidomide in AUGMENT (FDG section 3.8). The committee concluded that the results of the indirect treatment comparisons were highly uncertain. It also noted that issues with the indirect treatment comparisons, including variables included and differences between study populations, contributed to the high level of uncertainty in the cost effectiveness estimate (section 3.16). 3. Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will specifically consider the degree of certainty and uncertainty around the ICER (section 3.16). For the comparison with rituximab plus lenalidomide, mosunetuzumab was more costly and less effective in the company's updated base case. Also, mosunetuzumab was more costly and marginally less effective than rituximab plus lenalidomide in the EAG's preferred base case (FDG section 3.15). The estimates are also associated with considerable uncertainty. Therefore, the committee concluded that

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
				mosunetuzumab did not represent a cost-effective use of NHS resources so could not be recommended.
	Company	Roche	**Revised base case** In response to the ACD [DG], the following changes to the company base case have been made: • **Subsequent treatments:** R-len has been excluded from the pool of subsequent treatments for the R-len comparator (as per EAG's preferred assumption). See DG response point 3 for further details. • **Utility values:** Changed from applying trial utilities to literature values from Wild et al. See DG response point 4 for further details. The deterministic cost-effectiveness results based on the revised company base case, and at the current approved mosunetuzumab PAS of [redacted] ([redacted] discount) are as follows: • For mosunetuzumab vs R-lenalidomide (R-len), incremental costs were [redacted] and incremental QALYs were [redacted], resulting in [redacted] • For mosunetuzumab vs R-bendamustine (RB), incremental costs were [redacted] and incremental QALYs were [redacted], resulting in an ICER of [redacted] **Comparator net prices** The company is aware both rituximab and lenalidomide are subject to confidential discounts. Competitor intelligence gathered by the company estimates the discounts for rituximab and lenalidomide to be in the range of [redacted]% and [redacted]%, respectively. Applying the midpoint of these estimates to the company base case has the following impact on the results: • For mosunetuzumab vs R-lenalidomide (R-len), incremental costs were [redacted] and incremental QALYs were [redacted], resulting in [redacted] • For mosunetuzumab vs R-bendamustine (RB), incremental costs were	The committee considered the company's revised cost effectiveness results. Please see sections 3.15 - 3.17 in the final draft guidance document.

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
			[redacted] and incremental QALYs were [redacted], resulting in an ICER of [redacted] **Estimated mosunetuzumab discount required** ***vs RB*** Applying estimated net prices for the comparators to the company base case would mean the following level of discount would be needed in order for mosunetuzumab to be cost-effective vs RB at willingness to pay thresholds of £30,000 per QALY gained and £20,000 per QALY gained: • WTP £30,000: [redacted] o incremental costs of [redacted] and incremental QALYs of [redacted], resulting in an ICER of [redacted] • WTP £20,000: [redacted] o incremental costs of [redacted] and incremental QALYs of [redacted], resulting in an ICER of [redacted] ***vs R-len*** Applying estimated net prices for the comparators to the company base case would mean that no level of discount could be applied to the price of mosunetuzumab for it to generate sufficient cost-savings to be considered cost-effective vs R-len by net monetary benefit at a willingness to pay threshold of £30,000 per QALY gained: • At zero price (100% discount): • Incremental costs of [redacted] and incremental QALYS of [redacted], resulting in an ICER of [redacted] **Please refer to Appendix A for further information.**	
	Company	Roche	**References** 1 National Institute for Health and Care Excellence. *Technology appraisal guidance [TA604]: Idelalisib for treating refractory follicular lymphoma*, <https://www.nice.org.uk/guidance/ta604> (October 2019).	

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
			2 National Institute for Health and Care Excellence (NICE). TA717: Duvelisib for treating relapsed follicular lymphoma after 2 or more systemic therapies (terminated appraisal). (2021). 3 National Institute for Health and Care Excellence (NICE). TA842: Tisagenlecleucel for treating follicular lymphoma after 2 or more therapies (terminated appraisal). (2022). 4 National Institute for Health and Care Excellence (NICE). TA783: Daratumumab monotherapy for treating relapsed and refractory multiple myeloma. (2022). 5 National Institute for Health and Care Excellence (NICE). TA796: Venetoclax for treating chronic lymphocytic leukaemia. (2022). 6 National Institute for Health and Care Excellence. *Technology appraisal guidance [TA627]: Lenalidomide with rituximab for previously treated follicular lymphoma*, <https://www.nice.org.uk/guidance/ta627> (07 April 2020). 7 Ali, M. S. *et al.* Propensity Score Methods in Health Technology Assessment: Principles, Extended Applications, and Recent Advances. *Frontiers in pharmacology* **10**, 973, doi:10.3389/fphar.2019.00973 (2019). 8 National Institute for Health and Care Excellence. *PMG36: NICE health technology evaluations: the manual*, <https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation accessed July 2022> (2022). 9 Faria, R., Hernandez Alava, A., M,, Manca, A. & Wailoo, A., J. NICE DSU Technical Support Document 17: The use of observational data to inform estimates of treatment effectiveness for Technology Appraisal: Methods for comparative individual patient data. *Available from http://www.nicedsu.org.uk* (2015).	
1	Commentator in web comments	National Cancer Research Institute (NCRI) Lymphoma Group	**Has all of the relevant evidence been taken into account?** All relevant evidence has not been considered and these additional data could sufficiently resolve the high level of uncertainty in the health economic model. Additional evidence that will become available within the next few years must be considered in the context of re-appraising mosunetuzumab for managed access. The comparators used in this appraisal were R2 and BR. Data for R2 came from the AUGMENT trial which was conducted exclusively in rituximab-sensitive patients with a median of two prior lines of therapy. The MAIC did not adjust for critical prognostic factors – line of therapy and rituximab-refractoriness. Additional R2 data in rituximab refractory and sensitive patients treated at 3L+ will become available and should be considered in an updated analysis: 1. NCT01996865. Lenalidomide Plus Rituximab Followed by Lenalidomide Versus Rituximab Maintenance for Relapsed/Refractory Follicular, Marginal Zone or Mantle Cell Lymphoma. (MAGNIFY). This randomised trial will recruit 503 participants and reach primary completion in April	Thank you for your comments. The committee took these comments into consideration (see points below) along with the company's updated model. 1. The FDG has been updated (section 3.18) to note stakeholder comments on the draft guidance that clinical studies with completion in the next few years may provide additional data on standard care. The committee noted these may provide useful information on comparators, but any comparison with mosunetuzumab would still be unanchored. It also noted that comparator studies cannot form part of a managed access agreement.

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
			2023. Final results for R2 induction have been reported (Lansigan et al, 2022). 2. NCT04680052. A Phase 3 Study to Assess Efficacy and Safety of Tafasitamab Plus Lenalidomide and Rituximab Compared to Placebo Plus Lenalidomide and Rituximab in Patients With Relapsed/Refractory (R/R) Follicular Lymphoma or Marginal Zone Lymphoma. (InMIND). This phase 3 trial will enrol 618 patients and reach primary completion in Feb 2024. 3. NCT04712097. A Study Evaluating the Efficacy and Safety of Mosunetuzumab in Combination With Lenalidomide in Comparison to Rituximab in Combination With Lenalidomide in Patients With Follicular Lymphoma After at Least One Line of Systemic Therapy (Celestimo). This Phase 3 trial will enrol 400 participants and reach primary completion in Aug 2025. As this trial is sponsored by Hoffmann-La Roche, data will be suitable for a propensity score analysis using individual patient data. The appraisal considered BR as a proxy for all types of immunochemotherapy and contested the notion that additional data collection would resolve uncertainty about whether rituximab plus bendamustine is representative of other types of rituximab plus chemotherapy (R-CHOP, R-CVP). This is not true. In clinical practice, bendamustine is restricted to fitter patients under 70 years of age, thus is neither a valid representative of immunochemotherapy in older and frailer patients, or a valid comparator for mosunetuzumab in this population. RCVP and RCHOP data are available from the Haematological Malignancy Research Network (HMRN) registry and have already been used to support a previous TA in the same indication (TA627: Lenalidomide with rituximab for previously treated follicular lymphoma). In this TA, RCHOP and RCVP were assumed to be clinically equivalent. In addition to HMRN data, a new study called Foundation UK will collect treatment and outcome data for 500 patients treated for r/r FL at 14 UK hospitals. The study is opening to recruitment in March 2023 and will run for two years. Results will provide the largest UK real world comparator dataset and may resolve some uncertainty over the relative clinical efficacy of different treatments by therapy line, sequence and patient group (e.g. by age or fitness). At this time, considering the uncertainty of the model, real world data series reporting '3L treatment' should be factored into the health economic model to represent the totality of 3L treatment. This includes the SCHOLAR-5 dataset (Ghione P et al, Blood. 2022), A US multi-centre cohort (Casulo et al, 2022) and a single centre UK dataset (Linton K et al, Blood 2021). The following randomised trial data sources will provide additional SOC comparator data in 2023-2026: 1. Relapsed Follicular lymphoma Randomised trial Against standard ChemoTherapy (REFRACT): A randomised phase II trial of investigator choice standard therapy versus sequential novel therapy experimental	2. The FDG has also been updated (section 3.5) to include stakeholder comments that real-world data sets could potentially have been incorporated into the indirect treatment comparisons. Considering this, the company noted that these data sets on comparators were not used because they included people who had treatment at an earlier line of therapy or included a mixed histology (not all follicular lymphoma). 3. In relation to the new FOUNDATION UK study, please refer to bullet 1 above. 4. Please also see the responses to the company's comments 5 and 6 (above) for further consideration of the indirect comparisons that were performed.

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
			arms. This UK-NCRI study will report outcomes for R-CHOP, R-CVP, rituximab and lenalidomide, bendamustine and obinutuzumab and rituximab and bendamustine. It will recruit 126 patients and report round 1 in Aug 2025. 2. NCT04745832 Phase 3 Study of Zandelisib (ME-401) in Combination With Rituximab in Patients With iNHL - (COASTAL). This phase 3 trial was planned to recruit 534 participants and report in Apr 2026. The study closed early and may report early. It will provide RCHOP and BR comparator data. 3. NCT02626455. Study of Copanlisib in Combination With Standard Immunochemotherapy in Relapsed Indolent Non-Hodgkin's Lymphoma (iNHL) (CHRONOS-4). This phase 3 trial aimed to recruit 551 patients and report in Feb 2023. It will provide RCHOP and BR data.	
2	Commentator in web comments	NCRI Lymphoma Group	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** For the comparison with rituximab plus lenalidomide, mosunetuzumab was more costly and less effective in both the company and EAG's preferred base cases. In relapsed FL, PFS reduces significantly with each line of therapy. Thus, this is not a fair interpretation as the analysis compared R2 in second line (median 2 lines, 24% >=3L) with mosunetuzumab in third line (median 3 lines, 62% >= 3L). The comparison was also unbalanced for other important prognostic factors including rituximab refractoriness and a greater proportion of high-risk patients in the mosunetuzumab arm. For the comparison with rituximab and bendamustine, the committee noted that the ICERs for the EAG base cases do not include any potential overall survival benefit for mosunetuzumab, which is likely to be too conservative. PFS benefit for a particular treatment seldom translates into an improvement in survival for FL. This is because FL has a long natural history, the patient population is very heterogenous and most patients get a similar range of treatments over the course of the disease. We would expect a difference in survival if these treatments were the only treatment (or one of few) given to a patient, but that is not the case for FL patients. Thus, PRIMA, GALLIUM, RELEVANCE, FOLL12, and AUGMENT all failed to show an overall survival benefit for one treatment over another. The model places too much emphasis on overall survival.	Thanks for your comments. The committee took these comments into consideration (see points below) along with the company's updated model. 1. The FDG has been updated (section 3.12) to include stakeholders comments that the model may place too much emphasis on overall survival, and that a progression-free survival benefit may not translate into improved overall survival in follicular lymphoma because of the long natural history of the condition and a heterogenous population having a range of treatments. 2. Please also see the responses to the company's comments 5 and 6 (above) for further consideration of the indirect comparisons and cost-effectiveness estimates. 3. The FDG notes that the committee concluded the EAG scenarios [where overall survival is pooled] could be plausible even though they are conservative. Please also see the response to the company's comment 1 (above), which includes that clinical experts noted that in this cancer type, progression-free survival may not impact overall survival (section 3.12).
3	Commentator in web comments	NCRI Lymphoma Group	**Are the recommendations sound and a suitable basis for guidance to the NHS?** The recommendations do not form a sound basis for addressing unmet need in	Thanks for your comments. The committee took these comments into consideration (see points below) along with the company's updated model.

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
			FL patients. • Unmet need #1 - lack of treatment options at 3L/4L Many r/r FL patients treated in the third line setting have either received one line of immunochemotherapy (ICT) followed by R2 or two lines of ICT. In fit patients, the most common treatment sequence is first line (1L) intensive immunochemotherapy (bendamustine/CHOP plus rituximab/obinutuzumab) followed by second line (2L) intensive ICT (using whichever chemotherapy they did not receive previously) or R2. In unfit/frail patients, the most common treatment sequence is non-intensive therapy, RCVP, followed by R2. Since the same treatment is very seldom re-used and more intensive therapy is typically contraindicated after non-intensive first line therapy, options become increasingly limited from 3L onwards, especially for unfit/frail patients where effectively there are no available standard treatments. Rituximab monotherapy, which may be offered outside the UK, is rarely used in this setting as it produces very short remissions. Some patients are also not candidates for selected immunochemotherapies due to co-morbidities, further limiting access to standard options; for example, CHOP is contraindicated in patients with cardiac disease and bendamustine is not recommended in patients with a high risk of infection. • Unmet need #2 - progressive chemo-refractoriness Patients with FL acquire increasing resistance to chemotherapy with each successive relapse and re-treatment event. This is evidenced by real world data demonstrating progressively shorter duration of response and progressive-free survival with each line of therapy (Batlevi CL, et al. 2020). Immunochemotherapy constitutes the mainstay of therapy reported in real world studies, suggesting that acquired chemo-refractoriness is the main reason for diminishing PFS. Further evidence for diminishing PFS over the disease course is presented in studies of autologous stem cell transplant consolidation (ASCT) in FL, a treatment where success is contingent upon preserved chemo-sensitivity. In a UK retrospective study, best outcomes were reported for patients receiving ASCT as 2L consolidation (Kothari et al, 2014). ASCT delivered in later lines of therapy is not recommended due to increasing chemo-refractoriness associated with inferior outcomes. • Unmet need #3 - early treatment failure Patients who relapse or progress within 2 years of starting ICT (POD24 subset) have an inferior survival (Casulo et al, 2015). This may reflect primary chemo-refractoriness and is typically associated with inferior outcomes to subsequent immunochemotherapy, underlining a need for novel therapies. Mosunetuzumab, a first-in class drug with a unique mode of action, offers substantially more benefits than risks to patients with r/r FL and has demonstrated remarkable activity. Similar or higher response rates than those seen in the overall study population were observed in high-risk subgroups (ORR all patients 79%; POD24 83%; age ≥65 83%, refractory to last therapy 76%, 3L+ 75%). Response rates, PFS, DOR, DOCR and time to next therapy or death	1. The FDG has been updated following stakeholder comments (section 3.1), noting that mosunetuzumab could provide an extra line of treatment. The FDG also includes comments from clinical experts that survival and remission duration worsen with each successive relapse. 2. Please also see the responses to comment 1 and 2 from the Association of Cancer Physicians (above) in consideration of treatment options in relapsed and refractory follicular lymphoma and the comparators selected. 3. The committee concluded, based on single-arm trial evidence, that mosunetuzumab was potentially a promising new treatment option in relapsed or refractory follicular lymphoma (FDG section 3.4). 4. Please also see the responses to the company's comments 2, 5 and 6 (above) for further consideration of the indirect comparisons and cost-effectiveness estimates that were considered in the committee's recommendations.

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
			were all improved for mosunetuzumab compared to last prior therapy (Bartlett et al, Blood 2022). Mosunetuzumab effectively provides an extra line of therapy in the critical areas of unmet need. Compared to chemotherapy which is unacceptably toxic in elderly/comorbid patients, or ineffective in high-risk patients, mosunetuzumab offers treatment that is both highly effective and very well tolerated. In this context, comparing mosunetuzumab to immunochemotherapy is inherently flawed. If indeed this drug is recommended for patients who have exhausted, or are not candidates for standard therapy, then the best comparator is 'best supportive care'.	
4	Commentator in web comments	NCRI Lymphoma Group	**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, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** We are concerned that this decision will discriminate against older/frailer patients who due to age and co-morbidity do not have equal access to the full range of standard immunochemotherapy options. They have an even greater need for novel therapies earlier in their disease course.	Thanks for your comment. The committee took this into consideration in the FDG (section 3.19), where the following has been added: 1. Stakeholders commented on the draft guidance that not recommending mosunetuzumab may disadvantage older or frailer people with follicular lymphoma because they do not have access to the full range of immunochemotherapy treatment options. They also noted that these people have an even greater need for novel therapies earlier in the disease course. As the committee's recommendation applies all people within the marketing authorisation indication for mosunetuzumab, this was not considered to be an equality issue. Please also refer to the Equality Impact Assessment Form.

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments
Stakeholder comments form – ACP	Association of Cancer Physicians (ACP)	None	2	
Company comments form	Roche	None	6	**AIC / CIC removed in this version**
Compiled web comments – NCRI Lymphoma Group	National Cancer Research Institute (NCRI) Lymphoma Group	[No answer given]	4	

NICE National Institute for Health and Care Excellence

Mosunetuzumab for treating relapsed or refractory follicular lymphoma [ID3931]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 31 January 2023. Please submit via NICE Docs.

Ross Dent

National Institute for Health and Care Excellence

2nd Floor, 2 Redman Place

London

E20 1JQ

31st January 2023

RE: Mosunetuzumab for the treatment of patients with relapsed or refractory follicular lymphoma who have received two or more prior lines of systemic therapy

Dear Ross

Thank you for the opportunity to comment on the ACD. We believe this appraisal raises a significant issue that requires special consideration by the committee and NICE more broadly.

While the company acknowledges that mosunetuzumab is not cost-effective against either rituximab-lenalidomide (R-len) or rituximab-bendamustine (RB), there is no level of additional discount that can be applied to the price of mosunetuzumab that would demonstrate it to be cost-effective vs R-len.

Specifically, if provided free of charge, mosunetuzumab would not generate sufficient cost-savings that would enable it to be considered cost-effective by net monetary benefit at a willingness-to-pay threshold of £30,000.

With the current preferred assumptions, the company would need to give the NHS approximately [redacted] per mg utilised, equating to [redacted] per patient for 8 cycles, or [redacted] for the full 17 cycles.

The company acknowledges the limitations associated with submitting evidence from a single-arm study. In this appraisal, evidence for mosunetuzumab is only available from an early phase non-randomised trial of 90 patients, while subsequent indirect treatment comparisons are subject to limitations due to a lack of robust evidence for those regimens in the 3L+ setting. Consequently, the cost-effectiveness results for mosunetuzumab vs R-len are likely to be underestimated given the potential bias in the compared populations towards R-len. It is also noteworthy that the EAG did not conduct alternative analyses and were therefore unable to improve upon the indirect treatment comparison presented in the Company's base case.

Please return to: **NICE DOCS**

Mosunetuzumab for treating relapsed or refractory follicular lymphoma [ID3931]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 31 January 2023. Please submit via NICE Docs.

Given these limitations, a robust data collection package has been proposed to help address the uncertainties in the current appraisal. However, it is unpalatable to the company to be required to give this medicine away for free in order to grant access to this medicine via the Cancer Drugs Fund, let alone for the company to have to pay the NHS to introduce it. As such, the PAS offer will not be increased as part of this response.

While the challenges with the current appraisal are apparent, the company is also conscious of the reality being that many treatments are obtaining regulatory approval on the basis of single arm, phase II data; particularly since large, randomised controlled trials may not be feasible or ethical in indications with small patient numbers (such as relapsed/refractory FL). Therefore, there is clearly a sizable disconnect between what evidence is acceptable for marketing authorisation versus what is required to demonstrate cost-effectiveness and achieve reimbursement. Consequently, patients are not getting access to much needed innovative treatment options as noted by the fact that some treatments in this setting with evidence based on single arm studies are not granted reimbursement (e.g. idelalisib [TA604]), or NICE appraisals have been terminated due to no evidence being submitted (duvelisib [TA717], tisagenlecleucel [TA842]).

The company is very disappointed to be in this situation but feels that this raises serious questions regarding the suitability of the current NICE methods to appraise evidence from single arm studies. The company is committed to engage with NICE on this matter further to understand what can be done to facilitate the future appraisals of evidence based on non-randomised studies with small patient numbers and with no clear standard of care. Committees will face similar challenges in the future as more treatments are granted regulatory approval on the basis of early phase evidence, therefore it is important that the uncertainty associated with those appraisals can be accounted for in decision making so that NICE can meet its commitment for delivering promising and innovative technologies.

Due to the issue described above, the company recognises that the additional responses to the ACD are unlikely to have a material impact on the committee's recommendation, however for completeness and to ensure the final decision reflects the available evidence, the company's responses are outlined below.

Kind regards

[redacted]

NICE National Institute for Health and Care Excellence

Mosunetuzumab for treating relapsed or refractory follicular lymphoma [ID3931]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 31 January 2023. 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):	Roche Products Ltd.
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]

NICE National Institute for Health and Care Excellence

Mosunetuzumab for treating relapsed or refractory follicular lymphoma [ID3931]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 31 January 2023. Please submit via NICE Docs.

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Underlying challenges of appraisals based on single arm evidence packages (ACD, Section 3.16)** The company acknowledges that in its base case mosunetuzumab is not cost-effective against either rituximab-lenalidomide (R-len) or rituximab-bendamustine (RB) when Commercial Medicine Unit prices and confidential discounts are applied to rituximab and lenalidomide. The company has explored alternative scenarios within the model to improve the cost-effectiveness estimates (see response point 4 regarding source of utilities and Appendix A), while also including the EAG's revised assumption on subsequent treatment use since this was verified by clinical experts to be clinically relevant (see response point 3). In this revised base case (including estimated discounts for the comparators), there is no level of additional discount that can be applied to the price of mosunetuzumab that would demonstrate it to be cost-effective vs R-len. Specifically, it is not possible to set any price (even £0) at which mosunetuzumab could generate sufficient cost-savings that would enable it to be considered cost-effective by net monetary benefit at a willingness-to-pay threshold of £30,000. For the comparison with RB, the company believes that additional discount would be needed to be cost-effective in the revised base case, however whatever level of discount is needed to be cost-effective against RB would not be sufficient to be cost-effective against R-len. The company is very disappointed to be in this situation but feels that this raises serious questions regarding the suitability of the current NICE methods to appraise evidence from single arm studies, as no scenario exists that mosunetuzumab can demonstrate cost-effectiveness vs R-len. It is important to acknowledge that there is no standard of care for the treatment of relapsed/refractory follicular lymphoma in the third-line+ setting. Mosunetuzumab offers patients and clinicians an innovative and much needed non-rituximab, non-chemotherapy based treatment option in a population that is increasingly refractory to immunochemotherapy. Moreover, clinical experts informed the company that mosunetuzumab would provide an additional line of active therapy, i.e. patients could receive mosunetuzumab in the third-line setting before receiving R-len or another R-chemotherapy, or mosunetuzumab could be given beyond third-line after other regimens, delaying the need for palliative care or clinical trial enrolment. As such, mosunetuzumab is not intended to replace anything in the current treatment pathway. Clinical experts recognise the innovation of mosunetuzumab, stating that the complete response rate observed in the GO29781 trial of 60% hugely exceeds what is currently seen with current available treatments for 3L+ FL (estimated at 30-40%). Moreover, the latest available data cut ([redacted], median follow up of [redacted] months) demonstrates that

Mosunetuzumab for treating relapsed or refractory follicular lymphoma [ID3931]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 31 January 2023. Please submit via NICE Docs.

patients continue to derive a benefit from mosunetuzumab ([redacted]

Consequently, the company strongly feels that further evidence is required to perform a robust comparison vs R-len, particularly given the uncertainty associated with the outcomes from this indirect treatment comparison (ITC) (see response point 6). While the model currently demonstrates a QALY loss for mosunetuzumab vs R-len, it is important to note that the committee concluded in the ACD that:

- *"the lower life-years gained by people in the model with mosunetuzumab compared with rituximab plus lenalidomide did not reflect the potential benefit of mosunetuzumab on tumour response suggested by the single-arm study data"*
- "*in the comparison with rituximab plus lenalidomide, the company's modelling of mosunetuzumab overall survival* [which is deemed to be worse than that of R-len] *was unlikely to be plausible*".

Ultimately, the comparison of mosunetuzumab vs R-len is limited by the available evidence base for mosunetuzumab and the restrictions of comparing against a population from the R-len AUGMENT study that does not truly reflect 3L+ FL patients (mainly 2L and non-refractory to rituximab). As such, the comparative effectiveness results are uncertain and likely underestimate the benefit of mosunetuzumab given the potential for bias towards R-len. These limitations are reflected by the committee's feedback highlighted above.

The company acknowledges the challenges of appraising evidence based on single arm studies, and would like to clarify that a randomised phase III trial comparing mosunetuzumab with the PI3 kinase inhibitor idelalisib was planned but did not go ahead due to safety concerns with this class and the withdrawal of FL indications for these treatments in the US. However, the reality is that many treatments are obtaining regulatory approval on the basis on single arm, phase II data, particularly since large, phase III randomised controlled trials may not be feasible or ethical in indications with small patient numbers, such as relapsed/refractory FL. It is noteworthy that some treatments in this setting with evidence based on single arm studies either did not achieve reimbursement (e.g. idelalisib [TA604][1]), or NICE appraisals were terminated as no evidence was submitted (duvelisib [TA717][2], tisagenlecleucel [TA842][3]).

Mosunetuzumab was granted accelerated assessment by the EMA and Orphan Drug Designation by the EMA and MHRA, based on the same single arm pivotal study presented in this Submission. This illustrates that there is a sizable disconnect between what evidence is acceptable for marketing authorisation versus what is required to demonstrate cost-effectiveness and achieve reimbursement. Consequently, despite medicines being granted regulatory approval, patients are not getting access to much needed innovative treatment options.

Mosunetuzumab for treating relapsed or refractory follicular lymphoma [ID3931]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 31 January 2023. Please submit via NICE Docs.

	The company is very keen to engage further with NICE on this matter to understand what can be done to facilitate appraisals of evidence based on single arm studies, with small patient numbers and with no clear standard of care.
2	**Criteria for managed access (ACD, Section 3.17)** The ACD notes that uncertainties in the cost-effectiveness estimates would not be sufficiently resolved with further data collection in a managed access period. The company disagrees with this assessment and cites examples below where treatments in analogous disease areas have achieved access via the CDF on the basis of similar evidence packages and data collection agreements. **Mosunetuzumab data from GO29781** Further analyses providing more robust, long-term data for mosunetuzumab from the GO29781 pivotal cohort is planned, with annual outcomes analyses conducted until at least 2024. In the context of the available evidence to date, in which there is currently [redacted] months follow up, an additional 2–3 years follow up of the GO29781 pivotal cohort would provide valuable data to inform and validate the long term survival extrapolations incorporated in the economic model. This additional data will certainly help to address the current level of uncertainty in the degree of benefit derived from mosunetuzumab. In addition, the company is planning a multi-national, prospective non-interventional study of mosunetuzumab monotherapy in real world clinical practice in the submitted indication for countries where the medicine is accessible. Inclusion of mosunetuzumab in the CDF would allow for local real-world data collection, with an anticipated data cut of [redacted]. The proposed non-interventional study will also allow for the collection of progression-free survival data, something that cannot be captured via SACT. **Comparator data** As highlighted in its Technical Engagement response, the company plans to generate more robust comparator data for the control arms of the ITC through sponsored projects and supporting investigator-initiated analyses of real world data. [redacted] These initiatives could also help address the uncertainty concerning whether RB is representative of all R-chemotherapy regimens by facilitating a retrospective cohort of patients receiving individual chemotherapy regimens.

Mosunetuzumab for treating relapsed or refractory follicular lymphoma [ID3931]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 31 January 2023. Please submit via NICE Docs.

	During Technical Engagement, the company submitted a comparative analysis of the GO29781 data set with US real-world data from Flatiron. This demonstrated a significantly higher CR rate and longer OS for mosunetuzumab compared to commonly available treatments for 3L+ FL in the US. With [redacted] and the company sponsored non-interventional study, the company intends to collect similar real world data based on UK clinical practice to demonstrate the clinical benefit of mosunetuzumab in a population representative of UK patients. Obviously, this evidence is only obtainable if access in the UK is granted. **Precedence from recent CDF reviews** The company believes that the proposed data collection methods are consistent with the evidence package submitted and appraised in recent NICE CDF reviews in haematological indications. For instance, daratumumab monotherapy was recommended as an option for multiple myeloma (TA783) following a period in the CDF[4]. This decision was based on further follow up of the single arm MMY2002 study, with comparator data sourced from the SACT dataset since this represented patients in UK clinical practice. Furthermore, venetoclax was recently recommended for the treatment of CLL (an indolent condition like FL) following its CDF review in TA796, with this reappraisal conducted on the basis of data collected in SACT[5]. The data collection plan proposed by the company aligns with evidence packages that have supported routine commissioning for treatments coming out of the CDF. The company therefore considers the proposed data collection to be robust enough to go some way to addressing the key uncertainties in this appraisal.
3	**Subsequent treatment assumption (ACD, Section 3.13)** The company accepts that the EAG's preferred assumption regarding subsequent treatment use following treatment on R-len (which excludes R-len given that patients would not be retreated with this regimen) is a fair reflection of clinical practice. The company base case now excludes R-len within the pool of subsequent treatments following 3L R-len. The pool of subsequent treatments (and associated proportion of patients receiving each treatment) for this comparator are modelled as the EAG suggested – R-chemo (50%), non R-chemo (20%), palliative care (10%) and trials (20%). However, the company wishes to express its disappointment regarding the timing of when this change was introduced to the appraisal. The change to this assumption should have been flagged as part of the EAG's report or at a minimum during the Technical Engagement period. In fact, the Company was first informed of the EAG's preference on this issue when it received the committee papers before the meeting. Consequently, there was no opportunity to explore this assumption with clinical experts or respond to this revision prior to the committee meeting.
4	**Post-progression utility values (ACD, Section 3.12)**

Mosunetuzumab for treating relapsed or refractory follicular lymphoma [ID3931]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 31 January 2023. Please submit via NICE Docs.

	The ACD notes that the company's approach to use utility values derived from the GO29781 trial was "*acceptable but associated with some uncertainty*", due to the number of observations in the post-progression health state (63 observations in total, 19 made after 1 year) and the EAG's comment that utility values in early post-progression are extrapolated forward many years in the model. To address this uncertainty, in the updated analysis provided in Appendix A, the company has changed the source of utilities in its base case to that from the literature, specifically Wild et al. Utility values in this publication were elicited from 222 UK patients and have been used in previous NICE appraisals in relapsed/refractory FL (TA604 and TA627)[1,6]. The company considers this to be a more robust source of utilities, than the values derived from the pivotal trial. This revision should help address the Committee's reservations on this issue.
5	**R-bendamustine as a representation of R-chemotherapy in the 3L+ relapsed/refractory FL setting (ACD, Sections 3.5, and 3.7)** The ACD notes that the committee concluded that *"rituximab plus bendamustine is a reasonable comparator in itself, but whether it is representative of other types of rituximab plus chemotherapy is highly uncertain"*. The company acknowledges that there is a paucity of trial evidence for rituximab-based chemotherapy regimens in later lines of FL, therefore there is no available evidence to demonstrate whether RB is representative of rituximab based chemotherapy regimens as a whole. Similar challenges with comparing against rituximab-chemotherapy regimens have been experienced in previous relapsed/refractory FL appraisals, specifically TA604 and TA627, in which idelalisib and R-len respectively were limited to comparisons against treatments from registry data only[1,6]. In the current appraisal, the company has been able to benefit from having access to individual patient data from the CONTRALTO and GO29365 studies to facilitate a propensity score analysis with patients who received RB. The company accepts there are limitations to this ITC due to the differences in populations resulting from varying eligibility criteria between the studies. However the company maintains that methods taken to account for differences in covariates believed to be prognostic factors or treatment-effect modifiers aligned with best practices in observational research methods[7,8] and recommendations in NICE TSD 17[9]. Despite the absence of trial evidence for different rituximab-chemotherapy regimens, the company feels this corroborates the clinical experts' view stated in the ACD that "*there is limited data to challenge whether rituximab plus bendamustine is representative of rituximab plus chemotherapy had by people at third line or later".* Furthermore, the company highlights that clinical experts also said that patients receiving RB would typically be "*younger and fitter*" than patients receiving other rituximab-chemotherapy regimens. The company believes the committee should take this into consideration when reviewing the cost-effectiveness estimate for mosunetuzumab vs RB,

Mosunetuzumab for treating relapsed or refractory follicular lymphoma [ID3931]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 31 January 2023. Please submit via NICE Docs.

	particularly if there are reservations that this regimen may not be representative of rituximab-chemotherapy, as this may mean the observed treatment effect of mosunetuzumab vs R-chemotherapy is underestimated.
6	**ITC vs R-lenalidomide (ACD, Section 3.6)** The ACD notes that the ITC vs R-len "*excluded some important variables*". The company wishes to clarify the reasons why the following important prognostic factors and effect modifiers were excluded from the comparison: • Number of previous therapies: This data is not available from the FL cohort of the R-len AUGMENT study • Refractory status to previous anti-CD20 inhibitor: patients were non-rituximab refractory in AUGMENT so it was not possible to match for this variable • Previous stem cell transplant: No data were reported in AUGMENT but this is not expected to be relevant as stem cell transplant is uncommon in this setting (as mentioned in ACD) • Size of largest lymph node: This was not reported in AUGMENT but is controlled for by matching for bulky disease (which is derived from size of largest lymph node) Controlling for all prognostic factors (high and low priority) was included within the original ITC analysis as an alternative scenario, however this reduced the effective sample size to 20.9 (compared to 32.9 in the base case analysis). Therefore, this scenario was not pursued for the economic evaluation since reducing the sample size by 36.5% would serve to increase the overall uncertainty associated with the ITC, rather than reduce it. Furthermore, the ACD also states that the analysis has the potential for bias, but the amount and direction of this bias is unclear. To mitigate concerns about residual imbalances, during Technical Engagement the company provided baseline characteristics with all priority factors reported before and after weighting. This analysis demonstrated that there is an important residual bias against mosunetuzumab for all factors that weren't included in the adjustment. Therefore, the comparative effectiveness of mosunetuzumab vs R-len is likely to be underestimated given this high potential for bias towards R-len. The ACD also states that low haemoglobin should have been excluded from the analysis as this was imputed from the full GO29781 population. The company wishes to clarify that excluding low haemoglobin as a variable does marginally increase the effective sample size to 35.3 and improves the hazard ratio for overall survival. However, clinical expert opinion obtained at the time of conducting the ITC stated that low haemoglobin was an important prognostic variable to control for, therefore the company prioritised controlling for as many high priority variables as possible in this analysis, even though the overall survival hazard ratio was worse.

Mosunetuzumab for treating relapsed or refractory follicular lymphoma [ID3931]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 31 January 2023. Please submit via NICE Docs.

	The company would like to reiterate that it has conducted this ITC in line standard methodology as per NICE Technical Support Documents. It is also noteworthy that the EAG did not conduct alternative analyses to improve the ITC in its base case. The company acknowledges the limitations with the analysis, which is a result of absence of robust data for R-len in the 3L+ setting for FL. Given the differences between study populations compared, with the mosunetuzumab population reflecting a poorer prognosis, the relative effectiveness of mosunetuzumab in the ITC vs R-len is likely to be underestimated.
	Revised base case In response to the ACD, the following changes to the company base case have been made: • **Subsequent treatments**: R-len has been excluded from the pool of subsequent treatments for the R-len comparator (as per EAG's preferred assumption). See ACD response point 3 for further details. • **Utility values:** Changed from applying trial utilities to literature values from Wild et al. See ACD response point 4 for further details. The deterministic cost-effectiveness results based on the revised company base case, and at the current approved mosunetuzumab PAS of [redacted] ([redacted] discount) are as follows: • For mosunetuzumab vs R-lenalidomide (R-len), incremental costs were [redacted] and incremental QALYs were [redacted], resulting in [redacted] • For mosunetuzumab vs R-bendamustine (RB), incremental costs were [redacted] and incremental QALYs were [redacted], resulting in an ICER of [redacted] **Comparator net prices** The company is aware both rituximab and lenalidomide are subject to confidential discounts. Competitor intelligence gathered by the company estimates the discounts for rituximab and lenalidomide to be in the range of [redacted]% and [redacted]%, respectively. Applying the midpoint of these estimates to the company base case has the following impact on the results: • For mosunetuzumab vs R-lenalidomide (R-len), incremental costs were [redacted] and incremental QALYs were [redacted], resulting in [redacted] • For mosunetuzumab vs R-bendamustine (RB), incremental costs were [redacted] and incremental QALYs were [redacted], resulting in an ICER of [redacted] **Estimated mosunetuzumab discount required** ***vs RB***

NICE National Institute for Health and Care Excellence

Mosunetuzumab for treating relapsed or refractory follicular lymphoma [ID3931]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 31 January 2023. Please submit via NICE Docs.

	Applying estimated net prices for the comparators to the company base case would mean the following level of discount would be needed in order for mosunetuzumab to be cost-effective vs RB at willingness to pay thresholds of £30,000 per QALY gained and £20,000 per QALY gained: • WTP £30,000: [redacted] o incremental costs of [redacted] and incremental QALYs of [redacted], resulting in an ICER of [redacted] • WTP £20,000: [redacted] o incremental costs of [redacted] and incremental QALYs of [redacted], resulting in an ICER of [redacted] ***vs R-len*** Applying estimated net prices for the comparators to the company base case would mean that no level of discount could be applied to the price of mosunetuzumab for it to generate sufficient cost-savings to be considered cost-effective vs R-len by net monetary benefit at a willingness to pay threshold of £30,000 per QALY gained: • At zero price (100% discount): • Incremental costs of [redacted] and incremental QALYS of [redacted], resulting in an ICER of [redacted] **Please refer to Appendix A for further information.**

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 [redacted] and information that is [redacted]. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.

NICE National Institute for Health and Care Excellence

Mosunetuzumab for treating relapsed or refractory follicular lymphoma [ID3931]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 31 January 2023. Please submit via NICE Docs.

- 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 draft guidance 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.

References

1 National Institute for Health and Care Excellence. *Technology appraisal guidance [TA604]: Idelalisib for treating refractory follicular lymphoma*, <https://www.nice.org.uk/guidance/ta604> (October 2019).

2 National Institute for Health and Care Excellence (NICE). TA717: Duvelisib for treating relapsed follicular lymphoma after 2 or more systemic therapies (terminated appraisal). (2021).

3 National Institute for Health and Care Excellence (NICE). TA842: Tisagenlecleucel for treating follicular lymphoma after 2 or more therapies (terminated appraisal). (2022).

4 National Institute for Health and Care Excellence (NICE). TA783: Daratumumab monotherapy for treating relapsed and refractory multiple myeloma. (2022).

5 National Institute for Health and Care Excellence (NICE). TA796: Venetoclax for treating chronic lymphocytic leukaemia. (2022).

6 National Institute for Health and Care Excellence. *Technology appraisal guidance [TA627]: Lenalidomide with rituximab for previously treated follicular lymphoma*, <https://www.nice.org.uk/guidance/ta627> (07 April 2020).

7 Ali, M. S. *et al.* Propensity Score Methods in Health Technology Assessment: Principles, Extended Applications, and Recent Advances. *Frontiers in pharmacology* **10**, 973, doi:10.3389/fphar.2019.00973 (2019).

8 National Institute for Health and Care Excellence. *PMG36: NICE health technology evaluations: the manual*, <https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation accessed July 2022> (2022).

9 Faria, R., Hernandez Alava, A., M,, Manca, A. & Wailoo, A., J. NICE DSU Technical Support Document 17: The use of observational data to inform estimates of treatment effectiveness for Technology Appraisal: Methods for comparative individual patient data. *Available from http://www.nicedsu.org.uk* (2015).

NICE National Institute for Health and Care Excellence

Mosunetuzumab for treating relapsed or refractory follicular lymphoma [ID3931]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 31 January 2023. 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):	Association of Cancer Physicians
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Mosunetuzumab for treating relapsed or refractory follicular lymphoma [ID3931]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 31 January 2023. Please submit via NICE Docs.

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.
Example 1	We are concerned that this recommendation may imply that ……..
1	Comparing cost effectiveness against R-bendamustine and R-lenalidomide is of limited value for patients that have already received these treatments previously. Patients who have had multiple lines of R-chemotherapy and R-lenalidomide essentially have no further treatment options available to them, so mosunetuzumab so may be a life changing treatment for them.
2	Retreatment with the same form of chemotherapy on relapse is not often used due to cumulative toxicities and is not recommended if the patient has demonstrated prior refractoriness to the regime. RCHOP has also been cited as an R-chemo treatment option in the guidance documentation however at our centre it is not frequently used as it usually reserved for treatment of high grade transformation and furthermore is also avoided in patients with cardiac co-morbidity. Therefore the number of suitable alternative treatments may have been over estimated.
3	
4	
5	
6	

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 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- 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 draft guidance document, please submit these separately.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Mosunetuzumab for treating relapsed or refractory follicular lymphoma [ID3931]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 31 January 2023. Please submit via NICE Docs.

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.

Please return to: **NICE DOCS**

Single Technology Appraisal

Mosunetuzumab for treating relapsed or refractory follicular lymphoma [ID3931]

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

Name	[redacted]
Role	
Other role	
Organisation	NCRI Lymphoma Group
Location	
Conflict	
Notes	
Comments on the DG:	

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

All relevant evidence has not been considered and these additional data could sufficiently resolve the high level of uncertainty in the health economic model. Additional evidence that will become available within the next few years must be considered in the context of re-appraising mosunetuzumab for managed access.

The comparators used in this appraisal were R2 and BR. Data for R2 came from the AUGMENT trial which was conducted exclusively in rituximab-sensitive patients with a median of two prior lines of therapy. The MAIC did not adjust for critical prognostic factors – line of therapy and rituximab-refractoriness. Additional R2 data in rituximab refractory and sensitive patients treated at 3L+ will become available and should be considered in an updated analysis:

1. NCT01996865. Lenalidomide Plus Rituximab Followed by Lenalidomide Versus Rituximab Maintenance for Relapsed/Refractory Follicular, Marginal Zone or Mantle Cell Lymphoma. (MAGNIFY). This randomised trial will recruit 503 participants and reach primary completion in April 2023. Final results for R2 induction have been reported (Lansigan et al, 2022).

2. NCT04680052. A Phase 3 Study to Assess Efficacy and Safety of Tafasitamab Plus Lenalidomide and Rituximab Compared to Placebo Plus Lenalidomide and Rituximab in Patients With Relapsed/Refractory (R/R) Follicular Lymphoma or Marginal Zone Lymphoma. (InMIND). This phase 3 trial will enrol 618 patients and reach primary completion in Feb 2024.

3. NCT04712097. A Study Evaluating the Efficacy and Safety of Mosunetuzumab in Combination With Lenalidomide in Comparison to Rituximab in Combination With Lenalidomide in Patients With Follicular Lymphoma After at Least One Line of Systemic Therapy (Celestimo). This Phase 3 trial will enrol 400 participants and reach primary completion in Aug 2025. As this trial is sponsored by Hoffmann-La Roche, data will be suitable for a propensity score analysis using individual patient data.

The appraisal considered BR as a proxy for all types of immunochemotherapy and contested the notion that additional data collection would resolve uncertainty about whether rituximab plus bendamustine is representative of other types of rituximab plus chemotherapy (R-CHOP, R-CVP). This is not true. In clinical practice, bendamustine is restricted to fitter patients under 70 years of age, thus is neither a valid representative of immunochemotherapy in older and frailer patients, or a valid comparator for mosunetuzumab in this population. RCVP and RCHOP data are available from the Haematological Malignancy Research Network (HMRN) registry and have already been used to support a previous TA in the same indication (TA627: Lenalidomide with rituximab for previously treated follicular lymphoma). In this TA, RCHOP and RCVP were assumed to be clinically equivalent. In addition to HMRN data, a new study called Foundation UK will collect treatment and outcome data for 500 patients treated for r/r FL at 14 UK hospitals. The study is opening to recruitment in March 2023 and will run for two years. Results will provide the largest UK real world comparator dataset and may resolve some

uncertainty over the relative clinical efficacy of different treatments by therapy line, sequence and patient group (e.g. by age or fitness).
At this time, considering the uncertainty of the model, real world data series reporting '3L treatment' should be factored into the health economic model to represent the totality of 3L treatment. This includes the SCHOLAR-5 dataset (Ghione P et al, Blood. 2022), A US multi-centre cohort (Casulo et al, 2022) and a single centre UK dataset (Linton K et al, Blood 2021).
The following randomised trial data sources will provide additional SOC comparator data in 2023-2026:

1. Relapsed Follicular lymphoma Randomised trial Against standard ChemoTherapy (REFRACT): A randomised phase II trial of investigator choice standard therapy versus sequential novel therapy experimental arms. This UK-NCRI study will report outcomes for R-CHOP, R-CVP, rituximab and lenalidomide, bendamustine and obinutuzumab and rituximab and bendamustine. It will recruit 126 patients and report round 1 in Aug 2025.

2. NCT04745832 Phase 3 Study of Zandelisib (ME-401) in Combination With Rituximab in Patients With iNHL - (COASTAL). This phase 3 trial was planned to recruit 534 participants and report in Apr 2026. The study closed early and may report early. It will provide RCHOP and BR comparator data.

3. NCT02626455. Study of Copanlisib in Combination With Standard Immunochemotherapy in Relapsed Indolent Non-Hodgkin's Lymphoma (iNHL) (CHRONOS-4). This phase 3 trial aimed to recruit 551 patients and report in Feb 2023. It will provide RCHOP and BR data.

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

For the comparison with rituximab plus lenalidomide, mosunetuzumab was more costly and less effective in both the company and EAG's preferred

base cases. In relapsed FL, PFS reduces significantly with each line of therapy. Thus, this is not a fair interpretation as the analysis compared R2 in second line (median 2 lines, 24% >=3L) with mosunetuzumab in third line (median 3 lines, 62% >= 3L). The comparison was also unbalanced for other important prognostic factors including rituximab refractoriness and a greater proportion of high-risk patients in the mosunetuzumab arm.
For the comparison with rituximab and bendamustine, the committee noted that the ICERs for the EAG base cases do not include any potential overall survival benefit for mosunetuzumab, which is likely to be too conservative. PFS benefit for a particular treatment seldom translates into an improvement in survival for FL. This is because FL has a long natural history, the patient population is very heterogenous and most patients get a similar range of treatments over the course of the disease. We would expect a difference in survival if these treatments were the only treatment (or one of few) given to a patient, but that is not the case for FL patients. Thus, PRIMA, GALLIUM, RELEVANCE, FOLL12, and AUGMENT all failed to show an overall survival benefit for one treatment over another. The model places too much emphasis on overall survival.

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

The recommendations do not form a sound basis for addressing unmet need in FL patients.

- Unmet need #1 - lack of treatment options at 3L/4L

Many r/r FL patients treated in the third line setting have either received one line of immunochemotherapy (ICT) followed by R2 or two lines of ICT. In fit patients, the most common treatment sequence is first line (1L) intensive immunochemotherapy (bendamustine/CHOP plus rituximab/obinutuzumab) followed by second line (2L) intensive ICT (using whichever chemotherapy they did not receive previously) or R2. In unfit/frail patients, the most common treatment sequence is non-intensive therapy, RCVP, followed by R2.

Since the same treatment is very seldom re-used and more intensive therapy is typically contraindicated after non-intensive first line therapy, options become increasingly limited from 3L onwards, especially for unfit/frail patients where effectively there are no available standard treatments. Rituximab monotherapy, which may be offered outside the UK, is rarely used in this setting as it produces very short remissions. Some patients are also not candidates for selected immunochemotherapies due to co-morbidities, further limiting access to standard options; for example, CHOP is contraindicated in patients with cardiac disease and bendamustine is not recommended in patients with a high risk of infection.

- Unmet need #2 - progressive chemo-refractoriness

Patients with FL acquire increasing resistance to chemotherapy with each successive relapse and re-treatment event. This is evidenced by real world data demonstrating progressively shorter duration of response and progressive-free survival with each line of therapy (Batlevi CL, et al. 2020). Immunochemotherapy constitutes the mainstay of therapy reported in real world studies, suggesting that acquired chemo-refractoriness is the main reason for diminishing PFS. Further evidence for diminishing PFS over the disease course is presented in studies of autologous stem cell transplant consolidation (ASCT) in FL, a treatment where success is contingent upon preserved chemo-sensitivity. In a UK retrospective study, best outcomes were reported for patients receiving ASCT as 2L consolidation (Kothari et al, 2014). ASCT delivered in later lines of therapy is not recommended due to increasing chemo-refractoriness associated with inferior outcomes.

- Unmet need #3 - early treatment failure

Patients who relapse or progress within 2 years of starting ICT (POD24 subset) have an inferior survival (Casulo et al, 2015). This may reflect primary chemo-refractoriness and is typically associated with inferior outcomes to subsequent immunochemotherapy, underlining a need for novel therapies.

Mosunetuzumab, a first-in class drug with a unique mode of action, offers substantially more benefits than risks to patients with r/r FL and has demonstrated remarkable activity. Similar or higher response rates than those seen in the overall study population were observed in high-risk subgroups (ORR all patients 79%; POD24 83%; age ≥65 83%, refractory to last therapy 76%, 3L+ 75%). Response rates, PFS, DOR, DOCR and time to next therapy or death were all improved for mosunetuzumab compared to last prior therapy (Bartlett et al, Blood 2022).

Mosunetuzumab effectively provides an extra line of therapy in the critical areas of unmet need. Compared to chemotherapy which is unacceptably toxic in elderly/comorbid patients, or ineffective in high-risk patients, mosunetuzumab offers treatment that is both highly effective and very well tolerated. In this context, comparing mosunetzumab to immunochemotherapy is inherently flawed. If indeed this drug is recommended for patients who have exhausted, or are not candidates for standard therapy, then the best comparator is 'best supportive care'.

- **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, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?**

We are concerned that this decision will discriminate against older/frailer patients who due to age and co-morbidity do not have equal access to the full range of standard immunochemotherapy options. They have an even greater need for novel therapies earlier in their disease course.

EAG Response to Company Draft Guidance Comments

The company provided comments structured into six headings. The EAG responds to each of these now, followed by a review of the revised company base case and the associated analyses presented by the company.

1. Underlying challenges of appraisals based on single arm evidence packages (ACD, Section 3.16)

The EAG agrees that there are many complex problems that can arise from relying on a single arm trial as the main source of evidence when appraising a health technology. However, the approaches implemented by the company have been used in many other appraisals that have resulted in positive recommendations. In this appraisal, the results of the indirect comparisons appeared inconsistent, hence there is a very high degree of uncertainty over the effect and potential benefit of mosunetuzumab which should be factored into consideration.

2. Criteria for managed access (ACD, Section 3.17)

The company describes how additional follow-up from their single arm trial GO29781 alongside data on real world use of mosunetuzumab and new sources of comparator data would resolve some of the uncertainties raised in the original appraisal. It is possible that these will provide alternative sources of evidence to inform the statistical and economic analyses and result in less uncertainty.

However there will still be reliance on indirect treatment comparisons, where the EAG has previously described concerns with the company's implementation. In the original appraisal, this led to small effective sample sizes, which may persist into any novel analyses and so there is no guarantee that extended follow-up of existing data will produce a meaningful reduction of the uncertainty. Real-world evidence of mosunetuzumab use will be unlikely to observe sufficient overall survival events to produce a reliable extrapolation, as experienced with the current follow-up of GO29781.

3. Subsequent treatment assumption (ACD, Section 3.13)

The EAG welcomes the company's acceptance to exclude patients who received rituximab-lenalidomide from receiving subsequent rituximab-lenalidomide treatment following disease

progression. The EAG had not noticed this error until the technical engagement stage, where changes by the company led the EAG to review this part of the model and so it was not possible to raise this any earlier.

4. Post-progression utility values (ACD, Section 3.12)

The company has changed the utility value for post-progression survival used in its economic model, as there were concerns over the suitability of the estimate obtained from the GO29781 study. The previous value of 0.75 (derived from GO29781) has been updated to 0.62 from Wild et al.[1] The company also changes the pre-progression utility from 0.80 to 0.81, again switching between the same two sources.

Making this change causes a much larger difference between the utility values of pre- and post-progression. The company previously considered using this alternative source for the utility values. In the appendix to their original submission, the company excluded the abstract from their systematic literature review as it does not report utility data and so their use relies on their utility values as reported in other technology appraisal submissions. The company originally favoured using the utility values from GO29781. Both sources have their weaknesses and so the EAG maintains the trial utility values in their base case, but also presents a scenario using the company's preferred values.

5. R-bendamustine as a representation of R-chemotherapy in the 3L+ relapsed/refractory FL setting (ACD, Sections 3.5, and 3.7)

The company accept that rituximab-bendamustine may not be representative of the wider rituximab-chemotherapy group of treatments, and describes some of the strengths and weaknesses of their propensity score analysis. The company has omitted the EAG's concerns about the selection of variables included in the analysis, and has not presented alternative analyses to alleviate these concerns.

6. ITC vs R-lenalidomide (ACD, Section 3.6)

In the company's defence of their matching adjusted indirect comparison they outline how it was not possible to adjust for certain variables. The EAG accepts these, but the fact that these important variables is nonetheless a limitation of the analysis. The company describes the rationale for imputing the value for low haemoglobin, citing a desire to maximise the inclusion of high priority variables in the analysis. The EAG agrees that all available high

priority variables should be included, however it remains unclear why imputing a value from the GO29781 trial as the value for the AUGMENT study aligns with this motivation from the company's perspective.

The EAG was not provided with data to conduct a sensitivity analysis to explore the impact of removing low haemoglobin from the indirect treatment comparison.

Revised company base case

For reference, the EAG presents the company's previous base case analyses (Table 1). The EAG confirms it has been able to reproduce the company's new base case, as reported in Table 2, with the changes to utility values and the later line therapies. The EAG also presents the probabilistic sensitivity analyses (PSA) for the previous and current company base cases in Table 3 and Table 4 respectively. The EAG notes that the company's base case continues with the extrapolation of immature overall survival data from GO29781.

In the following tables, the net monetary benefit (NMB) is first presented for a willingness to pay threshold of £20,000 per QALY gained, and secondly for a threshold of £30,000 per QALY gained. An ICER presented with letters CS indicates the ICER is cost-saving.

Table 1. Deterministic company base case cost-effectiveness results (post-technical engagement as considered at AC1)

Technology	Total costs (£)	Total LYG	Total QALYs	Incr' costs (£)	Incr' LYG	Incr' QALYs	ICER (£/QALYs)	NMB 20k (30k)
Mosunetuzumab vs R^2								
Mosun	[redacted]	9.58	[redacted]					
R^2	[redacted]	10.36	[redacted]	[redacted]	-0.78	[redacted]	[redacted]	[redacted]
Mosunetuzumab vs RB								
Mosun	[redacted]	9.90	[redacted]					
RB	[redacted]	8.30	[redacted]	[redacted]	1.60	[redacted]	[redacted]	[redacted]

Table 2. Deterministic company base case cost-effectiveness results (AC2) with revised assumptions

Technology	Total costs (£)	Total LYG	Total QALYs	Incr' costs (£)	Incr' LYG	Incr' QALYs	ICER (£/QALYs)	NMB 20k (30k)
Mosunetuzumab vs R^2								
Mosun	[redacted]	9.58	[redacted]					
R^2	[redacted]	10.36	[redacted]	[redacted]	-0.780	[redacted]	[redacted]	[redacted]
Mosunetuzumab vs RB								
Mosun	[redacted]	9.90	[redacted]					
RB	[redacted]	8.30	[redacted]	[redacted]	1.60	[redacted]	[redacted]	[redacted]

Table 3. Probabilistic company base case cost-effectiveness results (post-technical engagement as considered at AC1)

Technology	Total costs (£)	Total LYG	Total QALYs	Incr' costs (£)	Incr' LYG	Incr' QALYs	ICER (£/QALYs)	NMB 20k
Mosunetuzumab vs R^2								
Mosun	[redacted]	9.18	[redacted]					
R^2	[redacted]	9.94	[redacted]	[redacted]	-0.77	[redacted]	[redacted]	[redacted]
Mosunetuzumab vs RB								
Mosun	[redacted]	9.95	[redacted]					
RB	[redacted]	8.27	[redacted]	[redacted]	1.69	[redacted]	[redacted]	[redacted]

Table 4. Probabilistic company base case cost-effectiveness results (AC2) with revised assumptions

Technology	Total costs (£)	Total LYG	Total QALYs	Incr' costs (£)	Incr' LYG	Incr' QALYs	ICER (£/QALYs)	NMB 30k
Mosunetuzumab vs R^2								
Mosun	[redacted]	9.14	[redacted]					
R^2	[redacted]	9.99	[redacted]	[redacted]	-0.84	[redacted]	[redacted]	[redacted]
Mosunetuzumab vs RB								
Mosun	[redacted]	9.77	[redacted]					
RB	[redacted]	8.24	[redacted]	[redacted]	1.53	[redacted]	[redacted]	[redacted]

For completeness, the EAG present their base case analysis (Table 5), which remains unchanged, alongside the associated PSA (Table 6). The EAG also presents an analysis applying the Wild et al. utility values in

Table 7.

Table 5: Deterministic EAG base case cost-effectiveness results (post-technical engagement as considered at AC1)

Technology	Total costs (£)	Total LYG	Total QALYs	Incr' costs (£)	Incr' LYG	Incr' QALYs	ICER (£/QALYs)	NMB 20k (30k)
Mosunetuzumab vs R^2								
Mosun	[redacted]	10.51	[redacted]					
R^2	[redacted]	10.51	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]
Mosunetuzumab vs RB								
Mosun	[redacted]	9.23	[redacted]					
RB	[redacted]	9.23	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]

Table 6: Probabilistic EAG base case cost-effectiveness results (post-technical engagement as considered at AC1)

Technology	Total costs (£)	Total LYG	Total QALYs	Incr' costs (£)	Incr' LYG	Incr' QALYs	ICER (£/QALYs)	NMB 20k
Mosunetuzumab vs R^2								
Mosun	[redacted]	10.12	[redacted]					
R^2	[redacted]	10.20	[redacted]	[redacted]	-0.07	[redacted]	[redacted]	[redacted]
Mosunetuzumab vs RB								
Mosun	[redacted]	9.21	[redacted]					
RB	[redacted]	9.23	[redacted]	[redacted]	-0.01	[redacted]	[redacted]	[redacted]

Table 7: Scenario Analysis Results: Alternative health state utility sources (Wild et al. utility)

Technology	Total costs (£)	Total LYG	Total QALYs	Incr' costs (£)	Incr' LYG	Incr' QALYs	ICER (£/QALYs)	NMB 20k (30k)
Mosunetuzumab vs R^2								
Mosun	[redacted]	10.51	[redacted]					
R^2	[redacted]	10.51	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]
Mosunetuzumab vs RB								
Mosun	[redacted]	9.23	[redacted]					
RB	[redacted]	9.23	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]

References

1. Wild D, Walker M, Pettengell R, Lewis G. PCN62 Utility elicitation in patients with follicular lymphoma. *Value Health* 2006;**9**(6):A294. http://dx.doi.org/10.1016/S1098-3015(10)63491-2