NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [ID1576]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [ID1576]

Contents:

The following documents are made available to consultees and commentators:

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

2. **Comments on the Appraisal Consultation Document from** Roche Products
   a. Appendix to ACD response
   b. Addendum to ACD response

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Lymphoma Action

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

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

6. **Letter to company following appraisal committee meeting 2**

7. **Company response to committee request for further analysis**

8. **Evidence Review Group critique of company response to committee request after appraisal committee meeting 2**

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

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Single Technology Appraisal

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

Type of stakeholder:

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

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

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

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

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

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Patient organisation	Lymphoma Action	We are concerned that this decision is based solely on a flawed cost-effectiveness analysis. The submitting company's analysis found lenalidomide plus rituximab to be cost-effective. We acknowledge that the committee had concerns over the methods and assumptions used in the company's cost-effectiveness model. However, the committee also expressed concerns over the ERG's methods, noting that the ERG's analysis 'did not capture the potential cure aspect of the disease and may therefore be conservative in its interpretation of the evidence.' Despite this, the committee has chosen to give more credence to the ERG's analysis, even though they acknowledge that it is flawed. The committee accepts that clinical trial data shows that polatuzumab vedotin significantly extends progression-free survival and overall survival. The committee also acknowledges that relapsed or refractory diffuse large B-cell lymphoma is a devastating condition with a poor prognosis and that patients have a high unmet need for effective treatments. This is consistent with the experiences of patients supported by our organisation, who tell us of the huge physical, psychological and financial impact of the disease and its current treatments, and the terrible uncertainty of the final outcome. We therefore question whether concerns over the precise methods used to analyse cost-effectiveness are sufficient to warrant withholding life-extending, and potentially curative, treatment from people with such a poor prognosis and limited alternative options.	Thank you for your comment. The committee agreed that there were limitations of the company's and evidence review group's (ERG) approaches to survival modelling. However, based on additional analyses provided by the company and the ERG in response to the appraisal consultation document (see section 3.10 of the final appraisal document [FAD]), the committee made a positive recommendation for polatuzumab vedotin with rituximab and bendamustine for relapsed or refractory diffuse large B-cell lymphoma in adults who cannot have a haematopoietic stem cell transplant.
2	Web comment	The Christie Hospital, Manchester	I am writing on behalf of the Lymphoma Team at the Christie Hospital to provide comments on the above Technology Appraisal. We have treated 9 patients with polatuzumab-BR at our institution so far and have found it to be a useful regimen for both bridging patients to more definitive therapies and for palliating patients with relapsed DLBCL that are unsuitable for intensive chemotherapy. Our only other option in this	Thank you for your comment. The committee agreed that there is high unmet need for this group of patients (see section 3.1 of the final appraisal document). Based on additional analyses provided by the company and the ERG in response to the appraisal consultation

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
			setting would be bendamustine-rituximab, which was was inferior to polatuzumab-BR in the recent randomized trial by Sehn *et al.* We appreciate that there are ongoing uncertainties regarding the curative potential and cost effectiveness of polatuzumab-BR. Nevertheless, this is one of very few randomized trials conducted in this relapsed DLBCL and shows a clear progression-free and overall survival benefit in favour of polatuzumab-BR. The appraisal already outlines the very clear unmet need in this patient population. Treatment options are now even further restricted by the temporary suspension of clinical trials during the COVID-19 pandemic. The deliverability of intensive therapies, such as transplant and CAR-T, is also compromised during the outbreak. In these circumstances, we feel that there is a strong case for allowing continuing access to polatuzumab-BR.	document (see section 3.10 of the final appraisal document), the committee made a positive recommendation for polatuzumab vedotin with rituximab and bendamustine for relapsed or refractory diffuse large B-cell lymphoma in adults who cannot have a haematopoietic stem cell transplant.
3	Company	Roche Products	We are disappointed that the committee could not make a positive recommendation for polatuzumab vedotin with bendamustine and rituximab for patients with relapsed or refractory diffuse large B-cell lymphoma that are not candidates for transplant. This was despite the recognition that polatuzumab vedotin addressed a significant unmet need and that polatuzumab vedotin was considered a promising treatment based on the demonstrated progression-free and overall survival benefit. In particular, at 30 months median follow up in the GO29365 study, 23% of patients in the polatuzumab vedotin arm were in disease remission versus 5% in the rituximab bendamustine arm. While there were some uncertainties in the economic modelling, the model approach taken provides clinically plausible results. The 'cure-mixture' type model was selected based on the natural history of the disease whereby a significant proportion of patients that achieve remission at 2-years (i.e. patients in PFS) are expected to remain in long-term remission. These patients are considered to be long-term survivors, albeit with a greater risk of mortality than the general population. There is therefore a time point between 2 and 5 years, where from that point onwards the rate of progression or death is close to, and approaches, the background mortality of the general population adjusted for a remaining increased mortality. This natural history of the disease was confirmed by clinical experts and also formed the basis of the	Thank you for your comment. The committee agreed that there is high unmet need for this group of patients (see section 3.1 of the FAD) and that polatuzumab vedotin is a promising new treatment (see section 3.6 of the FAD). The committee concluded that the cure-mixture model lacks face validity and is not suitable for decision making (see section 3.9 of the FAD). However, it agreed that the standard parametric models presented as scenario analysis were appropriate (see section 3.10 of the FAD). Based on these analyses, the committee made a positive recommendation for polatuzumab vedotin with rituximab and bendamustine for relapsed or refractory diffuse large B-cell lymphoma in adults who cannot have a haematopoietic stem cell transplant.

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
			modelling approach taken for CAR-Ts. A 'plateau' would not be predicted by our model, as there is a remaining proportion at risk of progression after 2 years. However, the proportion of people likely to remain in long-term remission can be estimated reliably from the observed data given the median 30 months follow up. Furthermore, this proportion is meaningful for long-term extrapolation beyond the follow up period as it provides clinically plausible estimates. However, the model was not meant, or required, to model the underlying disease biology at the early stage of treatment for individual patients, but to provide a good fit to the observed Kaplan-Meier for economic modelling purposes. In the appendix to our submission, we have also investigated alternative scenarios, where extrapolation does not rely on a long-term remission assumption, as in the ERGs preferred scenario. Of these approaches, the most plausible extrapolation was a scenario with a standard Generalised Gamma model for PFS and OS. A potential limitation of these alternative models is that long-term progression rates may be over-estimated as adjusted background mortality is expected to be reached in the long-term. To overcome this limitation we investigated so called hybrid scenarios where a time point to reach background mortality is externally set. Similar models had been used in the appraisals for CAR-Ts. All plausible alternative scenarios resulted in ICERs in the cost-effective range as discussed in the appendix.	
4	Company	Roche Products	We have further improved the robustness of our model approach by selecting a revised base case model with less variance in the parameter estimates. This improved the statistical variability in the probabilistic sensitivity analysis and reduced differences between deterministic and probabilistic results. However, such differences between probabilistic and deterministic results are to be expected and expressed in the cost-effectiveness acceptability curve for decision-making. It is also expected that calculated parameters, such the average survival time for patients on BR, do not follow a normal distribution, leading to differences between deterministic and probabilistic estimates that we investigate further in a separate appendix to our response. However, as shown in the appendix, the majority of simulations are close to the deterministic values and the statistical uncertainty in parameter estimates has been correctly propagated through the model to provide estimates that reliably characterise the uncertainty.	Thank you for your comment. The committee discussed the cure-mixture model, including the changes made in response to the appraisal consultation document. It concluded that it lacks face validity and is not suitable for decision making (see section 3.9 of the FAD). However, it agreed that the standard parametric models presented as scenario analysis were appropriate (see section 3.10 of the FAD). Based on these analyses, the committee made a positive recommendation for polatuzumab vedotin with rituximab and bendamustine for relapsed or refractory diffuse large B-cell lymphoma in adults who cannot have a haematopoietic stem cell transplant.

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 addition, we have conducted sensitivity analyses on the long-term remission rates used in the model. While in our base case the rates are fitted from the observed data, we have investigated scenarios where the long-term remission rates were taken as an external input with values around the actual estimates. These scenarios demonstrated that the ICER was sensitive to the assumptions regarding long-term remission rates. However, conservative scenarios with significantly higher rates in the bendamustine with rituximab arm or significantly lower rates in the polatuzumab vedotin arm compared to the actual estimates, resulted in clinically implausible assumptions on the future hazards of progression or death.	
5	Company	Roche Products	Based on the concerns expressed by the committee, we have provided further evidence regarding the validity of our in-house code in R to estimate 'cure-mixture' model parameters in the appendix to our response, confirming that our code replicates the original work by Lambert in STATA (The Stata Journal (2007) 7, Number 3, pp. 351–375) as intended.	Thank you for your comment. The committee agreed that this exercise showed that the in-house code used was valid.
6	Company	Roche Products	The scenarios that are plausible fits and long-term extrapolations of the GO29365 data investigated in the appendix to this response all fall within the cost-effective ICER range. However, it remains the case that for all models considered, uncertainty could be reduced by further follow up data from the ongoing GO29365 study.	Thank you for your comment. The committee agreed that the most plausible incremental cost-effectiveness ratio (ICER) would be derived from a standard parametric model (see section 3.10 of the FAD). Based on these analyses, the committee made a positive recommendation for polatuzumab vedotin with rituximab and bendamustine for relapsed or refractory diffuse large B-cell lymphoma in adults who cannot have a haematopoietic stem cell transplant.

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Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [ID1576]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 18 March 2020 **email:** 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]

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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.
1	We are disappointed that the committee could not make a positive recommendation for polatuzumab vedotin with bendamustine and rituximab for patients with relapsed or refractory diffuse large B-cell lymphoma that are not candidates for transplant. This was despite the recognition that polatuzumab vedotin addressed a significant unmet need and that polatuzumab vedotin was considered a promising treatment based on the demonstrated progression-free and overall survival benefit. In particular, at 30 months median follow up in the GO29365 study, 23% of patients in the polatuzumab vedotin arm were in disease remission versus 5% in the rituximab bendamustine arm. While there were some uncertainties in the economic modelling, the model approach taken provides clinically plausible results. The 'cure-mixture' type model was selected based on the natural history of the disease whereby a significant proportion of patients that achieve remission at 2-years (i.e. patients in PFS) are expected to remain in long-term remission. These patients are considered to be long-term survivors, albeit with a greater risk of mortality than the general population. There is therefore a time point between 2 and 5 years, where from that point onwards the rate of progression or death is close to, and approaches, the background mortality of the general population adjusted for a remaining increased mortality. This natural history of the disease was confirmed by clinical experts and also formed the basis of the modelling approach taken for CAR-Ts. A 'plateau' would not be predicted by our model, as there is a remaining proportion at risk of progression after 2 years. However, the proportion of people likely to remain in long-term remission can be estimated reliably from the observed data given the median 30 months follow up. Furthermore, this proportion is meaningful for long-term extrapolation beyond the follow up period as it provides clinically plausible estimates. However, the model was not meant, or required, to model the underlying disease biology at the early stage of treatment for individual patients, but to provide a good fit to the observed Kaplan-Meier for economic modelling purposes. In the appendix to our submission, we have also investigated alternative scenarios, where extrapolation does not rely on a long-term remission assumption, as in the ERGs preferred scenario. Of these approaches, the most plausible extrapolation was a scenario with a standard Generalised Gamma model for PFS and OS. A potential limitation of these alternative models is that long-term progression rates may be over-estimated as adjusted background mortality is expected to be reached in the long-term. To overcome this limitation we investigated so called hybrid scenarios where a time point to reach background mortality is externally set. Similar models had been used in the appraisals for CAR-Ts. All plausible alternative scenarios resulted in ICERs in the cost-effective range as discussed in the appendix.
2	We have further improved the robustness of our model approach by selecting a revised base case model with less variance in the parameter estimates. This improved the statistical variability in the probabilistic sensitivity analysis and reduced differences between deterministic and probabilistic results. However, such differences between probabilistic and deterministic results are to be expected and expressed in the cost-effectiveness acceptability curve for decision-making. It is also expected that calculated parameters, such the average survival time for patients on BR, do not follow a normal distribution, leading to differences between deterministic and probabilistic estimates that we investigate further in a separate appendix to our response. However, as shown in the appendix, the majority of simulations are close to the deterministic values and the statistical uncertainty in parameter estimates has been correctly propagated through the model to provide estimates that reliably characterise the uncertainty. In addition, we have conducted sensitivity analyses on the long-term remission rates used in the model. While in our base case the rates are fitted from the observed data, we have investigated

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	scenarios where the long-term remission rates were taken as an external input with values around the actual estimates. These scenarios demonstrated that the ICER was sensitive to the assumptions regarding long-term remission rates. However, conservative scenarios with significantly higher rates in the bendamustine with rituximab arm or significantly lower rates in the polatuzumab vedotin arm compared to the actual estimates, resulted in clinically implausible assumptions on the future hazards of progression or death.
3	Based on the concerns expressed by the committee, we have provided further evidence regarding the validity of our in-house code in R to estimate 'cure-mixture' model parameters in the appendix to our response, confirming that our code replicates the original work by Lambert in STATA (The Stata Journal (2007) 7, Number 3, pp. 351–375) as intended.
4	The scenarios that are plausible fits and long-term extrapolations of the GO29365 data investigated in the appendix to this response all fall within the cost-effective ICER range. However, it remains the case that for all models considered, uncertainty could be reduced by further follow up data from the ongoing GO29365 study.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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

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

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ID1576: Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma

Appendix to ACD Response

File name	Version	Contains confidential information	Date
ID1576_Polatuzumab vedotin RR DLBCL_Appendix ACD 180320 [Redacted]	Final	Redacted	18 March 2020

Contents

Tables

Figures

Revised company base case and model scenarios

In response to the ACD, a revised base case for the economic analysis is provided, as outlined in Table 1. Points where changes were made to the model submitted at technical engagement are in **bold.**

Table 1. Revised company base case

Input	Assumption	Justification
Data set	Inclusion of covariate-adjusted PFS and OS data from the GO29365 March 2019 data cut	Appropriate according to ACD.
PFS and OS extrapolation models	**PFS and OS are extrapolated using cure-mixture modelling with the Log-Normal function. Mixture modelling for OS informed by PFS. PFS-IRC was the selected outcome.**	**Log-Normal cure-mixture models provides statistically better fits that reduce probabilistic uncertainty while providing similar visual fit and long-term extrapolations compared to other plausible models.**
Background mortality distribution	**ERG single age (69 years) cohort.**	**Committees preferred assumption in ACD.**
Background mortality adjustment	An increased relative risk of mortality of 1.41 for long-term survivors applied to model excess mortality compared to the general population.	As per technical engagement response A conservative assumption by the ERG reflecting an increased risk of mortality for long-term survivors.
Survival limited by background mortality	**Survival limited by general population mortality for all scenarios. Conditional background survival was used rather than OS.**	**ERG amendment to the model at clarification stage. More conservative restriction than ERG to assure transition probability to death is always at least adjusted background value.**
Time point for assuming background cost and QALYs for long-term remission	HRQoL and costs of patients in PFS health state equivalent to age- and sex-matched general population after 3 years.	The ERG's preferred assumption given the uncertainty surrounding the costs and HRQoL of long-term survivors.
Vial size scenarios	Calculated treatment costs according to vial sizes of 140 mg with no vial sharing.	Based on the PAS, vial sizes of 30 mg and 140 mg will have the same acquisition costs and ICERs.
PAS for polatuzumab vedotin	PAS prices	As above. PAS approved after 1st ACM.
Number of maximum cycles for Pola+BR or BR	Assumed a maximum of 6 cycles of Pola+BR and BR were received in the model.	Appropriate according to ACD.
AE incidence	All AEs reported as Grade 3 and above in the company submission, wherever possible.	As per technical engagement and ERGs amendment.

Subsequent treatment cost	The costs for post-progression SCT were included in the model	ERG preferred assumption.

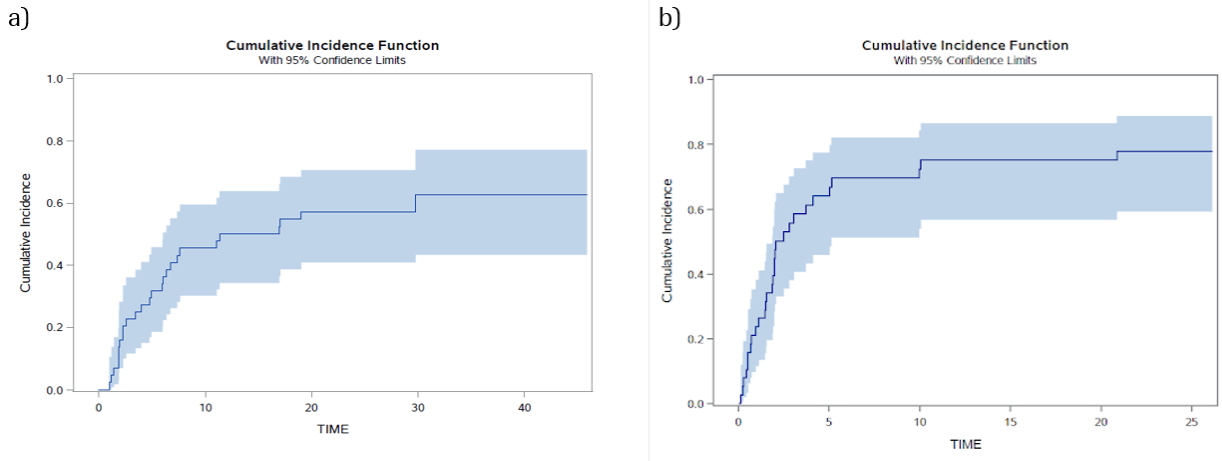
AE, adverse event; BR, bendamustine with rituximab; Pola+BR, polatuzumab vedotin with bendamustine and rituximab; EMA, European Medicines Agency; ERG, Evidence Review Group; HRQoL, health-related quality of life, ICER, incremental cost-effectiveness ratio; IRC, independent review committee; NA, not applicable; PAS, patient access scheme; PFS progression free survival; OS overall survival; SCT, stem cell transplant; TTOT, time-to-off-treatment; QALY, Quality Adjusted Life Years

Summary of scenario analysis and steps taken to improve the robustness of the economic model and revised base case

Based on clinical expert opinion and observations from studies with long-term follow-up in R/R DLBCL patients treated with R-chemo, a significant proportion of patients that achieve 2-year remission (i.e. patients in PFS) are expected to remain in long-term remission. These patients are considered to be long-term survivors. There is therefore a time point after 2 years from where on the rate of progression or death is close and approaches the background mortality of the general population adjusted for a remaining increased mortality. This natural history of the disease also formed the basis of the modelling approach taken for CAR-Ts, where the committee concluded the cure point to be between 2 and 5 years (1). Due to the expected long-term behaviour, standard models may in general not provide plausible fits or long-term extrapolations.

The natural history of the disease with a significantly declining hazard of progression (and therefore death) over time is also evident in the data from the GO29365 study. As presented in Figure 1, it can be observed that most progression events occur within the first 12 months in both arms of GO29365, and that patients are at a very low risk of progression after 24 months.

Figure 1: Cumulative incidence of progression (INV) from GO29365 a) Pola+BR and b) BR



BR, bendamustine + rituximab; INV, investigator assessed; Pola+BR, polatuzumab + bendamustine + rituximab

Therefore, simple parametric models may not be able to provide plausible fits and long-term extrapolations as they may not be able to model the more complex hazard over time. More complex models, such as cure-mixture models (CMM), are more suitable to provide plausible fits and long-term extrapolations. To further ensure the robustness of the CMM results, we have undertaken the following steps outlined below and provided further alternative scenarios:

1. **Revised base case with reduced statistical variability in PSA**

In our submission and revised base case, the CMM approach was used and as outlined previously, this approach has high external validity in terms of the fit to the observed data and the plausibility of extrapolation results.
We like to note that cure-mixture models are statistical constructs fitting the parameters to the basic cure-mixture model specification:

$$S(t) = p \times B(t) + (1 - p) \times S_D(t) \qquad (1)$$

Here p is the proportion achieving long-term remission, $B(t)$ the background survival and $S_D(t)$ the survival function for people not achieving long-term remission. In our base case models, it was assumed that long-term remission rates were different between the arms (and correspond to long-term survival rates) and that the progression-free survival function for non-long term survivors was as similar as possible. This was achieved by fitting a joint model for the progression-free survival to estimate long-term remission rates and then fitting the progression free and overall survival functions for non-survivors.
Importantly, in the application in the R/R DLBCL setting cure-mixture models are meaningful because the data in GO29365 is sufficiently mature: the proportion of people in long-term remission can be estimated reliably from the GO29365 data from PFS as the majority of progression events will have happened before 2 years. Fitting cure-mixture models does not necessarily require a 'plateau' in the KM curve. For example, long-term survival rates were estimated by Howlader et al. in the front line setting without a clear 'plateau' in the observed KM OS (2).The proportion identified in the model as in long-term remission is therefore determined by the posterior knowledge that patients had achieved 2 years in remission. It was assumed that long-term remission and survival difference between the arms was due to the difference in treatment received. Although, it would not have been possible to identify the proportion of people achieving long-term remission early on in the treatment. As such, the notion of a 'cure-fraction', or long-term remission proportion, is only meaningful after treatment and could be determined from follow up after around 2 years. In particular, for

long-term extrapolation beyond the follow up period it was assumed that there is a difference in the rates of long-term remission and survival but that the risk of progression or death for patients not long-term survivors should be similar between the arms. During the observed follow up period and early on in the treatment, it is only important that the model fits the overall observed PFS and OS curves of the cohort. The model was not meant, or required, to model the underlying disease biology at the early stage of treatment for individual patients, but to fit the observed data for economic modelling purposes and provide a plausible long-term extrapolation beyond the trial follow up.

However, the committee noted deviations in the probabilistic results. Therefore, we have validated and corrected the model with a revised PSA and selected a statistically better-defined base case model using a log-normal function with a cure-mixture approach. Further details are discussed below.

2. Validation of the in-house cure-mixture code versus other packages

We have also further validated the results of our in-house code against alternative software packages in simplified scenarios. These results are presented below and confirm concordance between different codes (in-house and STATA).

3. Scenario analysis with external long-term remission & survival ('cure') rates

The robustness of this approach is further justified by the fact that the results in long-term remission rates and 5-year PFS and OS rate projections fall in a reasonably narrow range independent of the choice of the parametric function for the non-long term survivors. As suggested in the ACD, a scenario analysis was performed where the long-term remission and survival rates could be input externally in the model. With any externally given rate, the standard parametric functions in the 'cure-mixture' model were fitted to the observed data. In the revised model, a range of external remission rate scenarios was implemented. These scenarios confirmed that assuming a significantly lower difference in long-term remission rates than the base case would not be plausible as it required the hazard for progression or death in the Pola+BR arm to exceed the hazard on BR, i.e. the hazard ratio crossing 1, before or around 2 years. Results from these scenarios are presented below.

4. Alternative scenarios without 'cure-mixture' model for extrapolation

a) Standard parametric model

The limitations of standard parametric models in providing reasonable fits and plausible long-term extrapolations can be minimised by selecting the Generalized Gamma function for PFS and OS as this function is most flexible to fit different types of hazard function (3). This scenario results in plausible fits to the observed data and 5 years PFS and OS rates are closer aligned, overcoming the limitation of the ERGs scenario. The 5 year PFS rates are closer to the range seen with cure-mixture models and indicate a plausible long-term remission rate and survival for patients that had a achieve 2 year PFS rates (Table 6). Based on standard parametric extrapolation functions alone, the Generalized Gamma is therefore the most plausible scenario.

b) Hybrid model

Alternative models to cure-mixture models investigated and used for decision making for CAR-T appraisals are so call hybrid models: PFS and OS are modelled by standard parametric fit functions until an externally defined cure time-point when (adjusted) background mortality is applied. This cure point is between 2 and 5 years and different time points for PFS and OS may be required to allow for post progression survival time. Compared to the cure-mixture models these models rely on the external input on cure point that is not a fit parameter. However, applying these hybrid models also allows for fitting the observed data and achieving clinically plausible long-term extrapolations. As fewer parameters are estimated, statistical uncertainty is reduced. It should be noted that hybrid models seem to have been preferred to cure-mixture approach in TA567 (1) mainly because the manufacture's cure-mixture approach was applied to OS and PFS independently and produced inconsistent PFS and OS long-term extrapolations. However, this limitation does not apply to our approach using cure-mixture models, where OS is informed by PFS. In our revised model we implemented hybrid models and investigated in scenario analyses using the Generalized Gamma function for PFS and OS and, alternatively, the ERGs preferred Long-Normal function for PFS. We investigated a 3 year cure-point for long-term remission and selected the time point for background mortality for OS at the section of PFS and OS.

c) Change-point model

Finally, we investigated a change-point model scenario and attempted to fit piecewise Weibull functions to the data. However, this resulted in less plausible long-term extrapolations compared with the base case or a standard parametric model scenario.

In conclusion, the revised base case provided the most plausible fit and long-term extrapolation with a manageable uncertainty in the parameter estimates. Sensitivity analysis demonstrated that scenarios assuming long-term remission rates significantly different from the estimated base case values are not plausible fits and extrapolations of the data. Among alternative not cure-mixture type models, selecting a standard Generalised Gamma model for PFS and OS provided the most plausible option. PFS and OS prediction for the different models are reported in Table 6 and cost-effectiveness results in Table 13.

Selection of revised cure-mixture model base case

In the revised model provided in the ACD response, we have validated and corrected the PSA for cure-mixture models. There was an error in the model submitted after technical engagement as it did not pick up the correct covariance-variance matrices for the PFS-IRC cure-mixture extrapolations. This has now been corrected in the revised model.

In general, all extrapolations model are expected to result in statistical uncertainty in the parameter estimates due to the limited number of events and in the revised version of the model the observed variation in PSA results is reflective of the respective parameter uncertainty of the models.

For standard models, we note that more complex models, such as the Generalized Gamma function, come with increased parameter uncertainty, although they may fit the observed data visually and provide plausible a long-term extrapolation. The statistical parameter uncertainty is further increased from standard models when moving to cure-mixture models due to the fit of the additional parameter for the long-term remission rate (‘cure-rate’ parameter). As shown in Table 2 and Table 3 below, Log-Normal or Log-Logistic cure-mixture models have high AIC/BIC ranking, compared to the Generalized Gamma cure-mixture selected initially at submission (based on PFS-INV). In, particular Generalized Gamma cure-mixture ranks lowest in BIC due to the complexity of the model. On the other and, a simple Exponential cure-mixture model provides a reasonable visual fit and plausible long-term extrapolation with the lowest statistical variance among the cure-mixture models investigated. As the Log-Normal function with cure-mixture provides and equal visual fit and plausible long-term extrapolation compared to the Generalized Gammma with cure-mixture function, the Log-Normal function cure-mixture was selected for the revised base case for PFS and OS to reduce parameter uncertainty.

Table 2 AIC/BIC and visual fit for PFS-IRC cure-mixture models (adjusted analysis)

	Pola-BR			BR		
Function	**AIC(Rank)**	**BIC(Rank)**	**Visual**	**AIC(Rank)**	**BIC(Rank)**	**Visual**
Exponential	43.1(5)	125(1)	+	80.7(4)	162.6(1)	+
Weibull	43(4)	145.9(4)		80.7(5)	183.6(4)	
Log-Normal	40.9(2)	143.8(3)	+	78.1(1)	181(2)	++
Generalized Gamma	43(3)	161.7(6)	++	79.6(3)	198.4(6)	++
Log-Logistic	40.2(1)	143.1(2)	+	79(2)	181.9(3)	+
Gompertz	44.9(6)	147.8(5)		82.2(6)	185.1(5)	

Table 3 AIC/BIC and visual fit for OS cure-mixture models informed by PFS (adjusted analysis)

	Pola+BR			BR		
Function	**AIC(Rank)**	**BIC(Rank)**	**Visual**	**AIC(Rank)**	**BIC(Rank)**	**Visual**
Exponential	63.7(4)	145.6(1)	+	86.7(3)	168.6(1)	+
Weibull	64.8(6)	167.7(5)	+	87.3(4)	190.2(4)	+
Log-Normal	61.5(2)	164.4(3)	+	85.6(1)	188.5(2)	++
Generalized Gamma	63.2(3)	182(6)	+	87.6(5)	206.4(6)	++
Log-Logistic	61(1)	163.9(2)	+	85.6(2)	188.5(3)	+
Gompertz	64.3(5)	167.2(4)		88.9(6)	191.8(5)	+

The revised base case extrapolation for PFS and OS are shown in Figure 2 below.

Figure 2. Revised base case extrapolation for PFS and OS (Log-Normal CMM, adjusted analysis, COO March 2019)

BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab, CMM cure-mixture model

Figure 3 below shows the hazards of progression or death (PFS) and survival (OS) in relation to the adjusted background mortality hazard, i.e. 1.41 times worse than the population norm. A value of 1 in the graph means that the hazard of PFS or OS is equal to the adjusted background. As expected, all hazards tend towards the adjusted background mortality, with the PFS hazard converging between the two arms after around 4 years and approaching the adjusted background mortality after around 5 years.

Figure 3. Ratio of hazards (PFS and OS) to adjusted background mortality for revised base case

BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab, CMM cure-mixture model

Comparison of company's in-house cure-mixture code to other packages

In our response to technical engagement we validated our In-house code in R versus the flexsurvcure R package for a simple CMM model, i.e. for PFS in the Pola-BR arm under simplified assumptions of the background mortality and demonstrated that if models converged, very similar estimates were obtained.

However, we were not able to operate the flexsurvcure package to accept more complex models (such as joint models or informed by PFS) or use background mortality for the cure fraction by age, gender, country, and year of trial as in our code. We therefore investigated the use of STATA *strsmix* function as the original method was implemented in this application (4) and our in-house code was designed to replicate this. We were able to test our in-house code against the STATA package using single arm data (independent models only, OS not informed by PFS) in using a Weibull or Log-Normal model for PFS-IRC (ITT, unadjusted, independent models) and OS (not informed by PFS but independent of PFS, independent). For example, for using Weibull PFS-IRC for Pola+BR the call was:

strsmix if armcdn==2,distribution(weibull) bhazard(rate_mod_pfsirc) link(logistic).

As sown in Table 4 below, a close match in results was obtained for CMM parameters when models converged and when mapping the different parametrizations used in R and STATA. We are therefore confident that the method described by Lambert (4, 5) was correctly implemented in our in-house R code and allowed specification and fit of CMM as described in the submission.

Table 4 CMM parameters with in-house R code versus STATA

Arm	EP	Dist	Par R	Value in-House R	Par STATA	Value STATA	R value mapped to STATA
Pola + BR	OS	Weibull	shape	[redacted]	ln_lambda	[redacted]	[redacted]
Pola + BR	OS	Weibull	scale	[redacted]	ln_gamma	[redacted]	[redacted]
Pola + BR	OS	Weibull	cure	[redacted]	cure	[redacted]	[redacted]
Pola + BR	OS	Lognormal	meanlog	[redacted]	mu	[redacted]	[redacted]
Pola + BR	OS	Lognormal	sdlog	[redacted]	ln_sigma	[redacted]	[redacted]
Pola + BR	OS	Lognormal	cure	[redacted]	cure	[redacted]	[redacted]
Pola + BR	PFSIRC	Weibull	shape	[redacted]	ln_lambda	[redacted]	[redacted]
Pola + BR	PFSIRC	Weibull	scale	[redacted]	ln_gamma	[redacted]	[redacted]
Pola + BR	PFSIRC	Weibull	cure	[redacted]	cure	[redacted]	[redacted]
Pola + BR	PFSIRC	Lognormal	meanlog	[redacted]	mu	[redacted]	[redacted]
Pola + BR	PFSIRC	Lognormal	sdlog	[redacted]	ln_sigma	[redacted]	[redacted]
Pola + BR	PFSIRC	Lognormal	cure	[redacted]	cure	[redacted]	[redacted]
BR	OS	Weibull	shape	[redacted]	ln_lambda	[redacted]	[redacted]
BR	OS	Weibull	scale	[redacted]	ln_gamma	[redacted]	[redacted]
BR	OS	Weibull	cure	[redacted]	cure	[redacted]	[redacted]
BR	OS	Lognormal	meanlog	[redacted]	mu	[redacted]	[redacted]
BR	OS	Lognormal	sdlog	[redacted]	ln_sigma	[redacted]	[redacted]
BR	OS	Lognormal	cure	[redacted]	cure	[redacted]	[redacted]
BR	PFSIRC	Weibull	shape	[redacted]	ln_lambda	[redacted]	[redacted]
BR	PFSIRC	Weibull	scale	[redacted]	ln_gamma	[redacted]	[redacted]
BR	PFSIRC	Weibull	cure	[redacted]	cure	[redacted]	[redacted]
BR	PFSIRC	Lognormal	meanlog	[redacted]	mu	[redacted]	[redacted]
BR	PFSIRC	Lognormal	sdlog	[redacted]	ln_sigma	[redacted]	[redacted]
BR	PFSIRC	Lognormal	cure	[redacted]	cure	[redacted]	[redacted]

BR, bendamustine + rituximab; NA: not available; Pola+BR, polatuzumab + bendamustine + rituximab; EP, Endpoint; PFS, progression free survival; OS, Overall survival

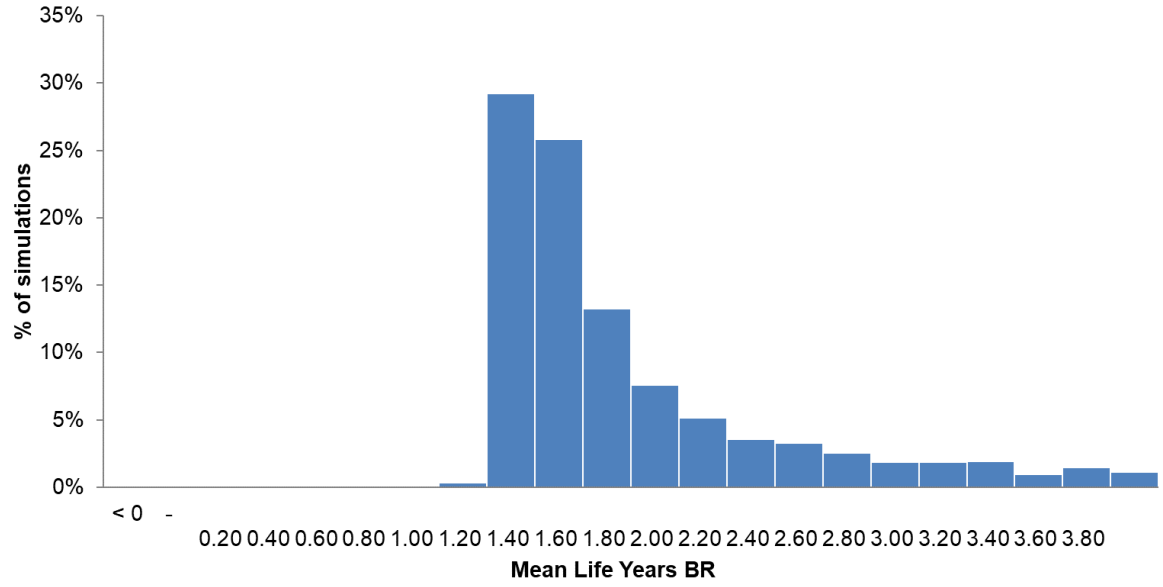
Differences in deterministic and probabilistic results

In general, cure-mixture models may result in a wider distributions around mean estimates compared to a standard parametric model due to the fact that the additional parameters for the long-term remission rates are estimated. In, particular for OS estimates, the distribution

is not expected to be normally distributed as OS is bound below (at least positive) but there can be scenarios with significantly higher than deterministic OS estimates due to long-term extrapolation leading to significantly longer survival for some patients. This is expected to lead to a skewed distribution in simulated mean OS values. Whereas deterministic estimates are bounded in the range deemed plausible by clinical experts, probabilistic scenarios in the model were not bounded, but take account for the full variability of parameter estimates given by the variance-covariance matrices. For example, long-term remission rates were not bounded by clinical plausibility constrains but were allowed to be varied significantly above the range of expect values. The probabilistic estimates propagated through the model are therefore conservative estimates of the variation in results.

The distribution of mean OS simulations for BR in the revised base case is shown in Figure 4.

Figure 4. Relative frequency of average LY BR PSA simulations (base case)



BR, bendamustine + rituximab; LY, Life years

As discussed above, the distribution is skewed towards higher than deterministic mean OS (1.55 life-years on BR) values with the most frequent value around the deterministic value. The majority of simulations (75%) result in mean OS values below 2 years. However, outliers in simulations that exceed 2 years significantly bring the average mean OS in the PSA to 2.0 years in the revised base case.

The distributions are further propagated in the probabilistic sensitivity analysis, resulting in the cost-effectiveness acceptability curve discussed below.

Sensitivity analysis on long-term remission rates

To instigate the sensitivity of the CMM results to the rates of long-term remission and survival, CMM with different parametric functions were fitted to the observed data with the long-term remission rate as input in the CMM specification, i.e. the standard parametric part only of the CMM was fitted given a pre-determined long-term remission rate.

In the model, scenarios can be selected by setting cells I156 & I206 in the 'Model Inputs' Sheet to 'External cure sel'. Input cure-rates for PFS and OS by arm can be selected in cells K168, K169, K209 & K210, respectively. In the base case Log-Normal CMM long-term remission rates fitted were 22.8% and [redacted]% for Pola+BR and BR, respectively.

With the externally set rates, we investigated conservative scenarios with a choice of 22.0% for the Pola+BR long-term remission rate and 10.0% for BR or 20.0% for Pola-BR and 8.0% for BR, respectively.

Whilst reasonable fits for the observed data were achieved in the two scenarios, these scenarios provided very conservative estimates as they required the hazard of progression on Pola-BR to be equal to BR at around 30 months or 40 months follow up, respectively (Figure 5, Figure 6) and potentially crossing over after 40 months (Figure 5).

Figure 5. Ratio of hazards (PFS and OS) to adjusted background for external long-term remission scenario 1 (22.0% and 10.0%)

BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab, CMM cure-mixture model

Figure 6. Ratio of hazards (PFS and OS) to adjusted background for external long-term remission scenario 2 (20.0% and 8.0%)

BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab, CMM cure-mixture model

If scenarios with even smaller differences in long-term remission/survival rates are selected, such as 20.0% for Pola-BR and 10% for BR, the hazard of progression or death on Pola+BR would have to exceed that of BR after about 24 months as shown in Figure 7. However, this was implausible given the natural history of the disease. There is no reason why people on Pola-BR arm should be at higher risk of progression or death in long-term follow up compared to people treated on BR alone. In addition, there was no indication of a significant change in the hazard ratio over the observed follow up period (as indicated in the log-cumulative hazard plots and by fitting independent parametric functions). The trend that the hazard of progression or death on Pola+BR would have to exceed that of BR significantly after 2 years (or less) continued for scenarios where even lower long-term remission rates on Pola+BR (such as those seen in independent cure-mixture models for PFS-IRC) and/or higher rates for BR were assumed.

Figure 7. Ratio of hazards (PFS and OS) to adjusted background for external long-term remission scenario 2 (20.0% and 10.0%)

BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab, CMM cure-mixture model

On the other hand, scenarios with a higher long-term remission rate on Pola+BR of 24% than the CMM base case and a lower long-term remission rate of 6% for BR produced still plausible results.

CMM scenarios with externally set cure rates therefore demonstrate that if a CMM model is assumed for long-term extrapolation and fit of the observed data, the scenarios with significantly lower difference in long-term remission rates compared to those fitted to the data in the base case CMM seem not plausible and the CMM estimates in the base case are robust.

Standard parametric model scenario

As outlined in our response to the technical consultation, standard parametric models did not provide the most clinically plausible long-term extrapolations, as they tended to underestimate PFS at the end of the follow up period and predict no long-term remission and survival rates as indicated by the low 5-year PFS rates (see Table 5 in Technical engagement response). We argued therefore that the ERGs preferred for PFS was not clinically plausible in our response to technical engagement due to the prediction that approximately 2/3 of patients in PFS at 2-years would progress or die by 5 years, leading to an under-estimate of the long-term PFS. This also leads to inconsistent values compared to OS estimates.

However, selecting a standard Generalized Gamma model for PFS (and OS) results in 5-year PFS rate of 16% and OS rates of 19% (Figure 8) which are more consistent.

Furthermore, the Generalized Gamma model predicted that less than half of patients that achieve 2-year remission would progress or die by 5 years (see Table 5 in our Technical engagement response). Compared to the CMM base case the standard Generalized Gamma function scenario predicts increased hazard for progression or death in both arms up to approximately 10 years of follow up (Figure 9). Among the standard parametric functions alone, the Generalized Gamma is therefore the most plausible scenario.

Figure 8 Scenario with standard Generalized Gamma extrapolation

BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab

Figure 9. Ratio of hazards (PFS and OS) to adjusted background for standard Generalized Gamma scenario

BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab

Hybrid model scenario

As an alternative to cure-mixture modelling, we have further investigated hybrid model scenarios similar to the models used in the CAR-T appraisals TA567 and TA559 (1, 6). Although cure-mixture modes were investigated, the manufacturer estimated OS cure-rates independently from PFS, leading to inconsistent long-term PFS and OS behaviour. Hybrid models rely on an external input of a 'cure point', from which point onwards PFS or OS follow an adjusted background mortality. The time point may not necessarily be the same for PFS and OS to allow for some post progression survival, i.e. OS can only fall to adjusted background mortality after PFS to allow for some survival time after progression. Before the time point where patients are considered in long-term remission or survival, hybrid models follow parametric curves fitted to the observed KM data. Plausible time points to apply adjusted background mortality were between 2 and 5 years in TA567 (1). We investigated a scenario with a 3 year long-term remission point for PFS (as per scenarios in TA567 and aligned with the assumption of PFS utility and costs) and a Generalized Gamma or Log-Normal parametric function. Long-term survival time point for OS was assumed at the point where the standard parametric OS extrapolation crossed the hybrid PFS curve. For the scenario with Generalized Gamma for PFS this was between 52 and 58 months and we selected 55 months for both arms. For the scenario with Log-Normal for PFS, PFS reached OS by around 72 months in both arms.

The hybrid scenarios are shown in Figure 10 and Figure 11 and result in long-term extrapolations and are comparable with the cure-mixture model base case.

Figure 10 Scenario with hybrid model (Generalized Gamma PFS and OS)

BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab

Figure 11 Scenario with hybrid model (Log-Normal PFS, Generalized Gamma OS)

BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab

While the hybrid models provide plausible long-term extrapolations they provide a crude approximation of the hazard function (by setting the hazard to adjusted background after a certain time point) and rely on the external input of a cure-point.

Change-point model scenario

Due to the natural history of the disease with a significant decline in hazard of progression or death over time, with most PFS events before 12 months, we investigated so-called change-point models as alternative scenarios to standard models. This class of models allows the modelling of more complex hazard functions and may therefore be suited for the observed data and long-term extrapolations. The segmented Weibull change-point model is described in Coelho-Barros, Achcar et al. (7) and specified in equation 1 below:

$$S(t) = \begin{cases} \exp\left[\left(\frac{t}{\mu_1}\right)^{\alpha_1}\right] & if\ 0 < t < change\ point \\ \exp\left[\left(\frac{t}{\mu_2}\right)^{\alpha_2}\right] & if\ t \geq change\ point \end{cases} \quad (2)$$

However, compared to CMM or standard models, the change-point model has the limitation that more parameters need to be estimated. We estimated parameters for the change-point Weibull model as for [redacted] by maximising the likelihood function over the observed data. The corresponding Maximum Likelihood Estimator (MLE) corresponds to a Bayesian approach, in which one assumes a uniform likelihood over the parameter space. We investigated random change-point models for PFS and OS where the change point, the shapes and scales were estimated. Table 5 provides the parameter estimates for PFS as Weibull change point models.

Table 5: Summary of the Weibull change-point model and parameters

Arm	Endpoint	Shape α_1	Scale μ_1	Change point (months)	Shape α_2	Scale μ_2	5-year estimate (%)
Pola+BR	PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14.6%
BR	PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8.0%
Pola+BR	OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23.3%
BR	OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10.0%

Pola: polatuzumab vedotin, BR bendamustine with rituximab, PFS: Progression free survival, OS: overall survival

Extrapolations using the change-point model are shown in Figure 12.

Figure 12 Scenario with change-point extrapolation

BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab

While the model models fitted the observed data, the long-term extrapolation had limited validity compared to the base case CMM, standard Generalised Gamma or Hybrid approach as the estimated 5-year PFS and OS rates were less consistent in the Pola+BR arm. This is likely due to the fact that the change-point was estimated after 12 months where most of the PFS/OS events had occurred, resulting in few events used to estimate the 2nd set of Weibull parameters that determine the function from the change point onwards. As the extrapolation is based on this later estimate, it may be less robust compared to the base case and alternative scenarios discussed above.

Summary of PFS and OS model predictions

A summary of revised based case and scenarios is presented in Table 6. In conclusion, the revised base case CMM provides a plausible fit and long-term extrapolation of the observed GO29365 data.

Table 6. 5-year model predictions for base case and scenarios (COO March 2019)

Scenario	Pola+BR PFS	Pola+BR OS	BR PFS	BR OS
Base case	20.9%	22.4%	6.9%	7.7%
External CMM – (Pola-BR 22%, BR 10%)	20.0%	21.7%	8.9%	10.3%
External CMM – (Pola-BR 20%, BR 8%)	18.5%	20.6%	7.3%	9.0%
External CMM – (Pola-BR 24%, BR 6%)	21.6%	23.0%	5.7%	7.9%
Standard Generalized Gamma PFS and OS	15.8%	18.8%	3.3%	6.6%
Hybrid model (Generalized Gamma PFS and OS)	19.8%	19.8%	6.3%	7.3%
Hybrid model (Log-Normal PFS and Gen. Gamma OS)	16.1%	18.8%	4.6%	6.6%
Change-point model	14.6%	23.3%	8.0%	10.0%

The standard Gompertz extrapolation did not converge. PFS values for this extrapolation are therefore not presented. PFS, progression-free survival

Further data collection can address the remaining uncertainty

The remaining uncertainty in the base case and scenario is driven by uncertainty in the GO29365 data. For all models considered, uncertainty could be reduced by further follow up data from GO29365. Firstly, longer-term follow up from the randomized phase of GO29365 will reduce the remaining uncertainty on long-term extrapolation in the base case and scenarios. Secondly, further data from the single arms G+H on Pola+BR is likely to also reduce uncertainty by providing additional data to validate the current model and reduce uncertainty in parameter estimates due to the larger number of patients/events in these cohorts.

Revised base case results

Base case incremental cost-effectiveness analysis results.

The base case pairwise comparison results for Pola+BR vs. BR are presented in Table 7. Pola+BR accrued a greater health benefit compared to BR, as demonstrated by an incremental QALY value of [redacted]. Pola+BR accrued an incremental cost of £[redacted] compared to BR, resulting in an incremental cost-effectiveness ratio of £31,808/QALY

Table 7. Revised base case deterministic results (with PAS)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (Δ£/ΔQALY)
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	31,808
BR	18,471	1.55	[redacted]	-	-	-	-

BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola+BR, polatuzumab + bendamustine + rituximab; QALYs, quality-adjusted life years

Sensitivity analyses

Probabilistic sensitivity analysis

The uncertainty arising from the imprecision associated with model input parameter estimates was investigated via probabilistic sensitivity analysis (PSA). A Monte-Carlo simulation was conducted using 1,000 iterations based upon model inputs randomly drawn from distributions around the mean (summarised in Table 8). Variation in the parameterisation of the PFS and OS extrapolations was based on normal distributions and where appropriate, covariance matrices.

Where available, the standard error (SE) calculated from the same data used to derive the mean value estimate was used to inform the distribution of the input parameter. Alternatively, the SE was calculated for AE disutility inputs as 10% of the mean estimate, or for cost inputs via the following equation:

$$SE = (LN(mean + 20\%) - LN(mean - 20\%))/4$$

Table 8. PSA parameter inputs

Parameter	Distribution	Mean	SE	Alpha	Beta
Survival modelling					
Parametric estimates for OS and PFS	Normal distribution around parameter estimates, informed where appropriate, by covariance matrices				
Utilities					
Utility in PFS, both treatment arms	Beta	0.72	0.03	62.44	160.56
Utility in PD, both treatment arms	Beta	0.65	0.06	21.76	40.42
Disutility due to adverse events					
Acute kidney injury	Normal	0.27	0.027	N/A Parameter input variation (SE) equal to 10% of mean estimate	
Atrial fibrillation	Normal	0.37	0.037		
Atrial flutter	Normal	0.37	0.037		
Anaemia	Normal	0.25	0.025		
Cytomegalovirus infection	Normal	0.15	0.015		
Decreased appetite	Normal	0.37	0.037		
Diarrhoea	Normal	0.10	0.010		
Febrile neutropenia	Normal	0.15	0.015		
Herpes virus infection	Normal	0.15	0.015		
Leukoencephalopathy	Normal	0.37	0.037		
Leukopenia	Normal	0.09	0.009		
Lower respiratory tract infection	Normal	0.20	0.020		
Meningoencephalitis herpetic	Normal	0.15	0.015		
Myelodysplastic syndrome	Normal	0.37	0.037		
Neutropenia	Normal	0.09	0.009		
Neutropenic sepsis	Normal	0.15	0.015		
Oedema peripheral	Normal	0.37	0.037		
Pneumonia	Normal	0.20	0.020		
Pulmonary oedema	Normal	0.37	0.037		
Pyrexia	Normal	0.11	0.011		
Septic shock	Normal	0.37	0.037		
Supraventricular tachycardia	Normal	0.37	0.037		
Thrombocytopenia	Normal	0.11	0.011		
Vomiting	Normal	0.05	0.005		
Administration costs, Pola+BR (£)					
Administration cost, first treatment cycle	Log-normal	686.86	0.1014		

Pharmacy cost, first treatment cycle	Log-normal	62.40	0.1014	N/A Parameter input variation (SE) calculated from upper and lower estimates of base case value ±20%
Administration cost, subsequent treatment cycles	Log-normal	686.86	0.1014	
Pharmacy cost, subsequent treatment cycles	Log-normal	62.40	0.1014	
Administration costs, BR (£)				
Administration cost, first treatment cycle	Log-normal	686.86	0.1014	N/A Parameter input variation (SE) calculated from upper and lower estimates of base case value ±20%
Pharmacy cost, first treatment cycle	Log-normal	31.20	0.1014	
Administration cost, subsequent treatment cycles	Log-normal	686.86	0.1014	
Pharmacy cost, subsequent treatment cycles	Log-normal	31.20	0.1014	
Supportive care costs (£)				
Residential care (day)	Log-normal	114.50	0.1014	N/A Parameter input variation (SE) calculated from upper and lower estimates of base case value ±20%
Day care (day)	Log-normal	58.00	0.1014	
Home care (day)	Log-normal	33.32	0.1014	
Hospice (day)	Log-normal	157.08	0.1014	
Oncologist (visit)	Log-normal	165.85	0.1014	
Haematologist (visit)	Log-normal	164.80	0.1014	
Radiologist (visit)	Log-normal	187.30	0.1014	
Nurse (visit)	Log-normal	38.45	0.1014	
Specialist nurse (visit)	Log-normal	38.45	0.1014	
GP (visit)	Log-normal	37.40	0.1014	
District nurse (visit)	Log-normal	38.45	0.1014	
CT scan	Log-normal	163.66	0.1014	
Full blood counts	Log-normal	2.51	0.1014	
LDH	Log-normal	2.51	0.1014	
Liver function	Log-normal	2.51	0.1014	
Renal function	Log-normal	2.51	0.1014	
Immunoglobulin	Log-normal	2.51	0.1014	
Calcium phosphate	Log-normal	2.51	0.1014	
Inpatient day	Log-normal	383.47	0.1014	
Palliative care team	Log-normal	117.84	0.1014	
Subsequent care costs, PD				
Chemotherapy	Log-normal	1,312.30	0.1014	N/A Parameter input variation (SE) calculated
R + chemotherapy	Log-normal	3,056.88	0.1014	

Rituximab	Log-normal	2,961.73	0.1014	from upper and lower estimates of base case value ±20%
Radiotherapy	Log-normal	162.88	0.1014	
ECG	Log-normal	107.84	0.1014	
MUGA	Log-normal	285.04	0.1014	
MRI	Log-normal	140.60	0.1014	
PET-CT	Log-normal	470.71	0.1014	
Bone marrow biopsy	Log-normal	519.82	0.1014	
Adverse event management costs (£)				
Acute kidney injury	Log-normal	332.50	0.101	N/A Parameter input variation (SE) calculated from upper and lower estimates of base case value ±20%
Atrial fibrillation	Log-normal	670.13	0.101	
Atrial flutter	Log-normal	670.13	0.101	
Anaemia	Log-normal	309.09	0.101	
Diarrhoea	Log-normal	392.26	0.101	
Febrile neutropenia	Log-normal	1,847.50	0.101	
Leukopenia	Log-normal	291.00	0.101	
Neutropenia	Log-normal	291.00	0.101	
Pneumonia	Log-normal	495.81	0.101	
Lower respiratory tract infection	Log-normal	377.90	0.101	
Pyrexia	Log-normal	309.56	0.101	
Septic shock	Log-normal	1,037.71	0.101	
Thrombocytopenia	Log-normal	281.96	0.101	
Vomiting	Log-normal	382.30	0.101	
Cytomegalovirus infection	Log-normal	393.65	0.101	
Decreased appetite	Log-normal	382.30	0.101	
Supraventricular tachycardia	Log-normal	670.13	0.101	
Herpes virus infection	Log-normal	377.90	0.101	
Meningoencephalitis herpetic	Log-normal	3,652.18	0.101	
Myelodysplastic syndrome	Log-normal	556.99	0.101	
Neutropenic sepsis	Log-normal	1,847.50	0.101	
Oedema peripheral	Log-normal	343.16	0.101	
Leukoencephalopathy	Log-normal	3,609.61	0.101	
Pulmonary oedema	Log-normal	2,189.85	0.101	

BR, bendamustine + rituximab; CT, computed tomography; ECG, electrocardiogram; GP, General Practitioner; LDH, lactate dehydrogenase test; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition scan; N/A, not applicable; OS, overall survival; PD, progressed disease; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab; R, rituximab; PSA, probabilistic sensitivity analysis; SE, standard error

The results of the PSA are presented in Table 9.

Table 9. Mean probabilistic results

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (∆£/∆QALY)
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36,337
BR	27,729	2.04	[redacted]	-	-	-	-

Costs and QALYs are discounted at 3.5%. BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola+BR, polatuzumab + bendamustine + rituximab; QALYs, quality-adjusted life years

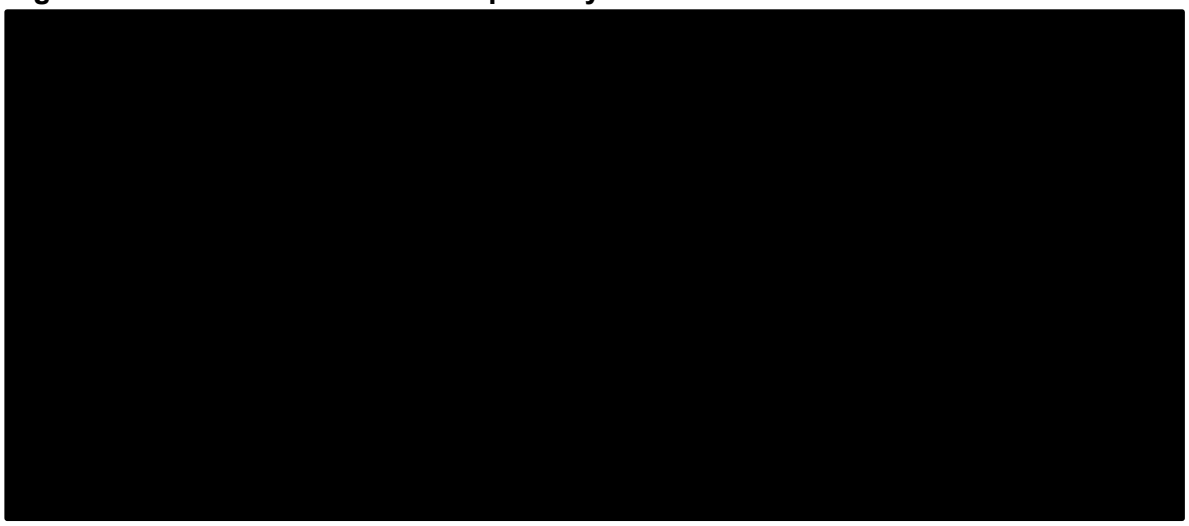
The cost-effectiveness plane is presented in Figure 13, including the percentile ranges (2.5% and 97.5%) for both incremental costs and QALYs and the 95% credibility ellipse.

The cost-effectiveness acceptability curve (CEAC) for Pola+BR versus BR is presented in Figure 14. Importantly, pola+BR was the more cost-effective option for a willingness to pay (WTP) above £36,337/QALY and the probability of Pola+BR being cost-effective relative to BR was at £50,000/QALY was 82%.

Figure 13. Cost-effectiveness plane for Pola+BR versus BR

BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab; QALY, quality-adjusted life year

Figure 14. Cost-effectiveness acceptability curve for Pola+BR versus BR



BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab; WTP, willingness to pay

Deterministic sensitivity analysis

Deterministic sensitivity analysis (DSA) was conducted by varying all parameters for which there were single input values. Each input parameter was set to its respective upper or lower bound and the deterministic results for the model recorded. For simplicity, the totals for each cost category were varied for the DSA whilst the impact of AE disutilities was investigated using the average disutility of all AEs, weighted by frequency and duration. The upper and lower bounds around the mean value for each input parameter were based upon the 10% and 90% percentile values obtained from the PSA input distribution. Where percentile estimates were not available, the input parameter was varied by ±20% (alternatively ±5 kg for mean weight, ±5% for mean BSA).

The DSA inputs and corresponding ICER values are summarised in Table 10.

Table 10. DSA results

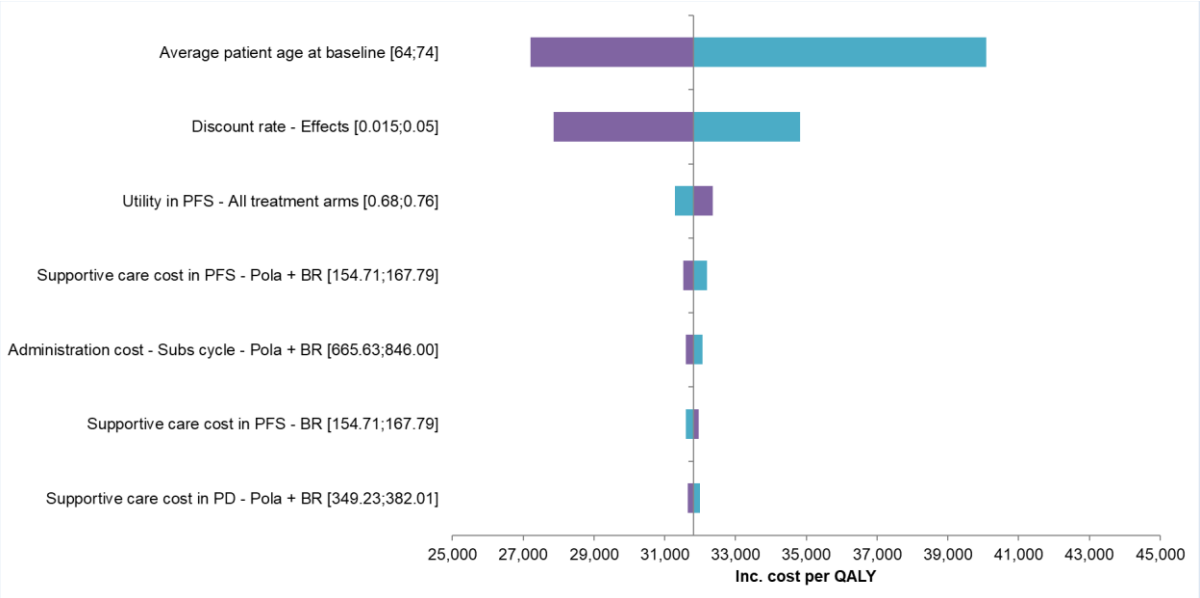
Parameter modified	Base value	Upper value	Lower value	Upper value ICER (£/QALY)	Lower value ICER (£/QALY)	Range (£/QALY)	% of base case
Base case				31,808		-	
Model settings							
Discount rate, costs	3.5%	5.00%	1.50%	31,679	32,007	328	1%
Discount rate, effects	3.5%	5.00%	1.50%	34,825	27,852	6,974	22%
Patient baseline characteristics							
Average patient age at baseline (+/- 5 years)	69.0	74.0	64.0	40,084	27,199	12,885	3%
Utilities							
Utility in PFS, all treatment arms	0.72	0.76	0.68	31,279	32,355	1,076	3%
Utility in PD, all treatment arms	0.65	0.71	0.57	31,801	31,816	16	0%
AE disutility, Pola+BR[b]	0.012	0.02	0.01	31,808	31,659	149	0%
AE disutility, BR[b]	0.014	0.03	0.01	31,808	31,973	166	1%
AE management costs							
AE management cost per patient, Pola+BR	855.02	1,058.20	680.94	31,961	31,676	285	1%
AE management cost per patient, BR	718.05	927.27	528.44	31,649	31,951	302	1%
Administration costs, Pola+BR							
Administration cost (first cycle)	749.26	848.63	666.79	31,883	31,745	138	0%
Administration cost (subsequent cycle)	749.26	846.00	65.63	32,059	31,590	469	1%
Administration costs, BR							

Administration cost (first cycle)	815.01	815.01	635.08	31,734	31,870	136	0%
Administration cost (subsequent cycle)	736.13	736.13	574.84	31,666	31,940	274	1%
Supportive care costs							
Supportive care cost in PFS - Pola+BR	160.21	167.79	54.71	32,191	31,529	662	2%
Supportive care cost in PFS - Pola+BR on treatment	460.22	484.42	441.86	31,808	31,808	0	0%
Supportive care cost in PFS - BR	160.21	167.79	154.71	31,591	31,965	375	1%
Supportive care cost in PFS - BR on treatment	460.22	484.42	441.86	31,808	31,808	0	0%
Supportive care cost in PD, Pola+BR	363.64	382.01	349.23	32,003	31,654	463	1%
Supportive care cost in PD, BR	363.64	382.01	349.23	31,616	31,958	528	1%
One-off costs, PD	2,374.08	2,848.90	1,899.26	56,426	56,470	44	0%

[a]Input parameter varied ±20% for the DSA; [b]Average of all AEs weighted by frequency and duration. AE, adverse event; BR, bendamustine + rituximab; BSA, body surface area; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab; QALY, quality-adjusted life year

A tornado diagram demonstrating the key drivers of ICER value in the comparison between Pola+BR and BR are presented in Figure 15.

Figure 15. Deterministic sensitivity analysis – tornado diagram of influential parameters for Pola+BR versus BR



BR, bendamustine + rituximab; PD, progressed disease; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab; QALY, quality-adjusted life year

Scenario analysis

Scenarios using alternative assumptions explored are described in detail above. All scenarios were run on the adjusted data set with the March 2019 data cut.

The model base case settings are presented in Table 11.

Table 11. Model base case settings

Cells/Base case setting (Model Inputs Sheet) PFS Extrapolation	Cells/Base case setting (Model Inputs Sheet) OS Extrapolation
I165=cure-mixture I168=Log-Normal I169= Log-Normal	I206=cure-mixture I209= Log-Normal I210= Log-Normal

The settings for the scenarios explored are summarized in

Table 12. Model scenario settings (all other settings as base case)

Cells/Base case setting (Model Inputs Sheet) – PFS	Cells/Base case setting (Model Inputs Sheet) – OS
External CMM – (Pola-BR 22%, BR 10%)	
I165= External cure sel I168= Log-Normal I169= Log-Normal K168=22% K169=10%	I206= External cure sel I209= Log-Normal I210= Log-Normal K209=22% K210=10%
External CMM – (Pola-BR 20%, BR 8%)	
I165= External cure sel I168= Log-Normal I169= Log-Normal K168=20% K169=8%	I206= External cure sel I209= Log-Normal I210= Log-Normal K209=20% K210=8%
External CMM – (Pola-BR 24%, BR 6%)	
I165= External cure sel I168= Log-Normal I169= Log-Normal K168=24% K169=6%	I206= External cure sel I209= Log-Normal I210= Log-Normal K209=24% K210=6%
Standard Generalized Gamma	
I165= Not proportional I168=Generalized Gamma I169=Generalized Gamma	I206= Not proportional I209= Generalized Gamma I210= Generalized Gamma
Hybrid with Generalized Gamma for PFS and OS	
I165= Hybrid I168=Generalized Gamma I169=Generalized Gamma J184=36	I206= Hybrid I209= Generalized Gamma I210= Generalized Gamma J226=55
Hybrid with Log-Normal for PFS and Generalized Gamma for OS	
I165= Not proportional I168= Log-Normal I169= Log-Normal J184=36	I206= Not proportional I209= Generalized Gamma I210= Generalized Gamma J226=72
Change-point model	
I165= Not proportional I168= Change_point_weibull I169= Change_point_weibull	I165= Not proportional I168= Change_point_weibull I169= Change_point_weibull

The results of the six scenario analyses for the original ITT and CHMP ITT population are presented in Table 13.

Table 13: Scenario analysis results

Scenario	LY Pola+BR	LY BR	Incremental LY	Incremental costs (£)	Incremental QALYs	ICER (Δ£/ΔQALY)
Base case	[redacted]	1.55	[redacted]	[redacted]	[redacted]	31,808
External CMM – (Pola-BR 22%, BR 10%)	[redacted]	1.84	[redacted]	[redacted]	[redacted]	39,015
External CMM – (Pola-BR 20%, BR 8%)	[redacted]	1.70	[redacted]	[redacted]	[redacted]	38,873
External CMM – (Pola-BR 24%, BR 6%)	[redacted]	1.57	[redacted]	[redacted]	[redacted]	29,351
Standard Generalized Gamma	[redacted]	1.43	[redacted]	[redacted]	[redacted]	35,510
Hybrid with Generalized Gamma for PFS and OS	[redacted]	1.67	[redacted]	[redacted]	[redacted]	33,919
Hybrid with Log-Normal for PFS and Generalized Gamma for OS	[redacted]	1.54	[redacted]	[redacted]	[redacted]	37,678
Change-point model	[redacted]	1.68	[redacted]	[redacted]	[redacted]	45,247

CHMP, Committee for Medicinal Products for Human Use; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITT, intent-to-treat; Pola+BR, polatuzumab + bendamustine + rituximab; PFS, progression-free survival; OS, overall survival; QALY, quality-adjusted life year

References

1. National Institute for Health and Care Excellence. Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [TA567]. 2019.
2. Howlader N, Mariotto AB, Besson C, Suneja G, Robien K, Younes N, et al. Cancer-specific mortality, cure fraction, and noncancer causes of death among diffuse large B-cell lymphoma patients in the immunochemotherapy era. Cancer. 2017;123(17):3326-34.
3. Cox C, Chu H, Schneider MF, Munoz A. Parametric survival analysis and taxonomy of hazard functions for the generalized gamma distribution. Stat Med. 2007;26(23):4352-74.
4. Lambert PC. Modeling of the cure fraction in survival studies. Stata Journal. 2007;7(3):351-75.
5. Lambert PC, Thompson JR, Weston CL, Dickman PW. Estimating and modeling the cure fraction in population-based cancer survival analysis. Biostatistics (Oxford, England). 2007;8(3):576-94.
6. National Institute for Health and Care Excellence. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies [TA559]. 2019.
7. Coelho-Barros EA, Achcar JA, Martinez EZ, Davarzani N, Grabsch HI. Bayesian Inference For The Segmented Weibull Distribution. Revista Colombiana de Estadística. 2019;42(2):225-43.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

ID1576: Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma

Addendum new data cut post ACD response

File name	Version	Contains confidential information	Date
ID1576_Polatuzumab vedotin RR DLBCL_ ACD Addendum 1 050520 [redacted]	**1**	**No, redacted**	**05 May 2020**

Contents

GO29365 KM PFS and OS data

A new updated data cut from the randomised part of GO29365 became available for analysis in [redacted] with a clinical cut off data of [redacted].

The median OS follow up for the [redacted] cut off was [redacted] months for BR and [redacted] months for Pola+BR (compared to the previous cut from March 2019 with 30 months median follow up).

The updated KM curves for the unadjusted ITT population for PFS-IRC and OS are shown in Figure 1 and Figure 2 below.

Figure 1: PFS-IRC GO29365 (ITT, unadjusted, cut off [redacted])

BR, bendamustine + rituximab; IRC, independent review committee assessed; Pola+BR, polatuzumab + bendamustine + rituximab

Figure 2: OS GO29365 (ITT, unadjusted, cut off [redacted])

BR, bendamustine + rituximab; INV, investigator assessed; Pola+BR, polatuzumab + bendamustine + rituximab

[redacted]

[redacted](9/40 in March 2019) [redacted](2/40 in March 2019), respectively.

GO29365 further data cuts

[redacted]

[redacted]

Final analysis of GO29365 is expected to be available in 2022.

NICE National Institute for Health and Care Excellence

Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [ID1576]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 18 March 2020 **email:** 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):	Lymphoma Action
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments

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Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [ID1576]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 18 March 2020 **email:** NICE DOCS

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that this decision is based solely on a flawed cost-effectiveness analysis. The submitting company's analysis found lenalidomide plus rituximab to be cost-effective. We acknowledge that the committee had concerns over the methods and assumptions used in the company's cost-effectiveness model. However, the committee also expressed concerns over the ERG's methods, noting that the ERG's analysis 'did not capture the potential cure aspect of the disease and may therefore be conservative in its interpretation of the evidence.' Despite this, the committee has chosen to give more credence to the ERG's analysis, even though they acknowledge that it is flawed. The committee accepts that clinical trial data shows that polatuzumab vedotin significantly extends progression-free survival and overall survival. The committee also acknowledges that relapsed or refractory diffuse large B-cell lymphoma is a devastating condition with a poor prognosis and that patients have a high unmet need for effective treatments. This is consistent with the experiences of patients supported by our organisation, who tell us of the huge physical, psychological and financial impact of the disease and its current treatments, and the terrible uncertainty of the final outcome. We therefore question whether concerns over the precise methods used to analyse cost-effectiveness are sufficient to warrant withholding life-extending, and potentially curative, treatment from people with such a poor prognosis and limited alternative options.
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Insert extra rows as needed

Checklist for submitting comments

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

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Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [ID1576]

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

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

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

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

Name	[redacted]
Role	[redacted]
Organisation	[redacted]
Location	
Conflict	
Notes	
Comments on the ACD:	

I am writing on behalf of [redacted] to provide comments on the above Technology Appraisal. We have treated 9 patients with polatuzumab-BR at our institution so far and have found it to be a useful regimen for both bridging patients to more definitive therapies and for palliating patients with relapsed DLBCL that are unsuitable for intensive chemotherapy. Our only other option in this setting would be bendamustine-rituximab, which was was inferior to polatuzumab-BR in the recent randomized trial by Sehn *et al.*

We appreciate that there are ongoing uncertainties regarding the curative potential and cost effectiveness of polatuzumab-BR. Nevertheless, this is one of very few randomized trials conducted in this relapsed DLBCL and shows a clear progression-free and overall survival benefit in favour of polatuzumab-BR.

The appraisal already outlines the very clear unmet need in this patient population. Treatment options are now even further restricted by the temporary suspension of clinical trials during the COVID-19 pandemic. The deliverability of intensive therapies, such as transplant and CAR-T, is also compromised during the outbreak. In these circumstances, we feel that there is a strong case for allowing continuing access to polatuzumab-BR.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

ID1576: Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma

Addendum 2

Critique of new evidence submitted by the company in response to the ACD

Produced by

Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Date completed

20/04/2020

1. Introduction

On February 2020, the National Institute for Health and Care Excellence (NICE) issued the Appraisal Consultation Document (ACD) in which polatuzumab vedotin with rituximab and bendamustine was not recommended, within its marketing authorisation, as an option for treating relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) in adults who cannot have a haematopoietic stem cell transplant.[1] The Committee considered that cost-effectiveness estimates for polatuzumab vedotin with rituximab and bendamustine were very uncertain because of limitations in the data and methods. It was considered a life-extending treatment at the end of life, but the cost-effectiveness estimates were too uncertain. Therefore, it could not be recommended for routine use in the NHS or for use in the Cancer Drugs Fund. The purpose of this addendum is to provide a critique of the new evidence submitted by the company as part of their ACD response.[2, 3]

2. Critique of the cost effectiveness evidence submitted by the company in response to the NICE ACD

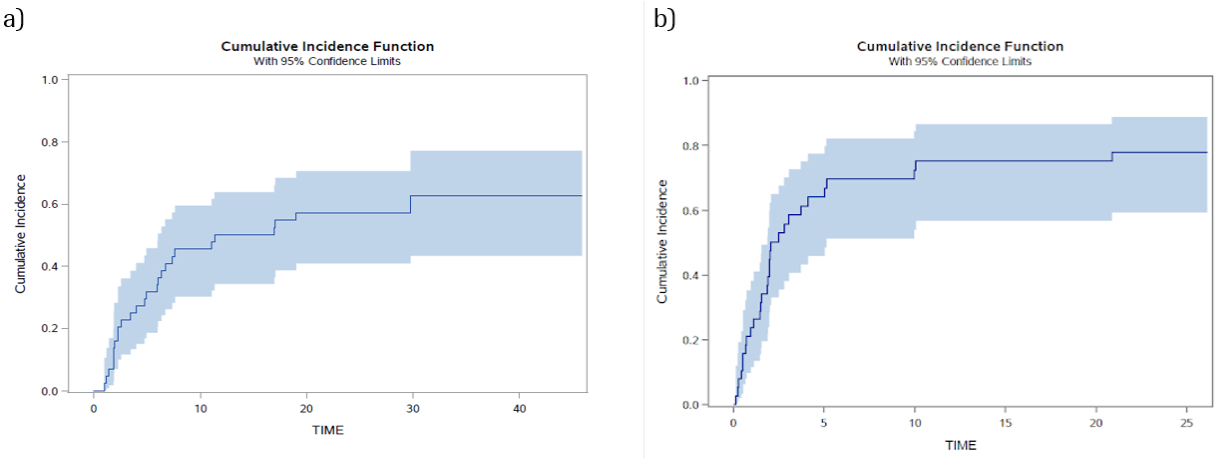
2.1 Company's revised base-case assumptions

2.1.1 Survival modelling approach

In their revised base-case, the company reiterated their preference for a cure-mixture model (CMM) approach to extrapolate overall survival (OS) and progression-free survival (PFS), since, according to the company, "*this approach has high external validity in terms of the fit to the observed data and the plausibility of extrapolation results*".[3] The company claimed that, based on clinical expert opinion and observations from studies with long-term follow-up in R/R DLBCL patients treated with R-chemo, a significant proportion of patients achieving 2-year remission (i.e. patients in PFS) is expected to remain in long-term remission. Therefore, it is assumed that at some time point after 2 years, the rate of progression or death will approach background mortality of the general population adjusted for an increased mortality. Therefore, the company concluded that standard survival parametric models may not be able to provide plausible fits and long-term extrapolations, as they may not be appropriately modelling more complex hazard over time, and that CMM may be more suitable to provide plausible fits and long-term extrapolations. Finally, the company indicated that this natural history of the disease also formed the basis of the modelling approach taken for CAR-Ts, where the committee accepted the existence of a cure point between 2 and 5 years.[3]

Furthermore, the company considered that the natural history of the disease, with a significantly declining hazard of progression (and death) over time is evident from the data observed in GO29365. As an example, the company presented in Figure 1 the cumulative incidence of progression in both treatment arms of GO29365, where according to the company, it is shown that most progression events occurred within the first 12 months (in both arms), and that patients are at a very low risk of progression after 24 months. In summary, the company concluded that, the application of CMM in the R/R DLBCL setting is meaningful because the data in GO29365 is sufficiently mature: the proportion of people in long-term remission can be estimated reliably from the GO29365 data on PFS as the majority of progression events will have happened before 2 years.

Figure 1. Cumulative incidence of progression (INV) from GO29365 a) Pola+BR and b) BR



Source: Figure 1 in company's appendix to ACD response.[3]
Abbreviations: BR, bendamustine + rituximab; INV, investigator assessed; Pola+BR, polatuzumab + bendamustine + rituximab.

Finally, in order to address one of the points raised by the ERG and discussed during the ACM (see ACD section 3.8),[1] the company mentioned that fitting CMMs does not necessarily require a 'plateau' in the Kaplan-Meier (KM) curve. For example, long-term survival rates were estimated by Howlader et al. 2017 in the front line setting without a clear 'plateau' in the observed KM OS.[4]

ERG comment: The company refers to the CMM as an approach with high external validity both in terms of fit to the observed data and the plausibility of the long-term extrapolations. The ERG is still uncertain about this statement, which is in line with the conclusions from the ERG report and the first ACM (see e.g. ACD sections 3.7 and 3.8).[1, 5] In particular, the ERG would like to highlight the following:

- The initial study cited by the company, Maurer et al. 2014, was not in the R/R setting.[6] This study showed no statistically significant difference in mortality between newly diagnosed DLBCL patients who were progression-free at 2 years and the general population. However, the relevant population for this appraisal is R/R DLBCL, thus, not newly diagnosed patients.
- Indeed this same study, Maurer et al. 2018, concluded that whilst progression-free at 24 months has been shown to be a predictor of long-term survival in a non-R/R setting, "*further evaluation is needed before utilization of the PFS24 end point can be extended to the relapsed setting*".[7]
- As stated in the ERG report, a different study (Howlader et al. 2017) based on a substantially larger sample of DLBCL patients suggests an excess mortality up to 5 years.[4, 5]
- The cure assumption was accepted in 2 previous appraisals of CAR-T therapies.[8, 9] The ERG would still maintain that polatuzumab is, however, quite different from CAR-T therapies.
- Clinical experts consulted by the company were supportive of the cure assumption. However, the experts attending the ACM were more uncertain. In the ACD it is mentioned that the "*committee heard from the clinical experts that it is too early to say whether polatuzumab vedotin will be a curative treatment. However, at least for the first-line treatment of diffuse large B-cell lymphoma, long-term survival may be improved when there has been an ongoing complete response lasting more than 24 months, and this is independent of the treatment used. The clinical experts explained that the evidence so far is suggestive of improved long-term survival in a small cohort of patients with relapsed or refractory disease, but further follow up would establish the amount of long-term benefit. The clinical experts also explained that patients who have had several lines of therapy might have improved long-term survival or be 'cured' but would be unlikely to have exactly the same risk of mortality as the general population. This is because some patients would relapse and the treatments themselves can affect long-term survival*".[1]".[1]
- The company further referred to visual inspection of KM curves, hazard plots, etc. from GO29365 data (like Figure 1 above) to support a significantly evident very low progression rate after 2 years. While this might be the case, it should be emphasised that the sample size in GO29365 is rather small. Therefore, statements about the strength of the evidence presented in the trial should be made with caution. As an example, the confidence intervals shown in Figure 1 are quite large, which illustrates the underlying uncertainty. The ERG considers it unlikely that the proportion of people in long-term remission can be estimated *reliably* from the GO29365 data. For example, while it is true that at 30 months median follow up in the GO29365 study, 23% of patients in the pola+BR were in disease remission (versus 5% in the BR arm), these are only 9 patients.
- Besides the small sample size and the limited number of events, the median follow-up is 30 months. The ERG also considers it unlikely that these additional 6 months (after two years) are

sufficient to determine whether the majority of progression events have already occurred and, therefore, reliably estimate the cure fraction.

- The company also mentioned that fitting CMM does not necessarily require a 'plateau' in the KM curve. The ERG agrees with this statement, but it does not necessarily imply that the underlying assumption is correct. For example, it would also be possible to fit a proportional hazards models even without a clear indication that proportional hazards will be observed. This would not mean that assuming proportional hazards would be correct.
- Conclusions from Howlader et al. indicate that "*although DLBCL-specific mortality levels off over time, there is no clear plateau, and even patients who achieve 2-year survival are still at risk of dying of their lymphoma*". This might suggest that these long-term survivors are in fact not cured. Also, the paper mentions that "*as stressed by others, fitting a cure model requires a long follow-up period after the diagnosis*".[4]
- The ERG would like to emphasise that assuming a CMM needs two main prerequisites from the data: 1) identifiability of the cure fraction, and 2) sufficient follow-up. The accuracy of the estimated cure fraction also depends on the sample size of the study population (and the length of patient follow-up).[10] Even though clinical experts have stated the possibility of a cure fraction based on expected long-term remission, the ERG considers that given the small sample size in GO29365 and that the potential cure fraction in this study may be small, longer follow-up may be required.

In summary, the ERG would conclude that, with the current data, the results of fitting a CMM to them would be very uncertain. Since the company did not present new data in their ACD response, the committee and ERG concerns remain unresolved. In particular, the ERG considers that, as mentioned in the ACD, "*there is a lack of robust evidence on long-term remission and cure with polatuzumab vedotin in patients with relapsed or refractory disease. However, the data from the trial so far suggest that a small proportion of people may have a durable response that could indicate cure*".[1]

2.1.2 Selection of cure-mixture model

Selection of CMMs to extrapolate PFS and OS was primarily based on Akaike information criterion (AIC) and Bayesian information criterion (BIC) values. Table 1 and Table 2 show these values for PFS and OS, respectively. In general, the Log-Logistic and the Log-Normal CMM resulted in the lowest AIC/BIC values. The Generalized Gamma CMM, selected initially at submission, has the highest BIC value. However, as the company noted, more complex models (with more parameters), such as the standard Generalized Gamma, are usually penalised with larger AIC/BIC values, even though they may provide a good visual fit and plausible long-term extrapolations. The company also indicated that, the simpler Exponential CMM provided a reasonable visual fit and plausible long-term extrapolation with the lowest BIC among the CMMs investigated. The company concluded that, since the Log-Normal CMM provided an equal visual fit and plausible long-term extrapolation compared to the Generalized Gamma CMM, the Log-Normal CMM was selected for the revised base-case for both PFS and OS to reduce parameter uncertainty.

Table 1. AIC/BIC and visual fit for PFS-IRC cure-mixture models (adjusted analysis)

	Pola+BR			BR		
Function	**AIC (Rank)**	**BIC (Rank)**	**Visual**	**AIC (Rank)**	**BIC (Rank)**	**Visual**
Exponential	43.1(5)	125(1)	+	80.7(4)	162.6(1)	+
Weibull	43(4)	145.9(4)		80.7(5)	183.6(4)	

Log-Normal	40.9(2)	143.8(3)	+	78.1(1)	181(2)	++
Generalized Gamma	43(3)	161.7(6)	++	79.6(3)	198.4(6)	++
Log-Logistic	40.2(1)	143.1(2)	+	79(2)	181.9(3)	+
Gompertz	44.9(6)	147.8(5)		82.2(6)	185.1(5)	

Source: Table 2 in company's appendix to ACD response.[3]
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; BR, bendamustine + rituximab; IRC, independet review committee; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab.

Table 2. AIC/BIC and visual fit for OS cure-mixture models informed by PFS (adjusted analysis)

	Pola+BR			**BR**		
Function	**AIC (Rank)**	**BIC (Rank)**	**Visual**	**AIC (Rank)**	**BIC (Rank)**	**Visual**
Exponential	63.7(4)	145.6(1)	+	86.7(3)	168.6(1)	+
Weibull	64.8(6)	167.7(5)	+	87.3(4)	190.2(4)	+
Log-Normal	61.5(2)	164.4(3)	+	85.6(1)	188.5(2)	++
Generalized Gamma	63.2(3)	182(6)	+	87.6(5)	206.4(6)	++
Log-Logistic	61(1)	163.9(2)	+	85.6(2)	188.5(3)	+
Gompertz	64.3(5)	167.2(4)		88.9(6)	191.8(5)	+

Source: Table 3 in company's appendix to ACD response.[3]
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; BR, bendamustine + rituximab; OS, overall survival; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab.

The revised base-case PFS and OS extrapolations are shown in Figure 2. In Figure 3, the company presented the hazards of progression or death (PFS) and survival (OS) in relation to the adjusted background mortality hazard (increased mortality risk = 1.41). A value of 1 in the graph (green line) represents the adjusted background mortality hazard. As time increases, PFS or OS hazards approach the adjusted background mortality. The company noted that the PFS hazards for the two treatment arms converged after approximately 4 years and approached the adjusted background mortality after approximately 5 years.

Figure 2. Revised base-case PFS and OS extrapolations (Log-Normal CMM, adjusted analysis, COO March 2019)

Source: Figure 2 in company's appendix to ACD response.[3]
Abbreviations: BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab, CMM cure-mixture model.

Figure 3. Ratio of hazards (PFS and OS) to adjusted background mortality for revised base-case

Source: Figure 3 in company's appendix to ACD response.[3]
Abbreviations: BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab, CMM cure-mixture model

ERG comment: In order to select the most plausible CMM extrapolation for PFS and OS, the company first relied on AIC and BIC values. The company indicated several times that some distributions resulted in good visual fit and plausible long-term extrapolations. However, especially for the plausibility of the long-term extrapolations, the company did not provide any criteria that can be used to validate this assumption. Therefore, what makes a long-term extrapolation plausible remains unclear (not only for CMMs but in general). In terms of AIC, there do not seem to be large differences between the different survival models for both PFS and OS. Regarding BIC, the Exponential model is clearly the one providing the lowest value, even though it might be possible that the other probability distributions are penalised by having more parameters. If the visual fit of the Exponential CMM is reasonable, as indicated by the company, and if reducing parameter uncertainty was one of the criteria used by the company to select one distribution over another (the Log-Normal was selected instead of the Generalised Gamma for this reason, although the ERG would not agree with this approach), the Exponential CMM could have also been an appropriate choice. The ERG explored this scenario in Section 3 of this addendum. Finally, based on Figure 3, the company noted that the PFS hazards for the two treatment arms converged after approximately 4 years. However, the ERG noticed that in the model, these rates are equal at 66 months (5.5 years). At year 4 the PFS hazard for Pola+BR is 2.39 and for BR is 2.69. Even though the difference seems small, the ERG is unsure whether that difference might be important or not. At year 5 the PFS hazard for Pola+BR is 1.58 and for BR is 1.63. Again, this difference seems small, but it was also small before 5 years and continued to be small (although not equal to 1) after 5 years. Similarly, the statement "*approached the adjusted background mortality after approximately 5 years*", is also not accurate. Regarding OS rates at year 5, these are 2.11 for Pola+BR and 3.68 for BR, and an OS benefit, even small towards the end, is observed up to 20 years. In summary, the ERG is not able to properly interpret this information, since, as mentioned above, the company did not provide clear criteria that can be used to validate the plausibility of these extrapolations.

2.1.3 Differences in deterministic and probabilistic results

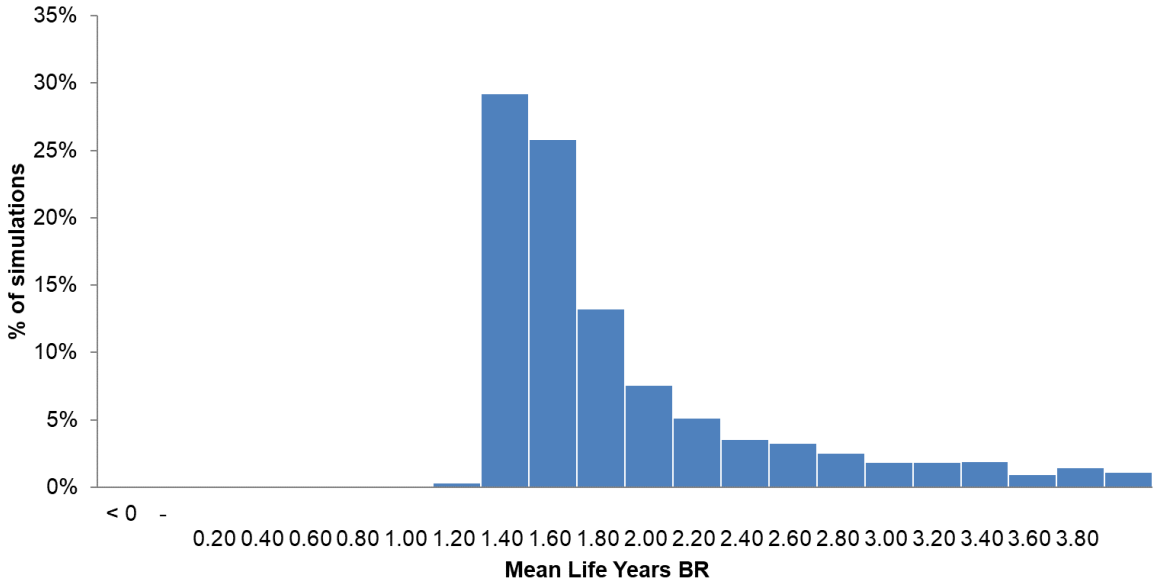
As mentioned in ACD Section 3.8, the "*committee was concerned about the reliability of the model outputs because of the large unexplained difference between the company's deterministic and probabilistic results*".[1] The company explored this issue and, by doing this, in the revised model provided with the ACD response, the company corrected an error in the model submitted after technical engagement (the previous models did not select the correct covariance matrices for the PFS-IRC CMM extrapolations).[3]

Regarding the unexplained differences between the deterministic and probabilistic model results, the company noted that in general, CMMs may result in wider distributions compared to standard parametric models. For OS estimates, the company expected a skewed distribution because while deterministic estimates were bounded by the range deemed plausible by clinical experts, probabilistic values were not bounded, but considered the full variability of parameter estimates given by the variance-covariance matrices. As an example, the company indicated that, in the PSA, long-term remission rates were not bounded by clinical plausibility but were allowed to be varied "significantly" above the range of expected values. Therefore, the company concluded that probabilistic estimates propagated through the model are conservative estimates of the variation in results.

In ACD Section 3.8, the "*committee also noted that the company's probabilistic analysis estimated the number of life years for the comparator arm to be more than 2 years, which seemed unrealistic and inconsistent with clinical opinion, and would cast doubt on whether polatuzumab vedotin meets the end-of-life criteria*".[1] In Figure 4, the company presented the distribution of life-years for BR simulated in the revised base-case PSA. It can be observed that the distribution is right-skewed. Most frequent

values were around the mean deterministic value (1.55 life-years) and 75% of the simulations resulted in values below 2 years. The company concluded that outliers in simulations that exceeded 2 years significantly, brought the average life-years in the PSA to 2.04 in the revised base-case (see Table 7 below).

Figure 4. Relative frequency of average LY BR PSA simulations (base-case)



Source: Figure 4 in company's appendix to ACD response.[3]
Abbreviations: BR, bendamustine + rituximab; LY, Life years

ERG comment: The company considered that the unexplained differences between the deterministic and probabilistic model results are likely to be caused by the full variability of parameter estimates in the PSA, given by the variance-covariance matrices, as opposed to deterministic values which were bounded by the range deemed plausible by clinical experts. While the ERG considers that the variability of the parameters in the PSA is likely to cause this difference, the following should be noted:

- PSA parameter values are in fact bounded by the probability distributions that are assumed for these parameters. If these result in clinically implausible values, it is most likely because the uncertainty around these parameters is large (wide probability distributions). However, this implausibility can go, in principle, in either direction.
- The company concluded that probabilistic estimates propagated through the model are thus conservative estimates of the variation in results. The ERG does not agree with this statement and considers this a reflection of the uncertainty associated with the current data.
- The ERG considers that the example provided by the company in Figure 4 illustrates very well the uncertainty with the data. However, the ERG does not agree with the term "outliers" for a large percentage (up to 25%) of the simulations. There is data uncertainty, and this must be acknowledged. If the company base-case resulted in implausible PSA results, this might have been an indication for selecting different OS or PFS extrapolations for their base-case.

2.2 Scenario analysis with external long-term remission and survival ('cure') rate

Following the suggestions in the ACD, the company performed scenario analyses where, instead of estimating "cure" rates from the data, these could be selected (externally) by the user in the model. With these external rates, the standard CMM functions were fitted to the observed data.

In the revised base-case, the estimated Log-Normal CMM long-term remission rates were 22.8% and [redacted]% for the Pola+BR and BR arms, respectively. The company investigated first two scenarios where the long-term remission rates were (externally) set to:

- 22.0% for the Pola+BR arm and 10.0% for the BR arm, and
- 20.0% for the Pola+BR arm and 8.0% for the BR arm.

The company considered that reasonable fits to the data were observed in these two scenarios. However, these scenarios were deemed as conservative by the company because, as shown in Figures 5 and 6, assuming these cure rates would result in the progression hazards of Pola+BR and BR being equal at approximately 30 months in the first scenario and approximately 40 months in the second scenario.

Figure 5. Ratio of hazards (PFS and OS) to adjusted background for external long-term remission scenario 1 (22.0% and 10.0%)

Source: Figure 5 in company's appendix to ACD response.[3]
Abbreviations: BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab, CMM cure-mixture model

Figure 6. Ratio of hazards (PFS and OS) to adjusted background for external long-term remission scenario 2 (20.0% and 8.0%)

Source: Figure 6 in company's appendix to ACD response.[3]
Abbreviations: BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab, CMM cure-mixture model

The company explored another scenario where a smaller difference in long-term remission was assumed: 20.0% for Pola-BR and 10% for BR. This resulted in the PFS hazard of Pola+BR being higher than the PFS hazard of BR after approximately 24 months, as can be seen in Figure 7. The company considered this implausible given the natural history of the disease. According to the company, patients on the Pola+BR arm should not be at higher risk of progression or death than patients on the BR arm.

Figure 7. Ratio of hazards (PFS and OS) to adjusted background for external long-term remission scenario 2 (20.0% and 10.0%)

Source: Figure 7 in company's appendix to ACD response.[3]
Abbreviations: BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab, CMM cure-mixture model

Additionally, even though the company did not report more results, it was mentioned that "*there was no indication of a significant change in the hazard ratio over the observed follow up period (as indicated in the log-cumulative hazard plots and by fitting independent parametric functions)*".[3] Also, the company indicated that the "*hazard of progression or death for Pola+BR would have to exceed that of BR significantly after 2 years (or less) for scenarios where even lower long-term remission rates on Pola+BR (such as those seen in independent cure-mixture models for PFS-IRC) and/or higher rates for BR were assumed*".[3] Finally, "*scenarios with a higher long-term remission rate on Pola+BR of 24% than the CMM base case and a lower long-term remission rate of 6% for BR produced still plausible results*".[3]

The company concluded that these scenarios confirmed that assuming a lower difference in long-term remission rates than in their revised base-case would not be plausible as it would result in hazards for progression or death in the Pola+BR arm exceeding the hazard for progression or death in the BR arm before or around 2 years.

ERG comment: It is unclear what criteria the company have used to decide the plausibility of the scenarios. This section focused on the shapes of the PFS and OS hazards over time. In the revised base-case, the company noted that the PFS hazards for the two treatment arms converged after approximately 4 years and approached the adjusted background mortality after approximately 5 years. The ERG understood that this is clinically plausible according to the company, even though a clear explanation was not provided: e.g. it is not mentioned when the progression hazards of Pola+BR and BR are expected to be equal. In the revised base-case, the estimated Log-Normal CMM long-term remission rates were 22.8% and [redacted]% for the Pola+BR and BR arms, respectively; thus a [redacted]% difference in long-term remission rates. The company has shown that assuming a lower difference in long-term remission rates than in their revised base-case (12% and 10% in the two scenarios, respectively) would

result in implausible scenarios since the hazards for progression or death in the Pola+BR arm would exceed the hazard for progression or death in the BR arm before or around 2 years. The ERG explored in Section 3 of this addendum scenarios where the difference in long-term remission rates was in accordance with the company's revised base-case, but both individual rates per arm were either higher or lower.

2.3 Alternative scenarios without 'cure-mixture' model for extrapolation

Besides CMMs, the company also explored assuming standard parametric models, hybrid models and change-point models, as alternative models to extrapolate PFS and OS. Additional details are provided below.

Standard parametric models

The company considered that, from all the standard parametric models included in their model, only assuming a Generalized Gamma distribution for both PFS and OS would result in reasonable fits and plausible long-term extrapolations, since this distribution is the most flexible, among the standard distributions.[3] Additionally, the difference in 5-year PFS and OS rates is smaller, which seems to overcome the main limitation of the ERG preferred assumption, as discussed in ACD Section 3.9.[1] The 5-year PFS rates are also closer to the range observed with CMMs, which according to the company indicate a plausible long-term remission rate and survival for patients achieving 2-year PFS rates (see e.g. Table 6). As shown in Figure 8, the standard Generalized Gamma function predicts increased hazard for progression or death (PFS) in the Pola+BR arm up to approximately 10 years, and even longer (not shown in the figure) for the BR arm.

Figure 8. Ratio of hazards (PFS and OS) to adjusted background for standard Generalized Gamma scenario

Source: Figure 9 in company's appendix to ACD response.[3]
Abbreviations: BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab

ERG comment: The ERG consider that it is crucial to clearly define the criteria as to which one scenario is deemed plausible or not. Such criteria seem unclear and inconsistent with the information presented in previous sections of this document. As shown in Figure 8, the scenario assuming a Generalized

Gamma distribution for PFS resulted in a hazard which equalled the adjusted background mortality after approximately 10 years in the Pola+BR arm (cure at approximately 10 years in Pola+BR), and even longer in the BR arm. Furthermore, Figure 8 also shows an OS benefit for Pola+BR over BR for more than 10 years (not shown in the figure). Based on this, the ERG wonders to what extent this scenario can be considered clinically plausible. It is true that the difference in 5-year PFS and OS rates is smaller, which minimises the main committee concern regarding the ERG's preferred assumption (see ACD Section 3.9).[1] However, this difference in 5-year PFS and OS rates becomes even smaller when the Log-logistic or the Log-normal distributions are chosen to extrapolate OS. Therefore, it is unclear why these two scenarios were not considered plausible or explored by the company in their ACD comments. Please see Section 3 of this addendum for further discussion on standard parametric models.

Hybrid models

Another alternative explored by the company were hybrid models, which were used for example in previous CAR-T appraisals.[8, 9, 11, 12] In these models, PFS and OS are modelled by fitting standard parametric distributions up to an externally defined cure time-point at which adjusted background mortality is applied. The company noted the following:

- The cure point is assumed to be between 2 and 5 years.
- Different time points for PFS and OS may be required to allow for post-progression survival.
- Compared to the CMMs, hybrid models rely on external inputs on cure points (not estimated by fitting data).
- Hybrid models allows for fitting the observed data and achieving clinically plausible long-term extrapolations.
- Since fewer parameters are estimated, statistical uncertainty is reduced.
- Hybrid models have been preferred to CMMs in TA567 mainly because the company's CMM approach was applied to OS and PFS independently which produced inconsistent extrapolations.

The company conducted scenario analyses assuming hybrid models with a Generalized Gamma distribution for PFS and OS and, alternatively, with a Log-Normal distribution for PFS (as this was the ERG's preferred choice). The company assumed a 3-year cure-point for long-term remission and the long-term survival time point for OS was assumed at the time point where the standard parametric OS extrapolation crossed the hybrid PFS curve. For the scenario with Generalized Gamma distribution for PFS this was between 52 and 58 months and the company selected 55 months for both treatment arms. For the scenario with the Log-Normal distribution for PFS, this was approximately 72 months in both arms. The resulting extrapolations are shown in Figures 9 and 10, respectively. According to the company, these long-term extrapolations are comparable with the CMM used in the revised base-case.

Figure 9. Scenario with hybrid model (Generalized Gamma PFS and OS)

Source: Figure 10 in company's appendix to ACD response.[3]
Abbreviations: BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab

Figure 10. Scenario with hybrid model (Log-Normal PFS, Generalized Gamma OS)

Source: Figure 11 in company's appendix to ACD response.[3]
Abbreviations: BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab

ERG comment: Assuming hybrid models needs the same two main prerequisites from the data as for CMMs: 1) identifiability of the cure fraction, and 2) sufficient follow-up. For further details, the ERG refers then to the critique in Section 2.1.1.

Change-point model

Finally, the company investigated change-point models as this type of models allows modelling more complex hazard functions. The Weibull change-point survival model is specified in Equation 1 below:[1]

$$S(t) = \begin{cases} \exp\left[\left(\frac{t}{\mu_1}\right)^{\alpha_1}\right] & if\ 0 < t < change\ point \\ \exp\left[\left(\frac{t}{\mu_2}\right)^{\alpha_2}\right] & if\ t \geq change\ point \end{cases} \quad (1)$$

The company estimated the parameters of change-point Weibull model by maximising the likelihood function over the observed data. A random change-point model for PFS and OS were assumed where the change point, shape and scale parameter were estimated. The estimated change-point model parameters are provided in Table 3 and the resulting extrapolations in Figure 11.

Table 3. Summary of the Weibull change-point model and parameters

Arm	Endpoint	Shape α1	Scale μ1	Change point (months)	Shape α2	Scale μ2	5-year estimate (%)
Pola+BR	PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14.6%
BR	PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8.0%
Pola+BR	OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23.3%
BR	OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10.0%

Source: Table 5 in company's appendix to ACD response.[3]
Abbreviations: Pola, polatuzumab vedotin; BR, bendamustine with rituximab; PFS, progression-free survival; OS, overall survival

Figure 11. Scenario with change-point extrapolation

Source: Figure 12 in company's appendix to ACD response.[3]
Abbreviations: BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab

The company considered that the change-point models fitted well the observed (KM) data, but that the long-term extrapolations had limited validity compared to the models discussed in the previous sections because "*the estimated 5-year PFS and OS rates were less consistent in the Pola+BR arm*", and that this was likely due to the change-point being estimated "*after 12 months where most of the PFS/OS events had occurred*", which results in limited events used to estimate the second part of Equation 1 (the function from the change point onwards). Since long-term extrapolations are based on this later estimate, the company considered this method as less robust compared to the other methods previously discussed.

ERG comment: The application and the reasons given by the company to doubt the validity of these models remain unclear to the ERG. The 5-year extrapolations predicted by the change-point models for the BR arm (see Table 3) seems to be in the range provided by the clinical experts. It is also unclear what the company meant by "*the estimated 5-year PFS and OS rates were less consistent in the Pola+BR arm*".[3] Regarding the change-point being estimated "*after 12 months where most of the PFS/OS events had occurred*", the ERG believes that, based on Table 3, this may only apply to the pola+BR arm. However, the ERG agrees with the company that given the limited events used to estimate the second part of Equation 1, long-term extrapolations are a concern for these models, but it is unclear why it is less of an issue for the other models discussed so far.

2.4 Summary of PFS and OS model predictions

A summary of the predicted 5-year OS and PFS for the revised company based-case and the scenarios introduced in the previous sections are summarised in Table 4. Based on these, the company concluded that the revised base-case provided a plausible fit and long-term extrapolation of the observed GO29365 data with a manageable uncertainty in the parameter estimates. Scenario analyses indicated that assuming long-term remission rates "significantly" different from those estimated in the revised base-case resulted in implausible fits and extrapolations. Among the standard parametric models, assuming a Generalised Gamma distribution for PFS and OS provided the most plausible option. The cost-effectiveness results for all these scenarios are reported in Table 8. .

Table 4. Five-year model predictions for base case and scenarios (COO March 2019)

Scenario	Pola+BR PFS	Pola+BR OS	BR PFS	BR OS
Revised company base case	20.9%	22.4%	6.9%	7.7%
External CMM – (Pola-BR 22%, BR 10%)	20.0%	21.7%	8.9%	10.3%
External CMM – (Pola-BR 20%, BR 8%)	18.5%	20.6%	7.3%	9.0%
External CMM – (Pola-BR 24%, BR 6%)	21.6%	23.0%	5.7%	7.9%
Standard Generalized Gamma PFS and OS	15.8%	18.8%	3.3%	6.6%
Hybrid model (Generalized Gamma PFS and OS)	19.8%	19.8%	6.3%	7.3%
Hybrid model (Log-Normal PFS and Gen. Gamma OS)	16.1%	18.8%	4.6%	6.6%

Change-point model	14.6%	23.3%	8.0%	10.0%

Source: Table 6 in company's appendix to ACD response.[3]
Abbreviations: BR, bendamustine + rituximab; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab
Note: The standard Gompertz extrapolation did not converge. PFS values for this extrapolation are therefore not presented.

ERG comment: The ERG refers to Section 4 of this document for overall conclusions.

2.5 Validation of in-house cure model

The company also validated the results of their in-house code against alternative software packages in simplified scenarios. The results shown in Table 4 of the company's appendix to the ACD response, indicate a close match between the estimated CMM parameters regardless of whether the code used was in R or STATA.[2] The company is, therefore, confident that the method described by Lambert was correctly implemented in their in-house R code.[3]

ERG comment: Whereas, as indicated in the ERG report, some aspects of the in-house code remain unclear, with this validation exercise shown by the company the ERG has gained confidence in the in-house code used by the company.

2.6 Revised cost effectiveness analyses

In response to the ACD, the company revised their base-case, which is summarised in Table 5. Overall, the company preferred assumptions are aligned to the ERG's/committee preferences.[3, 5] The only difference between the company and ERG approaches is the method chosen to extrapolate PFS and OS. However, as explained in the next section of this addendum, this choice has a substantial impact on the incremental cost effectiveness ratio (ICER).

Table 5. Revised company base-case assumptions

Input	Assumption	Justification	Changed with respect to TE/ACM
Data set	Inclusion of covariate adjusted PFS and OS data from the GO29365 March 2019 data cut	Appropriate according to ACD.	No
PFS and OS extrapolation models	PFS and OS are extrapolated using cure-mixture modelling with the Log-Normal function. Mixture modelling for OS informed by PFS. PFS-IRC was the selected outcome.	Log-Normal cure-mixture models provides statistically better fits that reduce probabilistic uncertainty while providing similar visual fit and long-term extrapolations compared to other plausible models.	Yes
Background mortality distribution	ERG single age (69 years) cohort.	Committees preferred assumption in ACD.	Yes
Background mortality adjustment	An increased relative risk of mortality of 1.41 for long-term survivors applied to model excess	As per technical engagement response	No

	mortality compared to the general population.	A conservative assumption by the ERG reflecting an increased risk of mortality for long-term survivors.	
Survival limited by background mortality	Survival limited by general population mortality for all scenarios. Conditional background survival was used rather than OS.	ERG amendment to the model at clarification stage. More conservative restriction than ERG to assure transition probability to death is always at least adjusted background value.	Yes
Time point for assuming background cost and QALYs for long-term remission	HRQoL and costs of patients in PFS health state equivalent to age- and sex-matched general population after 3 years.	The ERG's preferred assumption given the uncertainty surrounding the costs and HRQoL of long-term survivors.	No
Vial size scenarios	Calculated treatment costs according to vial sizes of 140 mg with no vial sharing.	Based on the PAS, vial sizes of 30 mg and 140 mg will have the same acquisition costs and ICERs.	No
PAS for polatuzumab vedotin	PAS prices	As above. PAS approved after 1st ACM.	No
Number of maximum cycles for Pola+BR or BR	Assumed a maximum of 6 cycles of Pola+BR and BR were received in the model.	Appropriate according to ACD.	No
AE incidence	All AEs reported as Grade 3 and above in the company submission, wherever possible.	As per technical engagement and ERGs amendment.	No
Subsequent treatment cost	The costs for post-progression SCT were included in the model	ERG preferred assumption.	No

Source: Table 1 in company's appendix to ACD response.[3]

Abbreviations: ACM, Appraisal Committee Meeting; AE, adverse event; BR, bendamustine with rituximab; Pola+BR, polatuzumab vedotin with bendamustine and rituximab; EMA, European Medicines Agency; ERG, Evidence Review Group; HRQoL, health-related quality of life, ICER, incremental cost-effectiveness ratio; IRC, independent review committee; NA, not applicable; PAS, patient access scheme; PFS, progression free survival; OS, overall survival; SCT, stem cell transplant; TE, Technical Engagement; TTOT, time-to-off-treatment; QALY, Quality Adjusted Life Years

2.6.1 Base case incremental cost-effectiveness analysis results.

The company's revised base-case cost effectiveness results are summarised in Table 6. These results indicated that pola+BR was more costly and more effective than BR, with [redacted] incremental QALYs and

£[redacted] incremental cost compared to BR. This resulted in an ICER of £31,808 per QALY gained. The base-case results were based on the patient access scheme (PAS) cost price of polatuzumab.

Table 6. Revised base case deterministic results (with PAS)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (Δ£/ΔQALY)
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	31,808
BR	18,471	1.55	[redacted]	-	-	-	-

Source: Table 7 in company's appendix to ACD response.[3]

Abbreviations: BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; Pola+BR, polatuzumab + bendamustine + rituximab; QALYs, quality-adjusted life years

2.6.2 Sensitivity and scenario analyses

Probabilistic sensitivity analysis

The input parameters, with their corresponding probability distributions, included in the probabilistic sensitivity analysis (PSA) are shown in Table 8 of the company's appendix to ACD response.[3] The probabilistic results, based on 1,000 Monte Carlo simulations, are summarised in Table 7. The probabilistic ICER was £36,337 per QALY gained (incremental costs were [redacted] and incremental QALYs were [redacted]), thus, £4,529 larger than the deterministic ICER. The resulting cost effectiveness plane (CE-plane) and cost effectiveness acceptability curve (CEAC) can be seen in Figures 12 and 13, respectively. The CEAC shows that the probability of pola+BR being cost effective was 82% at a threshold ICER of £50,000 per QALY gained.

Table 7 Mean probabilistic results

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (Δ£/ΔQALY)
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36,337
BR	27,729	2.04	[redacted]	-	-	-	-

Source: Table 9 in company's appendix to ACD response.[3]

Abbreviations: BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola+BR, polatuzumab + bendamustine + rituximab; QALYs, quality-adjusted life years

Figure 12. Cost-effectiveness plane for Pola+BR versus BR

Source: Figure 13 in company's appendix to ACD response.[3]
Abbreviations: BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab; QALY, quality-adjusted life year

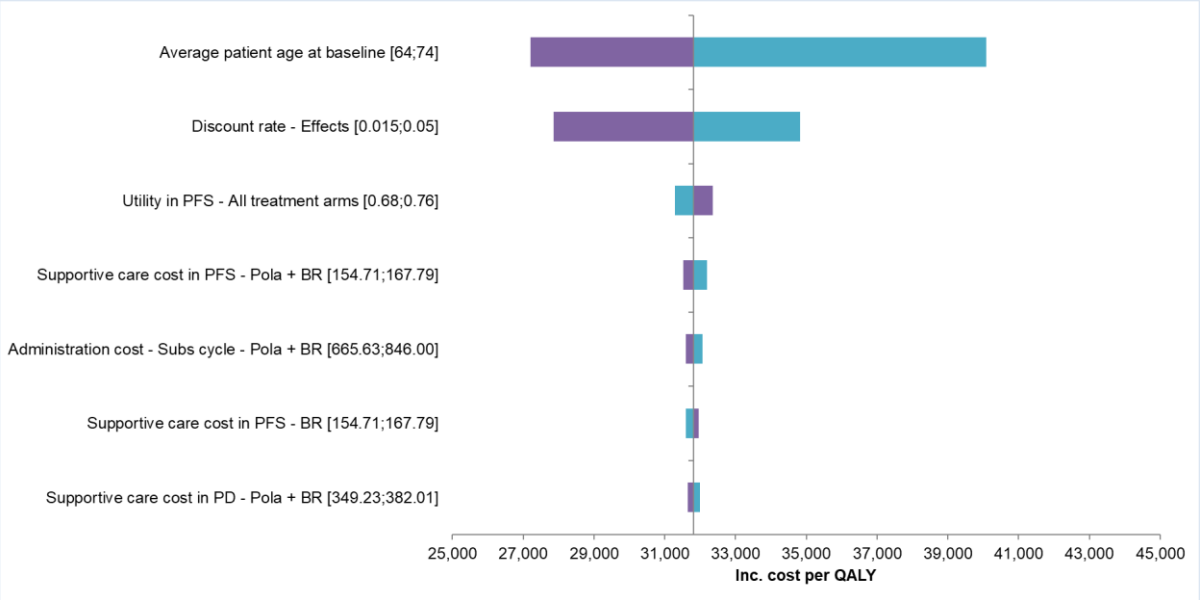
Figure 13. Cost-effectiveness acceptability curve for Pola+BR versus BR

Source: Figure 14 in company's appendix to ACD response.[3]
Abbreviations: BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab; WTP, willingness to pay

Deterministic sensitivity analysis

A detailed summary of the input parameter values and the corresponding ICERs obtained in the univariate, deterministic sensitivity analysis (DSA) performed by the company can be found in Table 10 of the company's appendix to ACD response.[3] Figure 14 shows the tornado diagram of the 7 most influential parameters according to the DSA. This shows that the largest impact on the ICER was caused by variation in the estimate for the patient age at baseline and the discount rate on health effects. In all scenarios the ICER was below £50,000 per QALY gained.

Figure 14. Deterministic sensitivity analysis – tornado diagram of influential parameters for Pola+BR versus BR



Source: Figure 15 in company's appendix to ACD response.[3]
Abbreviations: BR, bendamustine + rituximab; PD, progressed disease; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab; QALY, quality-adjusted life year

ERG comment: It should be noted that parameters such as discount rates are usually not included in the DSA. Furthermore, it seems that the input parameters related to the extrapolation of OS and PFS curves are not included in the DSA, although these are expected to have the largest impact on the ICER. Therefore, the results of the DSA should be interpreted with caution.

Scenario analysis

Additionally, the company conducted seven scenario analyses to assess the impact of assuming different forms of OS and PFS survival distributions on the cost effectiveness results. All these scenarios were run on the adjusted data set with the March 2019 data cut. The results of the scenario analyses are shown in Table 8. All scenarios, except the one assuming external cure rates of 24% for Pola+BR and 6% for BR, resulted in ICERs that were larger than in the base-case, ranging from £29,351 to £45,247 per QALY gained.

Table 8. Scenario analysis results

Scenario	LY Pola+BR	LY BR	Incremental LY	Incremental costs (£)	Incremental QALYs	ICER (Δ£/ΔQALY)
Base case	[redacted]	1.55	[redacted]	[redacted]	[redacted]	31,808
External CMM – (Pola-BR 22%, BR 10%)	[redacted]	1.84	[redacted]	[redacted]	[redacted]	39,015
External CMM – (Pola-BR 20%, BR 8%)	[redacted]	1.70	[redacted]	[redacted]	[redacted]	38,873
External CMM – (Pola-BR 24%, BR 6%)	[redacted]	1.57	[redacted]	[redacted]	[redacted]	29,351
Standard Generalized Gamma	[redacted]	1.43	[redacted]	[redacted]	[redacted]	35,510
Hybrid with Generalized Gamma for PFS and OS	[redacted]	1.67	[redacted]	[redacted]	[redacted]	33,919
Hybrid with Log-Normal for PFS and Generalized Gamma for OS	[redacted]	1.54	[redacted]	[redacted]	[redacted]	37,678
Change-point model	[redacted]	1.68	[redacted]	[redacted]	[redacted]	45,247

Source: Table 13 in company's appendix to ACD response.[3]
Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; Pola+BR, polatuzumab + bendamustine + rituximab; PFS, progression-free survival; OS, overall survival; QALY, quality-adjusted life year

ERG comment: The ERG refers to Section 3 of this addendum for additional scenarios.

3. Exploratory and sensitivity analyses undertaken by the ERG

3.1 ERG preferred base-case analysis after Technical Engagement

The results of the ERG base-case analysis after Technical Engagement are shown in Table 9.

Table 9. ERG base-case deterministic results (with PAS) – after Technical Engagement

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,540
BR	25,162	[redacted]	[redacted]	-	-	-	-

Source: Table 1 in Addendum 1 to the ERG report (after Technical Engagement).[13]

BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola+BR, polatuzumab + bendamustine + rituximab; QALYs, quality-adjusted life years

As shown in Table 5, the company's and ERG's preferred assumptions are now closely aligned, except for the choice of PFS and OS extrapolation models: the company extrapolated PFS and OS using CMM with the Log-Normal function, and the ERG assumed an independent generalised gamma distribution for OS and an independent lognormal distribution for PFS.[13] With the current version of the model, also received in response to the ACD, modelling OS and PFS according to the ERG's preferred choice (at Technical Engagement) resulted in an ICER of £48,837 per QALY gained, as shown in Table 10. Note a small difference of less than £1,000 between the ICERs in Tables 9 and 10, most likely due to the latest changes made by the company, the nature of which could not be determined by the ERG.

Table 10. ERG base-case deterministic results (with PAS) – after Technical Engagement with revised model version

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	48,837
BR	25,026	[redacted]	[redacted]	-	-	-	-

Source: Electronic model in response to ACD.[14]

BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola+BR, polatuzumab + bendamustine + rituximab; QALYs, quality-adjusted life years

Thus, the ERG preferred methods for extrapolating PFS and OS resulted in a base-case ICER that is approximately £17,000 larger than the company's base-case. However, the ERG's approach to survival modelling was criticised during the ACM and this was deemed as uncertain by the committee (see ACD Section 3.9).[1] In particular, the "*committee noted that the ERG's analyses did not capture the potential cure aspect of the disease and therefore it may be conservative in its interpretation of the evidence*". Furthermore, the committee "*was concerned that the proportion of people predicted to be alive at 5 or 10 years was substantially higher than the proportion predicted to be progression free at the same time points, indicating that some patients had long-term survival with progressed disease. The committee considered that this was not consistent with the comments from clinical experts that survival is associated with an ongoing complete response. The committee concluded that the mismatch between the predictions for progression-free survival and overall survival creates uncertainty about the robustness of the extrapolations*".[1] Because, as explained in previous sections of this document, the ERG is still concerned about the lack of robust long-term evidence to support the cure assumption, the ERG considers that, with the current data, using standard independent parametric survival modelling to

extrapolate PFS and OS is the most appropriate approach, despite its acknowledged limitations. In the next section, the ERG explored alternative scenarios to assess whether the current uncertainty associated to the ERG's and company's approach to survival modelling could be reduced.

3.2 ERG exploratory analysis after ACM

The following scenarios were explored by the ERG:

- ERG scenario 1- Exponential CMM: The Exponential model provided the lowest BIC value and similar AIC to the other models. The visual fit (according to the company) is reasonable. Reducing parameter uncertainty was one of the criteria used by the company to select the Log-Normal distribution over the Generalised Gamma – the Exponential CMM is the simplest form of distribution.
- ERG scenario 2 – lower external remission rates: The company has shown that assuming a lower difference in long-term remission rates than in their revised base-case resulted in implausible scenarios. The ERG explored in this scenario the impact on the ICER of keeping the difference in long-term remission rates as in the company's revised base-case but decreasing both individual rates per arm (external cure rates 20% Pola+BR and 6% BR).
- ERG scenario 3 – higher external remission rates: Same as ERG scenario 2 but increasing both individual rates per arm (external cure rates 24% Pola+BR and 10% BR).
- ERG scenario 4 – standard parametric modelling Log-logistic OS: The only scenario assuming standard parametric extrapolations explored by the company assumed a Generalised Gamma distribution for both PFS and OS. In this scenario, the difference in 5-year PFS and OS rates is smaller, which minimised the main committee concern regarding the ERG's preferred assumption (see ACD Section 3.9).[1] However, this difference in 5-year PFS and OS rates becomes even smaller when the Log-logistic distribution is chosen to extrapolate OS.
- ERG scenario 5 – standard parametric modelling Log-normal OS: Same as ERG scenario 4 but assuming a standard Log-normal distribution for OS.

The cost effectiveness results of these scenarios are summarised in Table 11. Assuming an Exponential CMM instead of a Log-Normal CMM increased the ICER by £1,738 due to a small increase in incremental costs and a small decrease in incremental QALYs caused by the Exponential extrapolation. When lower or higher long-term remission rates (but keeping the difference as in the company's revised base-case) were assumed in ERG scenarios 2 and 3, the ICERs were approximately £35,000 in both cases; thus, more than £3,000 larger than the company's revised base-case ICER. However, by looking at the ratio of hazards in Figures 15 and 16, the ERG is uncertain whether these scenarios would be deemed as plausible by the company.

The committee's main concern with the survival modelling approach selected by the ERG was that "*the proportion of people predicted to be alive at 5 or 10 years was substantially higher than the proportion predicted to be progression free at the same time points, indicating that some patients had long-term survival with progressed disease*" (see ACD Section 3.9).[1] The ERG approach predicted 6.6% of patients in OS and 1.8% of patients in PFS at year 5 (4.8% gap between OS and PFS) in the BR arm. As explained in Section 2.3, the company considered that only assuming a Generalized Gamma distribution for both PFS and OS would result in plausible long-term extrapolations. In this scenario, the difference in 5-year PFS and OS rates is smaller: 6.6% of patients in OS and 3.3% of patients in PFS at year 5 (3.3% gap between OS and PFS) in the BR arm. Therefore, the ERG agrees with the company that this scenario addresses partially the committee's concern regarding the ERG's preferred assumption. However, it should be noted that PFS at year 5 for the BR arm is still below the range

provided by clinical experts of 5%-10%. The OS prediction falls within this range. The ERG noticed that PFS at year 5 for the BR arm is indeed the highest (3.31%) when a Generalised Gamma distribution is assumed for PFS. However, if a Log-normal distribution is assumed for OS, the model predicts 5.22% of patients in OS and 3.3% of patients in PFS at year 5 (1.92% gap between OS and PFS) in the BR arm. When a Log-logistic distribution is assumed for OS, the model predicts 5.09% of patients in OS and 3.27% of patients in PFS at year 5 (1.82% gap between OS and PFS) in the BR arm. Thus, in both scenarios the estimated PFS at year 5 for the BR arm is still below the range provided by clinical experts, but the OS prediction falls within the 5%-10% range and with a smaller OS/PFS gap than with a generalised gamma OS. Therefore, these scenarios may also partially address the committee's concern regarding the ERG's preferred assumption of extrapolating survival using standard parametric distributions. In these two scenarios, the ICERs were £47,796 and £49,744, thus, more in line with the ERG preferred base-case after technical engagement, as shown in Table 10.

Table 11. ERG scenario analysis results

Scenario	LY Pola+BR	LY BR	Incremental LY	Incremental costs (£)	Incremental QALYs	ICER (Δ£/ΔQALY)
Base-case (company)	[redacted]	1.55	[redacted]	[redacted]	[redacted]	31,808
ERG scenario 1	[redacted]	1.66	[redacted]	[redacted]	[redacted]	33,546
ERG scenario 2	[redacted]	1.57	[redacted]	[redacted]	[redacted]	35,279
ERG scenario 3	[redacted]	1.84	[redacted]	[redacted]	[redacted]	35,159
ERG scenario 4	[redacted]	1.29	[redacted]	[redacted]	[redacted]	47,796
ERG scenario 5	[redacted]	1.30	[redacted]	[redacted]	[redacted]	49,744

Source: electronic model submitted with ACD response.[14]
Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; Pola+BR, polatuzumab + bendamustine + rituximab; OS, overall survival; QALY, quality-adjusted life year
ERG scenario 1 = Exponential cure-mixture model; ERG scenario 2 = external cure rates 20% Pola+BR and 6% BR; ERG scenario 3 = external cure rates 24% Pola+BR and 10% BR; ERG scenario 4: standard Log-logistic OS; ERG scenario 5: standard Log-normal OS

Figure 15. Ratio of hazards (PFS and OS) to adjusted background for external long-term remission – ERG scenario 2 (20.0% and 6.0%)

Source: electronic model in company's ACD response.[14]
Abbreviations: BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab

Figure 16. Ratio of hazards (PFS and OS) to adjusted background for external long-term remission – ERG scenario 3 (24.0% and 10.0%)

Source: electronic model in ACD response.[14]
Abbreviations: BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab

4. ERG conclusions

The following issues discussed during the Appraisal Committee Meeting that are relevant for this Addendum document and reported in the ACD are summarised below:[1]

1. There is a lack of robust long-term evidence on remission and cure (issue 3.7 in ACD).
2. The results of the company's cure-mixture model are highly uncertain (issue 3.8 in ACD).
3. The ERG's standard parametric survival modelling is uncertain (issue 3.9 in ACD).

As explained throughout this document, the ERG considers that with the new evidence submitted by the company, these issues are likely to remain unresolved because of the following reasons:

- The ERG is still uncertain about the validity both in terms of fit to the observed data and the plausibility of the long-term extrapolations. This does not only concern cure-mixture models but all survival modelling in general given the small sample size in GO29365 and the limited number of events.
- Regarding cure-mixture (and hybrid) models, the ERG would like to emphasise that assuming a cure model needs two main prerequisites from the data: 1) identifiability of the cure fraction, and 2) sufficient follow-up. The ERG considers that given the small sample size in GO29365 and that the potential cure fraction in this study may be small, longer follow-up may be required.
- The ERG feels that it is crucial to clearly define the criteria as to which one scenario is deemed plausible or not. At this point this remains unclear and often inconsistent (different criteria seem to have been used in different sections of this document).
- The ERG considers that the company have not provided any clear criteria that can be used to assess whether their base-case (or any other) long-term extrapolation is plausible or not.
- As mentioned in the ERG report, the ERG considers that the company could have explored other survival modelling options in addition to cure mixture modelling (e.g. flexible parametric modelling using splines, landmark models based on response, cure non-mixture models or other mixture modelling methods than cure). Another option could be using external data if these were available.[15] However, it is uncertain whether these models or using external data will resolve any of the issues mentioned above.

In summary, the ERG concluded that, with the current data, the results of fitting cure-mixture (and other survival) models to them would be very uncertain. Since the company did not present new data in their ACD response, the committee and ERG concerns remain unresolved. The ERG agrees with the company that further data collection is needed to address the remaining uncertainty.

5. References

[1] National Institute for Health and Care Excellence. *Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma. Appraisal consultation document [Internet]*. London: NICE, 2020 [accessed 20.4.20] Available from: https://www.nice.org.uk/guidance/GID-TA10463/documents/129

[2] Roche Products Ltd. *Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [ID1576]: Consultation on the appraisal consultation document*: Roche Products Ltd, 2020

[3] National Institute for Health and Care Excellence. *Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [ID1576]. Single technology appraisal. Appendix to ACD response*. London: NICE, 2020

[4] Howlader N, Mariotto AB, Besson C, Suneja G, Robien K, Younes N, et al. Cancer-specific mortality, cure fraction, and noncancer causes of death among diffuse large B-cell lymphoma patients in the immunochemotherapy era. *Cancer* 2017;123(17):3326-34.

[5] Armstrong N, Büyükkaramikli N, Penton H, Fayter D, Wetzelaer P, Corro Ramos I, et al. *Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma: a Single Technology Assessment*. York: Kleijnen Systematic Reviews Ltd, 2019

[6] Maurer MJ, Ghesquieres H, Jais JP, Witzig TE, Haioun C, Thompson CA, et al. Event-free survival at 24 months is a robust end point for disease-related outcome in diffuse large B-cell lymphoma treated with immunochemotherapy. *J Clin Oncol* 2014;32(10):1066-73.

[7] Maurer MJ, Habermann TM, Shi Q, Schmitz N, Cunningham D, Pfreundschuh M, et al. Progression-free survival at 24 months (PFS24) and subsequent outcome for patients with diffuse large B-cell lymphoma (DLBCL) enrolled on randomized clinical trials. *Ann Oncol* 2017;29(8):1822-7.

[8] National Institute for Health and Care Excellence. *Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [TA567]*: NICE, 2019. 25p. Available from: https://www.nice.org.uk/guidance/ta567

[9] National Institute for Health and Care Excellence. *Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies [TA559]*: NICE, 2019. 31p. Available from: https://www.nice.org.uk/guidance/ta559

[10] Yu XQ, De Angelis R, Andersson TM, Lambert PC, O'Connell DL, Dickman PW. Estimating the proportion cured of cancer: some practical advice for users. *Cancer Epidemiol* 2013;37(6):836-42.

[11] National Institute for Health and Care Excellence. *Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [TA567]*, 2019

[12] National Institute for Health and Care Excellence. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies [TA559]. 2019.

[13] Armstrong N, Büyükkaramikli N, Penton H, Fayter D, Wetzelaer P, Corro Ramos I, et al. *Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma: a Single Technology Assessment. Addendum 1*. York: Kleijnen Systematic Reviews Ltd, 2020

[14] Roche Products Ltd. Cost-effectiveness AUC model polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [ID1576] ACIC. v1.0 [Excel]. Roche Products Ltd, 2019.

[15] Jackson C, Stevens J, Ren S, Latimer N, Bojke L, Manca A, et al. Extrapolating survival from randomized trials using external data: a review of methods. *Med Decis Making* 2017;37(4):377-90.

Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma

21st May 2020

Dear Company,

Following the 2nd committee meeting for the appraisal of polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma on 12th May 2020, the committee have requested further information to aid their decision-making.

The committee reached the conclusion that the cure mixture model used in your base case was not appropriate for decision-making. It considered that the estimate of a cure rate is highly uncertain and it was not persuaded therefore that there is sufficient evidence to justify assuming a cured proportion from the outset of the model.

The committee preferred a standard parametric model, noting that this would also capture long-term survival. It noted that the ERG's base case analysis assumed a generalised gamma distribution for overall survival and a log-normal distribution for progression-free survival whereas your standard parametric scenario analysis assumed a generalised gamma distribution for both progression-free survival and overall survival. The committee noted that there was a substantial difference in the ICERs estimated from these models, and that the ERG's probabilistic base case ICER was above the range normally considered a cost-effective use of NHS resources for life-extending treatments at the end-of-life. It was unclear what was driving the difference between the two models, especially as both models predicted similar clinical benefit for polatuzumab compared with standard BR therapy.

The committee also noted that the probabilistic ICER for your standard parametric scenario analysis had not been presented in your response to the appraisal consultation document. It agreed that in order to understand the

uncertainty around the ICER, it was necessary to see both the probabilistic and deterministic analyses using a parametric modelling approach.

The committee noted that the ERG's cost-effectiveness results using the most recent version of the model (in particular the probabilistic results) were lower than those from the model after technical engagement. The ERG indicated that the reasons for this were unclear. Therefore, the committee seeks further information on any changes to the model between the 1st and 2nd committee meetings which might explain this.

The committee was also aware that a recent data cut was available, for which it has seen survival data. It heard that there was [redacted]. The committee agreed that inclusion of the most recent data cut in the economic model may help to reduce uncertainty around the estimate.

Given the above points, the committee kindly request that you provide the following:

1. An explanation for the differences in the ICERs between the company's standard parametric generalised gamma model (presented as a scenario analysis in your response to the appraisal consultation document) and the ERG's base case standard parametric model. Please also provide an explanation for the differences in ICERs between your standard parametric model and the ERG's scenario analyses 4 and 5 which use the log-logistic and log-normal parametric distributions for overall survival.

2. A probabilistic analysis of your standard parametric generalised gamma model, and for the parametric models considered by the ERG.

3. A log of the changes made to the economic model submitted in response to the appraisal consultation document.

4. If available, updated deterministic and probabilistic analyses using the latest data cut for your standard parametric generalised gamma model and for the parametric models considered by the ERG.

Please let us know the date by which you could supply this information and we will arrange a further committee discussion at the earliest opportunity. Please do not hesitate to contact me if you have any questions.

Kind regards,
Janet Robertson

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

ID1576: Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma

Response to information requested after 2nd ACM

File name	Version	Contains confidential information	Date
ID1576_Polatuzumab vedotin RR DLBCL_ ACD Addendum 2 290520 [ACIC]	**1**	**Yes [redacted]**	**29 May 2020**

Contents

Figures

Tables

Summary

In this response to the request for further information on standard parametric scenarios after the 2nd committee meeting the model was updated by adding the standard model extrapolations fitted to the latest [redacted] data cut. Results are based on this data cut unless otherwise indicated[1]. The main impact on updating to the latest data cut was mainly to increase OS predictions in the ERG Scenarios 4 and 5 from the 2nd committee meeting, getting closer to the company's preferred Generalised Gamma scenario. In addition to the probabilistic analyses presented below, using the standard approach implemented in the model, we have also explored an alternative bootstrapping approach to quantify uncertainty around OS and PFS extrapolations that demonstrates that the standard approach may overestimate the uncertainty.

We have revised our PAS offer to [redacted] net price per 140mg ([redacted]% discount) vial (before 30mg availability) and [redacted] net price per 140mg and [redacted] per 30mg vial ([redacted]% discount). Unless stated otherwise, ICERs and cost values reported are based on the revised PAS offer.

As shown in the summary Table 1 below, all deterministic and probabilistic scenarios result in ICERs below £50,000/QALY based on the [redacted] data cut.

Table 1 Summary of cost-effectiveness results for standard parametric model scenarios ([redacted] cut-off date)

Scenario	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Company standard parametric model, deterministic	[redacted]	[redacted]	[redacted]	35,663
Company standard parametric model, probabilistic	[redacted]	[redacted]	[redacted]	40,929
ERG base case, deterministic	[redacted]	[redacted]	[redacted]	47,101
ERG base case, probabilistic	[redacted]	[redacted]	[redacted]	48,839
ERG Scenario 4, deterministic	[redacted]	[redacted]	[redacted]	43,359
ERG Scenario 4, probabilistic	[redacted]	[redacted]	[redacted]	48,269
ERG Scenario 5, deterministic	[redacted]	[redacted]	[redacted]	44,347
ERG Scenario 5, probabilistic	[redacted]	[redacted]	[redacted]	48,052

[1] *Only standard parametric models for PFS-IRC and OS were updated based on the adjusted ITT population as per the committees preferred analysis at ACD.*

Table 2 Summary of cost-effectiveness results for standard parametric model scenarios (March 2019 cut-off date)

Scenario	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Company standard parametric model, deterministic	[redacted]	[redacted]	[redacted]	34,205
Company standard parametric model, probabilistic	[redacted]	[redacted]	[redacted]	39,706
ERG base case, deterministic	[redacted]	[redacted]	[redacted]	47,469
ERG base case, probabilistic	[redacted]	[redacted]	[redacted]	48,452
ERG Scenario 4, deterministic	[redacted]	[redacted]	[redacted]	46,032
ERG Scenario 4, probabilistic	[redacted]	[redacted]	[redacted]	50,049
ERG Scenario 5, deterministic	[redacted]	[redacted]	[redacted]	47,928
ERG Scenario 5, probabilistic	[redacted]	[redacted]	[redacted]	50,106

Further details on the differences between the scenarios and any changes made to the model submitted in response to technical engagement are in the sections below.

Standard parametric model scenarios

The company's preferred standard parametric model is to use the Generalized Gamma function for PFS and OS. We had commented on the reasons for this in our response to the ACD which are summarised below:

1. The Generalised Gamma function is the most flexible standard parametric model and provides visually the best fit to the observed data. The Generalised Gamma function contains other distributions, such as the Log-Normal, as a special case (1). It is therefore suited to model the observed behaviour which consists of a significant decline of hazard of progression and/or death over time, especially with most progression events occurring before 12-24 months. The models for PFS and OS score high in BIC/AIC statistics, although the differences to other models are less than 5 and therefore alternative models can't be ruled out based on AIC/BIC only. Alternative models, such as Long-Normal, appear to underestimate progression free survival (Figure 1) and survival (Figure 2) at the end of the follow up period.

2. The Generalised Gamma extrapolation provides the most clinically plausible long-term extrapolation for PFS and OS. According to clinical experts it is expected that a significant proportion of patients who remain in remission at 2 years would not progress by 5 years and that survival approaches the population norm, subject to

adjustment for and remaining increased risk. In the appraisals for CAR-T technologies this was deemed to occur between 2 and 5 years after treatment (2, 3).

Table 3 below summarises the key clinical predictions for the relevant scenarios as discussed below.

Table 3 Standard parametric model predictions Pola-BR ([redacted])

Scenario	Model 2-year remission rate (PFS)	Model 5-year remission rate (PFS)	Model % year survival rate (OS)	Proportion of patients in PSA at 2 years progressing or dying by 5 years	Ratio of hazard of death to adjusted population norm at 5 years
Company standard model	26%	15%	21%	44%	3
ERG base case	25%	9%	21%	65%	3
ERG Scenario 4	26%	15%	16%	44%	5
ERG Scenario 5	26%	15%	17%	44%	5

Difference between the company's preferred standard model and the ERG's base case

The ERGs base case assumed a Log-Normal function for PFS and a Generalized Gamma distribution for OS, whereas the Company's preferred standard parametric model use Generalised Gamma functions for PFS and OS. As shown in Figure 1 the Log-Normal model seems to overestimate PFS initially and then underestimate PFS as observed from 20 months. As shown in Table 3, the Long-Normal functions for PFS predicts that almost 2/3 (65%) of patients in remission at 2 years would progress or die by 5 years. The company is of the opinion this is not plausible based on the natural history of the disease as confirmed by clinical experts and the assumptions made in the appraisals of CAR-Ts CAR-T technologies (2, 3). On the other hand, the Generalised Gamma model predicts that about 44% that are in remission at 24 months would progress and die.

Figure 1 PFS-IRC extrapolation with Generalised Gamma (Company) or Log-normal (ERG base case); [redacted] cut.

In the ERGs base case the Generalised Gamma function is used to extrapolate OS therefore, incremental life-years gained would be the same between models. However, the ERGs base case estimates that majority of patients alive at 5 years is expected to be in the progressed disease state leading the committee to conclude that the ERGs approach was not robust at the first ACM.

As one significant difference between the PFS and progressed health state are the supportive care costs. These are significantly higher in the progressed disease state than in PFS. Therefore, significant higher post progression costs accrue in the Pola-BR arm compared in the ERGs base case model with an incremental costs in progressed disease of £13,465 compared to the company's preferred model of £2,413 ([redacted]). Whereas incremental QALYs are slightly lower in the ERGs base case compared to the company model, the incremental costs are however the main driver for the difference in ICER (see Table 4 and Table 5).

Difference between the company's preferred standard model and the ERG's scenarios 4 and 5

In the ERG Scenarios 4+5 Log-Logistic or Log-Normal functions are used for OS extrapolation compared to Generalised Gamma in the company's standard parametric model scenario.

As discussed above, the company is of the view that Log-Normal or Log-Logistic functions tend to underestimate long-term OS in this situation as they over-estimate long-term mortality hazard (Figure 2 below and Table 3). While the mortality is initially high due to a high proportion of patients in the progressed disease state, mortality is expected to decline significantly in the long-term when essentially only patients with long-term remission remain in the cohort. As the parametric functions are fitted over the entire follow up period, where overall mortality is still high, Log-Normal and Log-Logistic tend to overestimate OS before 2 years and then underestimate OS from 2 years onwards. A generalised Gamma model provides similar AIC/BIC statistics and a better visual fit.

Figure 2 OS extrapolation with Generalised Gamma (Company) or Log-Logistic and Log-normal (ERG Scenario 4+5) ([redacted])

For the Log-Norma and Log-Logistic OS extrapolations, the hazard of death at 5 years, for example, remains at approximately 5 times the adjusted population norm. This seems implausible given the natural history of the disease reported by experts and in CAT-T

appraisals, in particular, since virtually all patients would be in PFS state in these modelling scenarios, i.e., in remission for 5 years. On the other hand, the Generalised Gamma OS extrapolation results in a hazard of death 3 times above adjusted population norm. This may also be too conservative, however, approximately 1/3 of patients are in the progressed disease state at 5 years in this model scenario (Table 3).

We also like to note that the main impact on updating to the latest data cut ([redacted]) was mainly to increase OS predictions in Scenario 4 and 4 getting closer to the Generalised Gamma scenario. This could indicate that with longer follow up time, the range of predictions with alternative function may narrow further.

Probabilistic analyses results

Probabilistic analyses for all scenarios are presented below for all standard parametric scenarios discussed for the two latest data cuts, i.e. March 2019 and [redacted].

For each scenario we present the deterministic and probabilistic costs, QALYs, incremental costs and QALYs and resulting ICERs.

We present cost-effectiveness acceptability curves for all scenarios. Values were generated with 3000 simulations.

Table 4 Company standard model results ([redacted])

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Pola+BR	[redacted]	[redacted]	[redacted]	_	_	_	
BR	25,970	1.66	1.14	[redacted]	[redacted]	[redacted]	35,663
Probabilistic							
Pola+BR	[redacted]	[redacted]	[redacted]	_	_	_	
BR	29,485	1.85	1.26	[redacted]	[redacted]	[redacted]	40,929

Figure 3 Company standard model - Cost-effectivness acceptability curve ( )

Probability of being cost effective at a willingness to pay of £50,000/QALY is %.

Table 5 ERG base case results ( )

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Pola+BR							
BR	29,319	1.66	1.13				47,101
Probabilistic							
Pola+BR							
BR	32,810	1.85	1.25				48,839

Figure 4 ERG base case - Cost-effectivness acceptability curve ( )

Probability of being cost effective at a willingness to pay of £50,000/QALY is %.

Table 6 ERG Scenario 4 results ([redacted])

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Pola+BR	[redacted]	[redacted]	[redacted]	-	-	-	
BR	20,498	1.37	0.95	[redacted]	[redacted]	[redacted]	43,359
Probabilistic							
Pola+BR	[redacted]	[redacted]	[redacted]	-	-	-	
BR	21,977	1.42	0.98	[redacted]	[redacted]	[redacted]	48,269

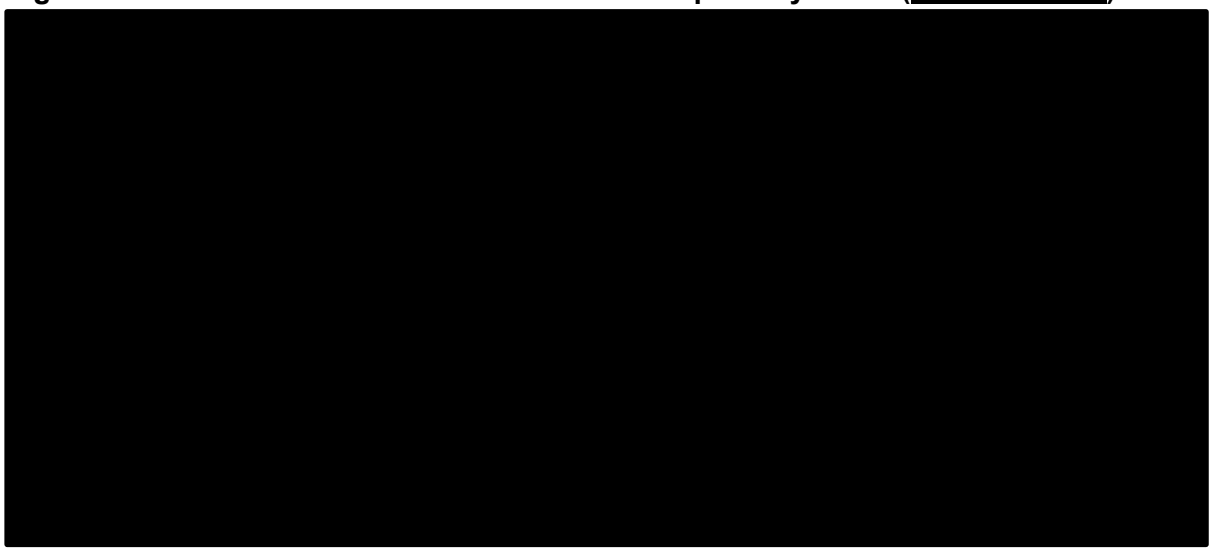
Figure 5 ERG Scenario 4 - Cost-effectivness acceptability curve ([redacted])

Probability of being cost effective at a willingness to pay of £50,000/QALY is [redacted]%.

Table 7 ERG Scenario 5 results ([redacted])

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Pola+BR	[redacted]	[redacted]	[redacted]	-	-	-	
BR	21,277	1.40	0.97	[redacted]	[redacted]	[redacted]	44,347
Probabilistic							
Pola+BR	[redacted]	[redacted]	[redacted]	-	-	-	
BR	22,908	1.45	1.00	[redacted]	[redacted]	[redacted]	48,052

Figure 6 ERG Scenario 5 - Cost-effectivness acceptability curve ([redacted])



Probability of being cost effective at a willingness to pay of £50,000/QALY is [redacted]%.

Table 8 Company standard model results (March 2019)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Pola+BR	[redacted]	[redacted]	[redacted]	-	-	-	
BR	22,585	1.43	0.99	[redacted]	[redacted]	[redacted]	34,205
Probabilistic							
Pola+BR	[redacted]	[redacted]	[redacted]	-	-	-	
BR	26,449	1.63	1.12	[redacted]	[redacted]	[redacted]	39,706

Figure 7 Company standard model - Cost-effectivness acceptability curve (March 2019)

Probability of being cost effective at a willingness to pay of £50,000/QALY is [redacted]%.

Table 9 ERG base case results (March 2019)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Pola+BR	[redacted]	[redacted]	[redacted]	-	-	-	
BR	25,026	1.43	0.98	[redacted]	[redacted]	[redacted]	47,469
Probabilistic							
Pola+BR	[redacted]	[redacted]	[redacted]	-	-	-	
BR	28,742	1.62	1.10	[redacted]	[redacted]	[redacted]	48,452

Figure 8 ERG base case - Cost-effectivness acceptability curve (March 2019)

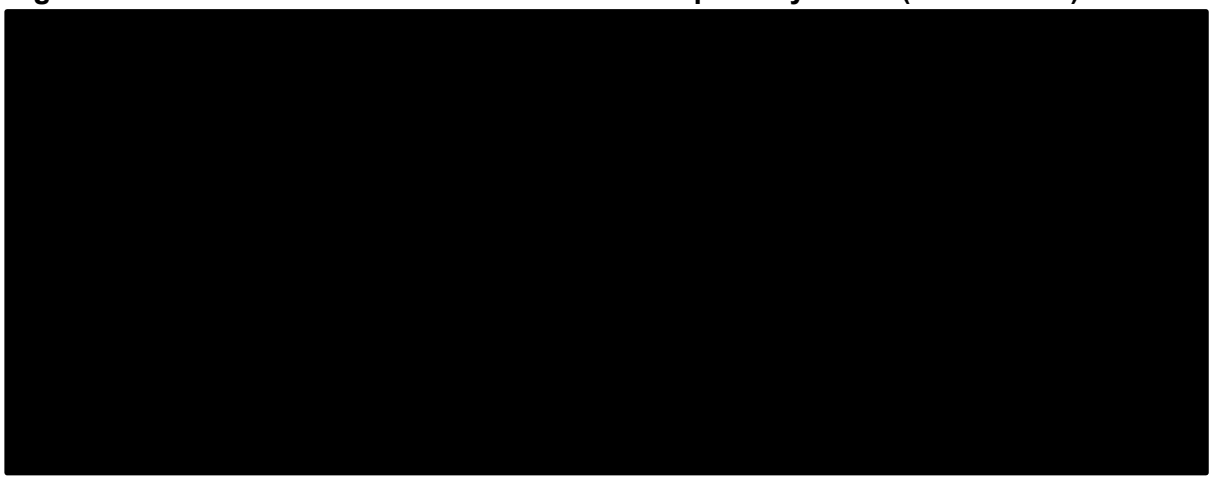
[redacted]

Probability of being cost effective at a willingness to pay of £50,000/QALY is [redacted]%.

Table 10 ERG Scenario 4 results (March 2019)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Pola+BR	[redacted]	[redacted]	[redacted]	-	-	-	
BR	20,083	1.29	0.90	[redacted]	[redacted]	[redacted]	46,032
Probabilistic							
Pola+BR	[redacted]	[redacted]	[redacted]	-	-	-	
BR	21,225	1.34	0.93	[redacted]	[redacted]	[redacted]	50,049

Figure 9 ERG Scenario 4 - Cost-effectivness acceptability curve (March 2019)



Probability of being cost effective at a willingness to pay of £50,000/QALY is [redacted]%.

Table 11 ERG Scenario 5 results (March 2019)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Pola+BR	[redacted]	[redacted]	[redacted]	-	-	-	
BR	20,119	1.30	0.90	[redacted]	[redacted]	[redacted]	47,928
Probabilistic							
Pola+BR	[redacted]	[redacted]	[redacted]	-	-	-	
BR	21,538	1.34	0.92	[redacted]	[redacted]	[redacted]	50,106

Figure 10 ERG Scenario 5 - Cost-effectivness acceptability curve (March 2019)

Probability of being cost effective at a willingness to pay of £50,000/QALY is [redacted]%.

Probabilistic analyses with bootstrapping for ERG scenario 5

The probabilistic analysis reported above was performed using the standard method whereby the uncertainty in the parameter estimates in the parametric functions is characterized by covariance-variance matrices. These are used to draw random parameters from a distribution around the mean parameter value. This is the standard in running probabilistic analyses using parametric functions. However, the method has limitations as it assumes the parameter distribution is normal, characterized by the covariance-variance matrices, and OS is independent from PFS (other than limiting PFS by OS in the model to avoid crossing of curves).

We investigated an alternative method of bootstrapping. In this method, 10% of patients are randomly removed from the study analysis set in each arm. Parametric curves, i.e. Log-Normal for PFS and Generalised Gamma for OS, are then fitted independently by arm to the sample. This is repeated to generate a list of bootstrapped parameter values that is used in the PSA by randomly selecting a parameter set from the list. The advantage of this method is that it does not make any assumptions on the distribution of the parametric function parameters and takes into account the correlation between PFS and OS (i.e. if a patients in long-term remission were to be removed from the sample it would affect PFS and OS extrapolations at the same time).

As the method is computationally intensive, we only implemented it for the ERG Scenario 5 with the results shown below (900 bootstrapped samples were generated and run in 2000 PSA simulations). The overall distribution of probabilistic simulations for incremental costs and incremental QALYs is narrower as evident in the cost-effectiveness acceptability curve (Figure 11). This results in probabilistic estimates closer to the deterministic values compared to using the standard method to sample the uncertainty around the parametric function estimates (Table 12). The standard method to quantify the uncertainty used in the model may therefore overestimate the uncertainty in the extrapolation results.

Table 12 ERG Scenario 5 restults with bootstrap PSA ([redacted])

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Pola+BR	[redacted]	[redacted]	[redacted]	-	-	-	
BR	21,277	1.40	0.97	[redacted]	[redacted]	[redacted]	44,347
Probabilistic							
Pola+BR	[redacted]	[redacted]	[redacted]	-	-	-	
BR	21,319	1.41	0.98	[redacted]	[redacted]	[redacted]	45,232

Figure 11 ERG Scenario 5 cost-effectivness acceptability curve with bootstrap results ([redacted]).

Probability of being cost effective at a willingness to pay of £50,000/QALY [redacted]%.

Changes made to the model at ACD response

There was only one change that affected standard parametric functions made in the model from the technical engagement version to the version submitted at ACD:

In the sheets ‘Pola + BR’ and ‘Comparator’ the columns with the OS ‘probability’ columns AL and AF, respectively, were amended with the statement “IF(cap_surv,MIN(AK11*AI11+(1-AK11)*AJ11,1-'Life Tables'!CH17),AK11*AI11+(1-AK11)*AJ11)”. This allows capping the conditional probability of survival at each time point by the adjusted background mortality by selecting the cell K206 in the ‘Model Inputs’ sheet as ‘TRUE’. This is more conservative than just capping OS as implemented by the ERG (max statement in OS trace), it ensures that the mortality rate at each time point in the model does not fall below that of the adjusted background mortality.

We would like to note that all scenarios presented in response to the ACD are based on a maximum of 6 cycles used per patient, i.e., cell J131 in the 'Model Inputs' sheet as '6', as agreed by the committee as the correct approach in the ACD. In contrast, the ERG base case at the 1st meeting used more than 6 cycles which resulted in effect double counting of delayed doses and overestimated the actual amount of drug given in the model compared to the values reported in the CSR, whereas our approach only slightly overestimated the amount.

The impact of the amendments and selections made on the ERG's base case is summarised in Table 13 below and explains the ICER values for this scenario as presented at the 2nd committee meeting.

Table 13 Impact on model amends and ACD prefferences on the ERG base case (March 2019 cut-off date, PAS as per 1st ACM)

Input in 'Model Input' Sheet cell selection	Comments	ICER
K206='FALSE' J131 = '>6'	ERG Base case as in company model submitted at response to technical engagement.	£49,590
K206='TRUE' J131 = '>6'	Ensure that mortality rate is always greater or equal to the adjusted background mortality	£50,971
K206='TRUE' J131 = '6'	Limit to 6 cycles as per ACD. Avoid double-counting of delayed cycles.	£48,837

Several other changes were made that related to the additional scenarios presented in response to the ACD only. In summary these were:

1. New 'Cure rate input calculations' and 'Cure rate input data' sheets were introduced to be able to run external cure-rate scenarios.

2. New 'Change_point Weibull' sheet with the change point model scenario calculation and data.

3. New hybrid scenario calculations in 'Life Tables' sheet columns CJ to DG.

4. Amended IF statements in the 'Pola + BR' sheet columns I to N and Y to AD, and sheet 'Comparator' columns I to N and V to AA to select cure-mixture or external cure-mixture models.

5. Amended IF statements in the ‘Pola + BR’ sheet columns S and AM, and sheet ‘Comparator’ columns S and AJ to select Hybrid model scenarios.

Changes made to the model in this response.

1. We included the Jan 2020 KM for PFS and OS data in the ‘KM PFS’ and ‘KM OS’ sheets respectively. This scenario can then be selected in the ‘Model inputs’ sheet by selecting the cut-off date in cell R3. Selections for some older data cuts before March 2019 were removed.

2. ‘Stat. Parameters’ sheet was amended with standard parametric functions and covariance-variance matrices refitted to the adjusted ITT population (‘CHMP-ITT’) for PFS-IRC and OS only (Rows 346 to 405 and 1625 to 1729). Only independent (not-proportional) modes were fitted, consistent with the previous approach. This allows selection of the revised extrapolations by selecting the cut-off date in cell R3

3. We corrected one error in the calculation of the Generalized Gamma function in Excel. In the Excel, GENGAMMA function requires on IF statement in column L in the ‘Pola + BR’ and ‘Comparator’ sheet to select 1-GENGAMMA or GENGAMMA in the PFS calculation, depending on the parameters of the functions. In the IF statement, e.g. for ‘Pola + BR’, *“IF(ph_pfs*INDEX('Stat. Parameters'!$G$39:$G$42, 3+ph_pfs) + (1-ph_pfs) * shape_PFS_new>0”*, the ‘*shape_PFS_new’* variable referenced the incorrect cell in the ‘Stat. Parameters’ G45 instead of G41 (in a similar way the ‘*shape_PFS_com’* reference was incorrect) as lines 41 and 45 contained an incorrect label. This led to incorrect Generalised Gamma calculations in some of the PSA draws but did not affect deterministic results or any PSA calculations previously discussed as these that did not involve the standard Generalised Gamma model for PFS.

4. In ‘Settings’ sheet a variable called "use_boot" in J51 was added. If select as "Yes", the PSA is done (for Log-normal in OS and Gen-Gamma in PFS-IRC, ERG Scenario 5 only) using the bootstrapped sample of parametric function parameters in the new sheet ‘Boot’. In the ‘Stat. Parameter’ sheet cells F105-111 and G39-G45 were amended with IF statements to use a random scenario from the bootstrapped scenarios in the new sheet ‘Boot’ if "use_boot" is selected as "Yes".

References

1. Cox C, Chu H, Schneider MF, Munoz A. Parametric survival analysis and taxonomy of hazard functions for the generalized gamma distribution. Stat Med. 2007;26(23):4352-74.
2. NICE. TA559 Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies. Available at: https://www.nice.org.uk/guidance/ta559. 2019.
3. National Institute for Health and Care Excellence. Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [TA567]. 2019.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

ID1576: Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma

ERG Addendum 3

Critique of new evidence submitted by the company after the 2nd ACM

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

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Date completed

09/06/2020

1. Introduction

On May 12th, 2020, the second Committee meeting for this technology appraisal was held. Following the meeting, the National Institute for Health and Care Excellence (NICE) requested the company to provide the following information:

- An explanation for the differences in incremental cost effectiveness ratios (ICERs) between the company's standard parametric generalised gamma (for both progression-free survival – PFS – and overall survival – OS) scenario and the ERG's base-case scenario (log-normal PFS and generalised gamma OS).
- An explanation for the differences in ICERs between the company's standard parametric generalised gamma (for both PFS and OS) scenario and the ERG's scenario analyses 4 and 5 which use the log-logistic and log-normal parametric distributions for OS, and a generalised gamma for PFS.
- A probabilistic sensitivity analysis (PSA) of the company's standard parametric generalised gamma scenario, and for the scenarios considered by the ERG.
- A log of the changes made to the economic model submitted in response to the appraisal consultation document.
- If available, updated deterministic and probabilistic analyses using the latest data cut.

In their response, the company confirmed that the economic model was updated by adding the standard parametric extrapolations fitted to the latest [redacted] data cut (only standard parametric extrapolations for PFS-IRC and OS were updated based on the adjusted ITT population as per the committees preferred analysis at ACD). Therefore, the new results presented by the company were based on this data cut, unless otherwise indicated. In addition to the standard PSA, the company also explored an alternative bootstrapping approach to quantify the uncertainty around OS and PFS extrapolations. Finally, the company also revised their patient access scheme (PAS) offer to [redacted] net price per 140mg ([redacted] % discount) vial (before 30mg availability) and [redacted] net price per 140mg and [redacted] per 30mg vial ([redacted]% discount). Unless stated otherwise, all new results presented by the company are based on this revised PAS offer.

The purpose of this addendum is to provide a critique of the new evidence submitted by the company.

2. Critique of the cost effectiveness evidence submitted by the company after the 2nd ACM

2.1 Company's standard parametric survival curves analysis – generalised gamma for PFS and OS

From all the standard parametric models included in their model, the company reiterated their preference for the generalized gamma distribution for modelling both PFS and OS due to the following reasons:

- It is the most flexible among the standard distributions. Thus, it is suited to model a decline of the hazard of progression and death over time.
- It provides the best fit to the observed data, even though Bayesian Information Criterion (BIC) and Akaike's Information Criterion (AIC) values for PFS and OS are higher in general for the generalised gamma. However, since the differences to other parametric models are less than 5, the generalised gamma cannot be ruled out based on AIC/BIC only.
- Alternative distributions, such as the log-normal, appear to underestimate PFS and OS at the end of the follow up period (according to the company).
- The company considered that the generalised gamma extrapolation provided the most clinically plausible long-term extrapolation for PFS and OS. According to clinical experts consulted by the company, it is expected that a significant proportion of patients who remain in remission at 2 years would not progress by 5 years and that survival approaches the population norm, subject to adjustment for and remaining increased risk. In the appraisals for CAR-T technologies this was deemed to occur between 2 and 5 years after treatment.[1]

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

- After an initial increase, the generalised gamma distribution shows a decline of the hazards of progression and death over time. The same behaviour is also observed in the log-normal and log-logistic distributions, which, therefore, cannot be ruled out based on this criterion.
- Claiming that the generalised gamma provided the best fit to the observed data is subjective, especially when AIC/BIC values are higher for the generalised gamma distribution than for the log-normal and log-logistic distributions. The ERG agrees with the company that since the differences in AIC/BIC are less than 5, the generalised gamma cannot be ruled out based on AIC/BIC only, but neither can the log-normal nor the log-logistic distributions.
- As discussed in the following sections, it is unclear if and to what extent the log-normal or the log-logistic distributions underestimate PFS and OS at the end of the follow up period. Even if that is the case, the ERG believes that, given the small sample size and the relatively short follow up, the focus should be on the plausibility of the long-term extrapolations.
- The ERG would like to reiterate the importance of defining the criteria as to which long-term extrapolations are deemed plausible or not. As discussed in the following sections, this remains unclear to the ERG.
- The ERG would still maintain that polatuzumab is quite different from CAR-T therapies. Therefore, a comparison between these two technologies might not be appropriate.

2.2 Differences between the company's preferred standard model and the ERG's base-case

Both the ERG's and company's base-case analyses assumed a generalized gamma distribution for OS. The difference was in the PFS, where the ERG assumed a log-normal distribution and the company a generalised gamma.

Figure 1 shows a comparison of PFS extrapolations with the log-normal and the generalised gamma distributions for both treatment arms. According to the company, compared to the Kaplan-Meier (KM)

data, the log-normal distribution seems to overestimate PFS initially and then underestimate it after approximately 20 months.

Figure 1. PFS-IRC extrapolation with generalised gamma (company) or log-normal (ERG base case); [redacted] cut.

Source: Electronic model. Figure 1 in company's addendum after 2nd ACM missed the log-normal curve for BR.[2]
Abbreviations: BR, bendamustine + rituximab; IRC, independent review committee; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab

Furthermore, as summarised in Section 2.4 (Table 3), assuming a log-normal distribution for PFS resulted in 65% of patients in remission at 2 years would progress or die by year 5. The company considered that this is not plausible based on the natural history of the disease, as confirmed by clinical experts, and the assumptions made in the appraisals of CAR-T technologies.[1] Assuming a generalised gamma distribution for both PFS and OS resulted in approximately 44% of patients in remission at 2 years would progress or die by year 5.

The company's and ERG's base-case cost effectiveness results are summarised in Table 1. Since both the ERG and company assumed a generalised gamma distribution to extrapolate OS, the incremental life-years gained were the same in both scenarios. Differences were due to the distribution assumed for PFS. In the ERG's base-case there were more patients in the progressed disease health state of the model, where supportive care costs are higher compared to PFS costs. In the ERG's base-case the incremental costs in the progressed disease health state were £13,465, while in the company's preferred analysis were £2,413 ([redacted]). Incremental QALYs were [redacted] lower in the ERG's base-case compared to the company's preferred analysis. Therefore, the incremental costs are considered the main driver for the difference in ICERs.

Table 1. Company and ERG base-case results ([redacted])

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Company							
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,663
BR	25,970	1.66	1.14				
ERG							
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,101
BR	29,319	1.66	1.13				

Source: Tables 4 and 5 in company's addendum after 2nd ACM.[2]
Abbreviations: BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola+BR, polatuzumab + bendamustine + rituximab; QALYs, quality-adjusted life years

ERG comment: The ERG agrees in general with the company. The ERG is aware that their base-case approach to survival modelling was criticised during the Committee meetings and has acknowledged the clinical implausibility of the PFS results. That was the main reason why the ERG explored alternative scenarios for modelling PFS and OS after reviewing the evidence submitted by the company in response to the ACD.[3] Therefore, the ERG considers that the focus of this addendum should not fall on the comparison against the ERG base-case (i.e. PFS modelled assuming a log-normal distribution) since this has been deemed as clinically implausible, but on the plausibility of the company's preferred analysis with the standard generalised gamma distribution for both PFS and OS and the ERG scenarios 4 and 5 where PFS was modelled with the standard generalised gamma distribution but OS was modelled according to a log-logistic or a log-normal distribution, respectively.

The ERG would like to emphasise that the generalised gamma extrapolation seems to provide the most plausible extrapolation for PFS. However, the ERG still considers it unclear what extrapolation is the most plausible for OS. The company have explicitly indicated that assuming a log-normal distribution for PFS resulted in 65% of patients in remission at 2 years would progress or die by year 5 and that this is considered by the company as clinically implausible. Assuming a generalised gamma distribution for PFS and OS resulted in approximately 44% of patients in remission at 2 years would progress or die by year 5, which is obviously less than 65%, but the plausibility of this 44% was not discussed. Furthermore, it should also be noted that, as shown in Section 2.4 (Table 3), the same 44% is obtained when a log-logistic or a log-normal distribution was assumed for OS. Therefore, based solely on this criterion, if the generalised gamma is deemed as a plausible extrapolation for OS then the log-normal and the log-logistic should be deemed as plausible too.

2.3 Differences between the company's preferred standard model and the ERG's scenarios 4 and 5

In the ERG's exploratory scenarios 4 and 5 a log-logistic and a log-normal distribution, respectively, was assumed to extrapolate OS (instead of a generalised gamma in the company's standard parametric model and the ERG base-case scenarios), while PFS was extrapolated according to a generalised gamma distribution (thus, PFS follows the same distribution in all 3 scenarios). The OS extrapolations for both treatment arms can be seen in Figure 2. Based on this figure, the company considered that both the log-normal and the log-logistic extrapolations tend to underestimate long-term OS, and based on the results shown in Section 2.4 (Table 3), they overestimate the long-term mortality hazard. The company explained that mortality is initially high due to a higher proportion of patients in the progressed disease health state. Afterwards, mortality is expected to decline in the long-term when essentially only patients

with long-term remission (in PFS) remain in the cohort. Because the parametric distributions are fitted to observed data, where overall mortality is higher, the log-normal and the log-logistic distributions tend to overestimate OS before 2 years and then underestimate OS from 2 years onwards. A generalised gamma model provides similar AIC/BIC statistics and a better visual fit.

Figure 2. OS extrapolation with generalised gamma (company) or log-logistic and log-normal (ERG Scenario 4 and 5) ([redacted])

Source: Electronic model. Figure 2 in company's addendum after 2nd ACM missed the log-logistic curve for pola+BR.[2]
Abbreviations: BR, bendamustine + rituximab; OS, overall survival; Pola+BR, polatuzumab + bendamustine + rituximab

Additionally, the company referred to the results in Section 2.4 (Table 3) to show that for the log-normal and log-logistic OS extrapolations, the hazard of death at 5 years remained at approximately 5 times the adjusted population norm. The company considers this implausible given the natural history of the disease reported by experts and in CAR-T appraisals, especially because practically all patients would be in PFS state in these scenarios at year 5. The generalised gamma OS extrapolation resulted in a hazard of death 3 times above adjusted population norm. The company considered that this may also be too conservative. However, approximately 1/3 of patients are in the progressed disease state at 5 years in this model scenario.

The company's and ERG's scenarios 4 and 5 cost effectiveness results ([redacted]) are summarised in Table 2. Since in all scenarios PFS is modelled according to a generalised gamma distribution, differences in incremental life-years gained were driven by the distribution assumed for OS. In the ERG's scenarios 4 and 5 these were similar and lower compared to the company's preferred scenario. This is expected since the generalised gamma provided the highest OS among the 3 distributions, especially for the pola+BR arm. The company's preferred scenario resulted in higher incremental costs and higher incremental QALYs, but this resulted in the lowest ICER, approximately £8,000 lower than in the ERG's scenarios 4 and 5.

Table 2. Company preferred scenario and ERG scenarios 4 and 5 results ([redacted])

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Company							
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,663
BR	25,970	1.66	1.14				
ERG scenario 4							
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,359
BR	20,498	1.37	0.95				
ERG scenario 5							
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,347
BR	21,277	1.40	0.97				

Source: Tables 6 and 7 in company's addendum after 2nd ACM.[2]
Abbreviations: BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola+BR, polatuzumab + bendamustine + rituximab; QALYs, quality-adjusted life years

ERG comment: Based on Figure 2, it seems that the log-normal and the log-logistic distributions may to overestimate OS before 2 years as the company mentioned, but the generalised gamma curve seems to be above the KM curves as well and, therefore, the generalised gamma may also overestimate OS before 2 years. This is more evident for the pola+BR arm. In the BR arm this is observed before 20 months but also for the 3 curves.

It is uncertain whether the log-logistic and the log-normal distributions underestimate OS from 2 years onwards. To validate such statement, it would be necessary to know how OS would behave after 2 years. What Figure 2 shows is that the generalised gamma distribution predicts higher long-term OS than the log-logistic and the log-normal distribution (especially in the pola+BR arm, in the BR arm there is not much difference). With the current evidence, the ERG cannot judge whether these extrapolations represent an overestimation, an underestimation or an accurate representation of OS.

The generalised gamma distribution provided similar (but higher) AIC/BIC statistics to those obtained with the log-logistic and the log-normal distributions. The company interpreted that the generalised gamma resulted in a better visual fit. The ERG considers this hard to judge but it might agree with the company that this is the case especially at the end of the KM curve. However, the ERG would like to emphasize that rather than focusing on the fit to the observed data, the aim should be on the plausibility of the long-term extrapolations.

It is unclear how to interpret the results presented in Section 2.4 (Table 3). These results indicate that for the log-normal and log-logistic OS extrapolations, the hazard of death at 5 years remained at approximately 5 times the adjusted population norm. For the generalised gamma OS extrapolation, the hazard of death was 3 times above adjusted population norm but approximately 1/3 of patients were in the progressed disease state at 5 years in this model scenario. It is unclear how these numbers were calculated; therefore, the ERG cannot comment on their interpretation.

2.4 Summary of key differences between the company's preferred standard model and the ERG's scenarios

Table 3 summarises the key clinical predictions for all the scenarios discussed by the company, while Table 4 summarises the cost effectiveness results.

Table 3. Standard parametric model predictions Pola-BR ([redacted])

Scenario	Model 2-year remission rate (PFS)	Model 5-year remission rate (PFS)	Model % year survival rate (OS)	Proportion of patients in PSA at 2 years progressing or dying by 5 years	Ratio of hazard of death to adjusted population norm at 5 years
Company standard model	26%	15%	21%	44%	3
ERG base case	25%	9%	21%	65%	3
ERG Scenario 4	26%	15%	16%	44%	5
ERG Scenario 5	26%	15%	17%	44%	5

Source: Table 3 in company's addendum after 2nd ACM.[2]
Abbreviations: OS, overall survival; PFS, progression-free survival

Table 4. Summary of cost-effectiveness results for standard parametric model scenarios ([redacted] cut-off date)

Scenario	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Company standard parametric model, deterministic	[redacted]	[redacted]	[redacted]	35,663
Company standard parametric model, probabilistic	[redacted]	[redacted]	[redacted]	40,929
ERG base case, deterministic	[redacted]	[redacted]	[redacted]	47,101
ERG base case, probabilistic	[redacted]	[redacted]	[redacted]	48,839
ERG Scenario 4, deterministic	[redacted]	[redacted]	[redacted]	43,359
ERG Scenario 4, probabilistic	[redacted]	[redacted]	[redacted]	48,269
ERG Scenario 5, deterministic	[redacted]	[redacted]	[redacted]	44,347
ERG Scenario 5, probabilistic	[redacted]	[redacted]	[redacted]	48,052

Source: Table 1 in company's addendum after 2nd ACM.[2]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

ERG comment: As mentioned in the previous section, it is unclear how the numbers shown in Table 3 were calculated; therefore, the ERG cannot comment on their interpretation.

2.5 Differences between deterministic and probabilistic results

Table 5 shows the results of the deterministic and probabilistic analyses for all scenarios based on the [redacted] data cut. The cost-effectiveness acceptability curves (CEACs) for all probabilistic scenarios (based on 3000 simulations) are shown in Figures 3 to 6. The probability that pola+BR is deemed cost effective at a willingness to pay of £50,000/QALY was [redacted]% for the company preferred standard model scenario and [redacted]% for the ERG base-case, ERG scenario 4 and ERG scenario 5.

Table 5. Comparison of company and ERG scenarios ([redacted])

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Company preferred standard modelling approach (deterministic)							
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,663
BR	25,970	1.66	1.14				
Company preferred standard modelling approach (probabilistic)							
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,929
BR	29,485	1.85	1.26				
ERG base-case (deterministic)							
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,101
BR	29,319	1.66	1.13				
ERG base-case (probabilistic)							
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,398
BR	32,810	1.85	1.25				
ERG scenario 4 (deterministic)							
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,359
BR	20,498	1.37	0.95				
ERG scenario 4 (probabilistic)							
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,269
BR	21,977	1.42	0.98				
ERG scenario 5 (deterministic)							
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,347
BR	21,277	1.40	0.97				
ERG scenario 5 (probabilistic)							
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,052
BR	22,908	1.45	1.00				

Source: Tables 4, 5, 6 and 7 in company's addendum after 2nd ACM.[2]

Abbreviations: BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola+BR, polatuzumab + bendamustine + rituximab; QALYs, quality-adjusted life years

Figure 3. Company standard model - Cost-effectivness acceptability curve ([redacted])

Source: Figure 3 in company's addendum after 2nd ACM.[2]
Abbreviations: BR, bendamustine + rituximab; OS, overall survival; Pola+BR, polatuzumab + bendamustine + rituximab

Figure 4. ERG base-case - Cost-effectivness acceptability curve ([redacted])

Source: Figure 4 in company's addendum after 2nd ACM.[2]
Abbreviations: BR, bendamustine + rituximab; OS, overall survival; Pola+BR, polatuzumab + bendamustine + rituximab

Figure 5. ERG Scenario 4 - Cost-effectivness acceptability curve ([redacted])

Source: Figure 5 in company's addendum after 2nd ACM.[2]
Abbreviations: BR, bendamustine + rituximab; OS, overall survival; Pola+BR, polatuzumab + bendamustine + rituximab

Figure 6. ERG Scenario 5 - Cost-effectivness acceptability curve ([redacted])

Source: Figure 6 in company's addendum after 2nd ACM.[2]
Abbreviations: BR, bendamustine + rituximab; OS, overall survival; Pola+BR, polatuzumab + bendamustine + rituximab

ERG comment: As mentioned in ACD Section 3.8, the "*committee was concerned about the reliability of the model outputs because of the large unexplained difference between the company's deterministic and probabilistic results*".[2] This seems to be less problematic now given the results shown in Table 5, even though except for the ERG base-case, there is a difference of approximately £5,000 between all deterministic and probabilistic ICERs (the latter are higher). The ERG is not able to explain what causes this difference.

In ACD Section 3.8, the "*committee also noted that the company's probabilistic analysis estimated the number of life years for the comparator arm to be more than 2 years, which seemed unrealistic and inconsistent with clinical opinion, and would cast doubt on whether polatuzumab vedotin meets the end-of-life criteria*".[2] As shown in Table 5, this seems to be no longer an issue.

2.5.1 Probabilistic analyses with bootstrapping for ERG scenario 5

In addition to the standard PSA, the company investigated an alternative method for assessing uncertainty based on bootstrapping. The approach taken by the company can be summarised as follows:

- The company randomly removed 10% of patients from the study data set in each treatment arm.
- Parametric survival models (e.g. log-normal for PFS and generalised gamma for OS) were then fitted independently by treatment arm to the sample.
- This was repeated to generate a list of bootstrapped parameter values that was used in the PSA by randomly selecting a parameter set from the list.

According to the company, the main advantage of this method is that it does not require to assume any probability distribution for the parameters of the survival curves and it also takes into account the correlation between PFS and OS (i.e. if patients in long-term remission were removed from the sample, this would affect both PFS and OS extrapolations).

Since the bootstrap method was computationally intensive, the company only implemented it for the ERG Scenario 5 (900 bootstrapped samples were generated and run in 2000 PSA simulations). The results of this scenario are shown in Table 6. Based on these results, the company concluded that overall distributions of the probabilistic simulations for incremental costs and incremental QALYs were narrower, as shown in the CEAC (Figure 7), where the probability that pola+BR was deemed cost effective at a willingness to pay of £50,000/QALY was [redacted]%. The probabilistic estimates with bootstrap were closer to the deterministic values than those obtained with the standard PSA. Thus, according to the company, the standard method to quantify the uncertainty used in the model may overestimate the uncertainty in the extrapolation results.

Table 6. ERG Scenario 5 results: deterministic, standard PSA and bootstrap PSA ([redacted])

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Deterministic							
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,347
BR	21,277	1.40	0.97				
Probabilistic (standard)							
Pola+BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,052
BR	22,908	1.45	1.00				
Probabilistic (bootstrap)							
Pola+BR	[redacted]	[redacted]	[redacted]	-	-	-	
BR	21,284	1.41	0.98	[redacted]	[redacted]	[redacted]	£44,866

Source: Tables 7 and 12 in company's addendum after 2nd ACM.[2]
Abbreviations: BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Pola+BR, polatuzumab + bendamustine + rituximab; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

Figure 7. ERG Scenario 5 cost-effectiveness acceptability curve with bootstrap results ([redacted]).

Source: Figure 11 in company's addendum after 2nd AC M.[2]
Abbreviations: BR, bendamustine + rituximab; Pola+BR, polatuzumab + bendamustine + rituximab

ERG comment: In a PSA, uncertainty around all input parameters is quantified, usually through probability distributions, in order to estimate the impact of all those uncertainties on the model outcomes simultaneously.[4] The company mentioned that the standard PSA, whereby the uncertainty around the parameters of the survival functions is characterized by covariance-variance matrices, has two main limitations: 1) it assumes a multivariate normal distribution for the parameters of the survival functions and 2) OS is drawn independently from PFS.

The ERG does not agree with the company here. If the company considers that the multivariate normal distribution was not an appropriate candidate to model the parameters of the survival functions (which would need to be assessed by the company), it is up to the company to propose an alternative probability distribution and include this in the model.[5]

Also, the ERG argues that drawing OS independently from PFS is not a limitation of the PSA itself, but a limitation of the modelling approach taken by the company. Partitioned survival modelling is often selected for its simplicity and because it can easily adapt survival data. However, one of its main limitations (and the usual point of criticism of these models) is that it is built under the assumption that OS is independent of PFS. The ERG considers that also in this aspect it is up to the company to propose an alternative modelling approach (e.g. state-transition, discrete event simulation, etc.) to overcome this limitation.

If, alternatively, the company would adopt a bootstrapping approach to reflect parameter uncertainty, the ERG considers that the following steps should have been taken:[6]

- Generate a bootstrap sample from the original study dataset, by resampling this dataset with replacement, such that the sample size of the bootstrap sample equals that of the original dataset. The company indicated that 10% of patients from the study data set were randomly removed. It is unclear why 10% (and not something else) was chosen, whether this was done with or without replacement and whether the 10% or the remaining 90% was used to estimate the parameters of the survival curves. In any case, it seems that this first step has not been correctly done by the company.
- Fit probability distributions to the bootstrap sample and record the estimated parameter values. Note that this should be done for all probability distributions fitted to the data included in the model, if any, not only survival curves.
- Repeat the first two steps as many times as PSA runs. However, the company generated 900 bootstrapped samples and ran 2000 PSA simulations.
- Run the PSA, using a different set of estimated parameter values to define the distribution(s) for each PSA iteration. However, within the 2000 PSA simulations, bootstrap samples were selected more than once (because only 900 were generated).

Based on these points, the ERG considers that the bootstrap approach to PSA was not correctly performed by the company. As mentioned above, the probabilistic point estimates with bootstrap were closer to the deterministic values than those obtained with the standard PSA (Table 6). However, the ERG would have expected that the difference between the two PSA approaches would be on the predicted uncertainty (e.g. 95% confidence ellipse) but not so much on the point estimates. The company did mentioned that the distributions of the probabilistic simulations for incremental costs and incremental QALYs were narrower for the bootstrap PSA and referred to the CEAC in Figure 7. to illustrate this. However, the ERG considers that this should have been better represented with the PSA outcomes plotted on the CE-plane. The company concluded that the standard PSA method may have overestimated the uncertainty in the extrapolation results. Because, as mentioned above, the company bootstrapped samples smaller than the original study sample and generated 900 samples instead of 2000, the ERG considers it more likely that the opposite has happened, and that the bootstrap PSA method may have underestimated the uncertainty in the results. In any case, given the small sample size in the trial, large uncertainty is expected regardless of the method used for assessing parameter uncertainty.

2.6 Differences between data cuts results

The company also presented the results of the analyses for all standard parametric scenarios based on the March 2019 data cut. These can be found in Tables 8 to 11 and Figures 7 to 10 in the company's addendum after 2nd ACM.[2] The results (not shown here) were similar to those obtained with the [redacted] data cut. All scenarios resulted in higher (but not much) incremental costs and incremental QALYs but this did not impact the ICER substantially. Based on the March 2019 data cut, the probability that pola+BR is considered to be cost effective at a willingness to pay of £50,000/QALY was [redacted]% for the company preferred standard model scenario and [redacted]% for the ERG base-case, [redacted]% for the ERG scenario 4 and [redacted]% for the ERG scenario 5. Thus, also similar to those obtained with the [redacted] data cut.

2.7 Changes made to the model

As mentioned in Section 1 of this addendum, NICE requested the company to provide a log of the changes made to the economic model submitted in response to the appraisal consultation document. These and those made after the 2nd ACM are summarised below.

Changes made to the model at ACD response

- Sheets 'Pola + BR' and 'Comparator' columns AL and AF were amended with the statement "IF(cap_surv,MIN(AK11*AI11+(1-AK11)*AJ11,1-'Life Tables'!CH17),AK11*AI11+(1-AK11)*AJ11)". This allows capping the conditional probability of survival at each time point by the adjusted background mortality by selecting the cell K206 in the 'Model Inputs' sheet as 'TRUE'. This is more conservative than just capping OS as implemented by the ERG (max statement in OS trace), it ensures that the mortality rate at each time point in the model does not fall below that of the adjusted background mortality.
- The scenarios presented in response to the ACD were based on a maximum of 6 cycles used per patient, i.e., cell J131 in the 'Model Inputs' sheet as '6', as agreed by the Committee as the correct approach in the ACD. The ERG base-case at the 1st meeting used more than 6 cycles, which resulted in double counting delayed doses and overestimating the actual amount of drug given in the model compared to the values reported in the CSR, whereas the company's approach only slightly overestimated this amount.

The impact of these changes was minor as can be seen in Table 7.

Table 7. Impact on model amends and ACD preferences on the ERG base case (March 2019 cut-off date, PAS as per 1st ACM)

Input in 'Model Input' Sheet cell selection	Comments	ICER
K206='FALSE' J131 = '>6'	ERG Base case as in company model submitted at response to technical engagement.	£49,590
K206='TRUE' J131 = '>6'	Ensure that mortality rate is always greater or equal to the adjusted background mortality	£50,971
K206='TRUE' J131 = '6'	Limit to 6 cycles as per ACD. Avoid double-counting of delayed cycles.	£48,837
Source: Tables 13 in company's addendum after 2nd ACM.[2] Abbreviations: ICER, incremental cost-effectiveness ratio		

Other changes made regarding the additional scenarios presented in response to the ACD only are the following:

- 'Cure rate input calculations' and 'Cure rate input data' sheets were added to run external cure-rate scenarios.
- 'Change_point Weibull' sheet with the change point model scenario calculation and data.
- Hybrid scenario calculations in 'Life Tables' sheet columns CJ to DG.
- Amended IF statements in the 'Pola+BR' sheet columns I to N and Y to AD, and sheet 'Comparator' columns I to N and V to AA to select cure-mixture or external cure-mixture models.
- Amended IF statements in the 'Pola+BR' sheet columns S and AM, and sheet 'Comparator' columns S and AJ to select Hybrid model scenarios.

Changes made to the model after the 2nd ACM

- The [redacted] KM for PFS and OS data was included in the 'KM PFS' and 'KM OS' sheets. This scenario can be selected in 'Model inputs' cell R3. Selections for some older data cuts before March 2019 were removed.

- ‘Stat. Parameters’ sheet was amended with standard parametric functions and covariance-variance matrices refitted to the adjusted ITT population (‘CHMP-ITT’) for PFS-IRC and OS only (Rows 346 to 405 and 1625 to 1729). Only independent (not-proportional) modes were fitted, consistent with the previous approach. This allows selection of the revised extrapolations by selecting the cut-off date in cell R3.
- The company corrected one error in the calculation of the generalized gamma function in Excel. The GENGAMMA function requires on the IF statement in column L in the ‘Pola + BR’ and ‘Comparator’ sheet to select 1-GENGAMMA or GENGAMMA in the PFS calculation, depending on the parameters of the functions. In the IF statement for ‘Pola+BR’, *“IF(ph_pfs * INDEX('Stat.Parameters'!$G$39:$G$42,3+ph_pfs) + (1-ph_pfs) * shape_PFS_new > 0)”*, the ‘*shape_PFS_new’* variable referenced the incorrect cell in the ‘Stat. Parameters’ G45 instead of G41 (in a similar way the ‘*shape_PFS_com’* reference was incorrect) as lines 41 and 45 contained an incorrect label. This led to incorrect generalised gamma calculations in some of the PSA draws but did not affect deterministic results or any PSA calculations previously discussed as these that did not involve the standard generalised gamma model for PFS.
- ‘Settings’ sheet: a variable called "use_boot" in J51 was added. If select as "Yes", the PSA is done (for log-normal in OS and generalised gamma in PFS-IRC, ERG Scenario 5 only) using the bootstrap sample of parametric function parameters in the new sheet ‘Boot’. In the ‘Stat. Parameter’ sheet cells F105-111 and G39-G45 were amended with IF statements to use a random scenario from the bootstrap scenarios in the new sheet ‘Boot’ if "use_boot" is selected as "Yes".

3. Additional analyses undertaken by the ERG

As mentioned in previous sections, the ERG considers that the focus of this addendum should fall on the plausibility of the company's preferred analysis with the standard generalised gamma distribution for both PFS and OS and the ERG scenarios 4 and 5 where PFS was modelled with the standard generalised gamma distribution but OS was modelled according to a log-logistic or a log-normal distribution, respectively. In summary, the ERG believes that it is up to the Committee's to decide which of these 3 scenarios is more clinically plausible. In the remaining of this section, the ERG presented additional evidence that it is considered relevant to help the Committee with this task.

5-year survival estimates

The company's approach (generalised gamma for OS and PFS) predicted 8.5% of patients in OS and 3.9% of patients in PFS at year 5 (4.6% gap between OS and PFS) in the BR arm. Note that in the previous version of the model these were 6.6% in OS and 3.3% in PFS (thus, 3.3% gap between OS and PFS). As explained in previous sections, the company still considers that this scenario resulted in the most plausible long-term extrapolations. In the ERG scenario 4 (log-logistic OS and generalised gamma PFS), the difference between PFS and OS at year 5 is smaller: 5.7% of patients in OS and 3.9% of patients in PFS at year 5 (1.8% gap between OS and PFS) in the BR arm. In the previous version of the model these were 5.1% in OS and 3.3% in PFS (1.8% gap). Finally, in the ERG scenario 5 (log-normal OS and generalised gamma PFS), the difference between PFS and OS at year 5 was also smaller than in the company's preferred scenario: 6.2% of patients in OS and 3.9% of patients in PFS at year 5 (2.3% gap between OS and PFS) in the BR arm. In the previous version of the model these were 5.2% in OS and 3.3% in PFS (1.9% gap). Thus, in all three scenarios PFS at year 5 for the BR arm was below the range provided by clinical experts of 5%-10%. The OS prediction falls within this range, but it is closer to the lower limit in the ERG scenarios. However, in both ERG scenarios the difference between OS and PFS was smaller than the difference observed in the company's preferred scenario.

Markov traces BR arm

The BR arm Markov traces for the company's preferred scenario, and the ERG scenarios 4 and 5 can be seen in Figures 8, 9 and 10, respectively. In the company's preferred scenario, the proportion of patients in the PFS health state becomes equal to the proportion of patients with progressed disease (PD) at approximately 40 months (3.33 years). Afterwards, the proportion of patients in the PD health state becomes larger than the proportion of patients in the PFS health state but both remain very similar and decreasing to 0. The proportion of patients still alive at year 10 (120 months) is 3.9% (1.6% in PFS and 2.3% in PD). In the ERG scenario 4, the BR Markov trace shows that at least for 10 years the proportion of patients in PFS is always larger than the proportion of patients in PD even though both tend to converge to 0. The proportion of patients still alive at year 10 is 2.4% (1.6% in PFS and 0.8% in PD). In the ERG scenario 5, the BR Markov trace shows a similar picture than in the ERG scenario 4. The main difference (even though still minor) is that the proportion of patients still alive at year 10 is 2.0% (1.6% in PFS and 0.4% in PD).

Figure 8. Markov trace for the BR treatment arm – OS and PFS extrapolation with generalised gamma (company); [redacted] cut.

Source: Electronic model after 2nd ACM.
Abbreviations: BR, bendamustine + rituximab; OS, overall survival; PFS, progression-free survival

Figure 9. Markov trace for the BR treatment arm – PFS extrapolation with generalised gamma and OS with log-logistic (ERG scenario 4); [redacted] cut.

Source: Electronic model after 2nd ACM.
Abbreviations: BR, bendamustine + rituximab; OS, overall survival; PFS, progression-free survival

Figure 10. Markov trace for the BR treatment arm – PFS extrapolation with generalised gamma and OS with log-normal (ERG scenario 5); [redacted] cut.

Source: Electronic model after 2nd ACM.
Abbreviations: BR, bendamustine + rituximab; OS, overall survival; PFS, progression-free survival

Markov traces pola+BR arm

The pola+BR arm Markov traces for the company's preferred scenario, and the ERG scenarios 4 and 5 can be seen in Figures 11, 12 and 13, respectively. In the company's preferred scenario, the proportion of patients in the PFS health state is always larger than the proportion of patients in the PD health state. The proportion of patients still alive at year 10 (120 months) is 13.2% (9.6% in PFS and 3.6% in PD). In the ERG scenario 4, the pola+BR Markov trace also shows that the proportion of patients in PFS is always larger than the proportion of patients in PD. The main difference with respect to the company's preferred scenario is that after 72 months (6 years) all alive patients are in the PFS health state (the proportion of patients in PD becomes 0). The proportion of patients still alive at year 10 is 7.5% (all in PFS). In the ERG scenario 5, the pola+BR Markov trace is similar the one in the ERG scenario 4. The only difference is that the proportion of patients still alive at year 10 is 7.1%, all of them in PFS, since the proportion of patients in PD becomes 0 at 76 months (6.3 years).

Figure 11. Markov trace for the pola+BR treatment arm – OS and PFS extrapolation with generalised gamma (company); [redacted] cut.

Source: Electronic model after 2nd ACM.
Abbreviations: pola+BR, polatuzumab + bendamustine + rituximab; OS, overall survival; PFS, progression-free survival

Figure 12. Markov trace for the pola+BR treatment arm – PFS extrapolation with generalised gamma and OS with log-logistic (ERG scenario 4); [redacted] cut.

Source: Electronic model after 2nd ACM.
Abbreviations: pola+BR, polatuzumab + bendamustine + rituximab; OS, overall survival; PFS, progression-free survival

Figure 13. Markov trace for the pola+BR treatment arm – PFS extrapolation with generalised gamma and OS with log-normal (ERG scenario 5); [redacted] cut.

Source: Electronic model after 2nd ACM.
Abbreviations: pola+BR, polatuzumab + bendamustine + rituximab; OS, overall survival; PFS, progression-free survival

Ratio of hazards

As shown in Figure 14, the scenario assuming a generalized gamma distribution for PFS and OS resulted in a hazard which equalled the adjusted background mortality after approximately 7.5 years in the Pola+BR arm (patients functionally cured at approximately 90 months in Pola+BR), and after approximately 8.3 years (100 months) in the BR arm. Furthermore, Figure 14 also shows an OS and PFS benefit for Pola+BR over BR for more than 100 months. As can be seen in Figure 15, the OS and PFS hazards have a different shape because different probability distributions were assumed to model OS (log-logistic) and PFS (generalised gamma) in the ERG scenario 4. This scenario resulted in a PFS hazard which equalled the adjusted background mortality after approximately 70 months (5.8 years) in the Pola+BR arm and after approximately 100 months (8.3 years) in the BR arm. At approximately 80 months the OS hazards seem to be equal for both treatment arms and equalled the adjusted background mortality after approximately 100 months. The hazards observed in the ERG scenario 5 (Figure 16) were similar to those observed in the ERG scenario 4. The OS and PFS hazards also have a different shape because a log-normal distribution was assumed to model OS and a generalised gamma was assumed for PFS. This scenario resulted in a PFS hazard which equalled the adjusted background mortality after approximately 80 months (6.6 years) in the Pola+BR arm and after 100 months (8.3 years) in the BR arm. Also, at approximately 100 months the OS hazards seem to be equal for both treatment arms and approached the adjusted background mortality.

Figure 14. Ratio of hazards (PFS and OS) to adjusted background – OS and PFS extrapolation with generalised gamma (company); [redacted] cut.

Source: Electronic model after 2nd ACM.
Abbreviations: BR, bendamustine + rituximab; OS, overall survival; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab

Figure 15. Ratio of hazards (PFS and OS) to adjusted background – PFS extrapolation with generalised gamma and OS with log-logistic (ERG scenario 4); [redacted] cut.

Source: Electronic model after 2nd ACM.
Abbreviations: BR, bendamustine + rituximab; OS, overall survival; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab

Figure 16. Ratio of hazards (PFS and OS) to adjusted background – PFS extrapolation with generalised gamma and OS with log-normal (ERG scenario 5); [redacted] cut.

Source: Electronic model after 2nd ACM.
Abbreviations: BR, bendamustine + rituximab; OS, overall survival; PFS, progression-free survival; Pola+BR, polatuzumab + bendamustine + rituximab

4. References

[1] National Institute for Health and Care Excellence. *Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies [TA559]*: NICE, 2019. 31p. Available from: https://www.nice.org.uk/guidance/ta559

[2] Roche Products Ltd. *Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [ID1576]: Response to information requested after 2nd ACM*: Roche, 2020. 19p.

[3] Armstrong N, Büyükkaramikli N, Penton H, Fayter D, Wetzelaer P, Corro Ramos I, et al. *Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma: a Single Technology Assessment. Addendum 1*. York: Kleijnen Systematic Reviews Ltd, 2020

[4] Briggs AH. Handling uncertainty in cost-effectiveness models. *PharmacoEcon* 2000;17(5):479-500.

[5] Briggs A. Probabilistic analysis of cost-effectiveness models: statistical representation of parameter uncertainty. *Value Health* 2005;8(1):1-2.

[6] Degeling K, Ijzerman MJ, Koopman M, Koffijberg H. Accounting for parameter uncertainty in the definition of parametric distributions used to describe individual patient variation in health economic models. *BMC Med Res Methodol* 2017;17(1):170.