NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ibrutinib for treating Waldenstrom's macroglobulinaemia [ID884]

The following documents are made available to the consultees and commentators:

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Janssen
   - Leukaemia Care
   - Lymphoma Association
   - Waldenström's macroglobulinaemia (WMUK)
   -
3. **Comments on the Appraisal Consultation Document from experts:**
   - Dr Shirley D'SA, Clinical expert nominated by Janssen
   - Dr Roger Owen, Clinical expert nominated by Royal College of Pathologist

4. **ERG commentary on the company's response to the ACD**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ibrutinib for treating Waldenstrom's macroglobulinaemia

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

Definitions:

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 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 determination (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, 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.

Comments received from consultees

Consultee	Comment [sic]	Response
Janssen	We are disappointed the Appraisal Committee's preliminary decision is that ibrutinib is not recommended within its marketing authorisation for treating Waldenström's macroglobulinaemia (WM) in adults who have had at least one prior therapy or as first-line treatment when chemo-immunotherapy is unsuitable; however, we are committed to working with NICE and this response aims to address the Appraisal Committee's key concerns as outlined in the ACD. Ibrutinib, with its unprecedented efficacy and well tolerated safety profile, represents the first technology licensed for treating this rare condition, offering a step-change to National Health Service (NHS) patients who are offered limited and ever-decreasingly effective treatment options – as evidenced by the Cancer Drugs Fund (CDF) delisting of bortezomib in 2015 and the recent decommissioning of stem cell transplant in this population.	This comment has been noted. The committee acknowledge the innovative nature of ibrutinib in section 4.14 of the Final appraisal determination (FAD).
Janssen	Comparative effectiveness: Given the rarity of WM, an ultra-orphan condition, there is a recognised scarcity of clinical data. Within this constraint, Janssen have used the most complete data available in WM and applied the most robust evidence synthesis approach possible for establishing ibrutinib's relative efficacy versus Physician's Choice (PC): a multivariate Cox regression analysis utilising patient-level data from Study 1118E and a pan-European chart review. To test uncertainty in the results, several approaches to the analysis were evaluated to create a matched (i.e., comparable) population for comparison. The resulting estimates of	This comment has been noted. The committee accepted that ibrutinib appears to be more clinically effective than existing treatments but concluded that there is considerable uncertainty about the size of the benefit because of limitations in the data available (FAD, section 4.8).

Consultee	Comment [sic]	Response
	ibrutinib's relative efficacy remain robust and consistent across scenarios, as do model results.	
Janssen	Modelling of pre-progression mortality – ibrutinib arm: The assumption that patients treated with ibrutinib would have an equivalent mortality risk as the general population is supported by clinical experts and the available clinical data. An alternative scenario in which the OS data from Study 1118E is projected directly does not have significant impact on model results. The Committee's consideration of the ERG's extreme assumption that pre-progression mortality would be equivalent between ibrutinib and PC is unsound and contradicts the available clinical evidence and input from clinical experts.	This comment has been noted. The committee accepted that there is uncertainty associated with estimating pre-progression mortality in the ibrutinib arm because of limitations in the data available. (FAD, section 4.11)
Janssen	Modelling of pre-progression mortality – PC arm: Given concerns raised by the ERG, a revised approach towards estimating pre-progression mortality for PC is provided to address the Committee's concerns. The revision results in similar mortality inputs without significant impact to model results.	This comment has been noted. The committee concluded that the company's revised approach to modelling pre-progression mortality in the comparator arm was acceptable for decision making (FAD, section 4.10)
Janssen	Additional data: With agreement from NICE, Janssen summarise additional clinical evidence that has become available since the initial company submission (CS) made in June 2016. These data pertain to updated results from Study 1118E and to additional preliminary results from arm C of an ongoing trial (iNNOVATE) in rituximab-refractory WM patients. The preliminary data from iNNOVATE report a 12-month PFS of 93%. These results not only support the data seen thus far from Study 1118E but further demonstrate the step-changing nature of ibrutinib in WM.	This comment has been noted and the committee has acknowledged the additional clinical evidence (see FAD, section 4.7)

Consultee	Comment [sic]	Response
Janssen	Clarifications and model revisions: The model and results have been updated to reflect certain comments from the ERG; other such comments were reviewed but did not necessarily result in any changes required to the model. These are discussed in further detail along with additional clarifications offered by Janssen.	Comments have been noted.
Janssen	Comparative effectiveness Section 4.8 The Committee concluded that there is uncertainty around the magnitude of relative clinical benefit associated with ibrutinib vs existing treatment (physician choice [PC]). The Committee suggests that this uncertainty may stem from the approach followed by Janssen to conduct the indirect comparison (IDC) and more specifically, in line with the ERG report, from the methods used to select patients from the pan-European chart review (CR) study and create the “matched” cohort. Janssen aim to address each point in turn beginning with the “matching” process.	This comment has been noted. The committee heard that the company had taken four approaches to estimating comparative effectiveness and that all four methods suggested a statistically significant reduction in the risk of disease progression with ibrutinib compared with existing Waldenstrom’s macroglobulinaemia therapies (FAD, section 4.8)
Janssen	Rationale and methods used to select patients in the “matched” cohort In the CS, Janssen explained that in order to apply the Cox regression method based on patient-level data, a “matched” cohort was required and it was therefore created by selecting a subset (n = 175) of the overall pan-European CR cohort (n = 454) that had received similar prior lines of therapy as Study 1118E. Matching is a commonly-used technique to adjust for confounding variables when there is a small overlap between treatment and control arms in these variables.1 Regression analyses are shown to perform poorly in terms of adjusting for residual confounding when there are large imbalances in confounding variables between treatment groups. The matching approach was used to create a balanced population prior to estimation of the treatment effect. In Study 1118E, the distribution of the prior lines	This comment has been noted. The committee was aware that the ERG had several concerns with the company’s approach, including the methods used to select patients in the matched cohort (FAD, section 4.5).However, it accepted that ibrutinib appears to be more clinically effective than existing treatments but that there is considerable uncertainty about the size of the benefit because of limitations in the data available (FAD, section 4.8).

Consultee	Comment [sic]	Response
	of treatment (Study 1118E enrolled patients that had received up to nine lines of prior treatment) was substantially different from that in the overall pan-European CR cohort (CR cohort had received up to four lines of prior treatment). To match the number of prior treatments between the ibrutinib and the PC arms,1 each patient from the CR was randomly sampled following two constraints: i) the same patient from the CR was not allowed to be in two lines at the same time ii) the distribution across lines of therapy of the final subset of patients selected from the CR matched the distribution of patients from Study 1118E as follows: 38% with one prior line, 30% with two prior lines, 17% with three prior lines and 15% with four prior lines. As a result, a total of 175 patients were selected from the CR to create this matched cohort. Janssen acknowledges the limitation to this approach, namely that the CR cohort did not capture heavily treated patients – i.e., patients who received five or more lines of treatment; therefore, the distribution across lines of therapy of the matched cohort can only reflect the distribution of the subset of the Study 1118E population who received no more than four lines of prior treatment (74.5% of the ITT population).	
Janssen	Primary and scenario IDC analyses The Committee questioned the magnitude of the treatment benefit conferred by ibrutinib in the WM setting. It is for this reason that, in addition to the primary analysis, Janssen provided two sensitivity analyses in the CS (i.e., no imputation of missing data and alternative imputation methods for imputing missing data) as well as a further analysis in response to the clarification question B30 (alternative sampling method). Overall, four PFS HR point estimates and their 95% confidence	This comment has been noted. The committee was aware that the company that had taken four approaches to estimating comparative effectiveness and that all four methods suggested a statistically significant reduction in the risk of disease progression with ibrutinib compared

Consultee	Comment [sic]	Response
	intervals have been presented by Janssen using different regression techniques and together these data provide the strongest available evidence of a consistent treatment benefit associated with ibrutinib when compared with PC. These data allow the Committee to observe that the minimum treatment benefit associated with ibrutinib remains notable and reflects the step-change nature of this treatment, which aims to not simply address the symptoms of the disease, but rather targets the disease itself. The methods and reasoning behind these four estimates based on a multivariate Cox regression model are detailed in full in the CS and the clarification responses. These estimates demonstrate clearly that multiple approaches were taken, all resulting in a clinically and statistically significant benefit that cannot be ignored. Furthermore, the ERG's specific critique that no "unique matched cohort" could be established (ERG Report, Section 4.4) could be made against any statistical analysis in which sampling is required and therefore reflects sampling variability, and not a weakness in the specific analyses used in this submission. In conclusion, Table 1 summarises the HRs which vary from [redacted] to [redacted] and all 95% confidence intervals (CI) remain significant. These data reflect a consistent finding regarding ibrutinib's relative clinical efficacy in terms of PFS and supports the assertion that the probabilistic sensitivity analysis using 95% CI accurately captured the variation in the HR of PFS. Figure 1 below further presents the impact of implementing each of the four point estimates for PFS in the model, illustrating that the PFS HR of PC remains relatively consistent across scenarios and consequently, the treatment benefit of ibrutinib remains notable even in the most unfavourable scenario.	with existing Waldenstrom's macroglobulinaemia therapies. (FAD, section 4.8)
Janssen	Modelling of pre-progression mortality	This comment has been noted.

Consultee	Comment [sic]	Response
	Section 4.11 The Committee felt that the dataset used to model PC pre-progression mortality was not clearly described and that as a result, the survival benefit assumed in the base-case analyses submitted by Janssen could be overestimated, leading to uncertainty in the true ICER. Janssen wish to clarify fully the data used to estimate the PC pre-progression mortality. In order to do so, it is important to first clarify the model health states as this may have caused undue confusion and second, to clarify and revise the approach used to estimate pre-progression mortality of PC in the model.	
Janssen	Health states in model First, Janssen wish to clarify that post-progression within the model (i.e., the health states currently referred to as 3L, 4L, and BSC) is an artefact of modelling that does not exist in the real world in exact form. WM patients, like most cancer patients, move from one treatment to the next, to palliation, and then to death. Patients are theoretically in post-progression from one treatment while at the same time in pre-progression on the next. Therefore, dividing the pan-European CR data into an artificial modelling construct of “post-progression” does not work perfectly and there are intrinsic issues which will arise regardless of the method by which the data are divided. In the model construct (see Figure 19, page 76 of the CS), the health state patients first enter is labelled as “2L” but can be considered as the relapsed or refractory (R/R) setting because this first health state makes use of as much data from Study 1118E as possible, bearing in mind the matching required for the IDC (i.e., data from patients with a mixed number of prior treatments ranging from 1 to 4 as discussed in Section 2.1). While the data from Study 1118E could have been sub-	This comment has been noted.

Consultee	Comment [sic]	Response
	divided by prior line of therapy and then assigned to associated health states, the sample size was too small to do so without severely compromising the analysis. Next, because the ibrutinib data applied in this initial health state ultimately consisted of patients with a heterogeneous number of prior treatments, the data for the PC comparator arm used in this initial health state were applied (matched) in a similar way to ensure the data were comparing like for like, in terms of patients with a heterogeneous number of prior lines of treatment. For example, the CR data could have been sub-divided by prior line of therapy and then applied into associated health states because the sample size may well have allowed for this without compromising the analysis (unlike with the Study 1118E data); however, the ibrutinib arm and PC arm data would then be mis-matched. The subsequent health states labelled as “3L”, “4L”, and “BSC” together ultimately represent the modelling artefact of “post-progression” from the initial health state, i.e. those patients who progress from ibrutinib or PC based on progression probabilities taken from Study 1118E and the IDC, less the respective pre-progression mortality (discussed in the next sub-section). The reason why “post-progression” has been sub-divided into three health states (3L, 4L, and BSC) is strictly to ensure the full burden of costs borne by the NHS were considered because it is clear from available data (whether the CR, Study 1118E, or expert clinical opinion) that patients with WM go through multiple treatment options and as such, the cost implications of this need to be captured. In order to populate these health states (with the same data whether patients progress from ibrutinib or PC), cost data were based on a distribution of treatments typically used in these health states as informed by UK clinical opinion; clinical data were from the CR and used for progression (from “3L” and from “4L”) and pre-progression mortality. Importantly,	

Consultee	Comment [sic]	Response
	these CR data are taken from a different, but overlapping, pool of patients (n = 454) than those used to populate the PC arm for the initial health state (n = 175). More specifically, these data were taken from the CR patients who had failed third line (n = 60 of the 454 CR patients). This "cut-off" to subdivide patients in order to assign data for "post-progression" was selected based on the fact that patients in Study 1118E had a median of 2 prior lines of treatment. In summary, every effort was made to use the full range of available data, to align patients (and data) to various health states as best as possible in a logical way, and to ensure the burden of costs faced by the NHS was considered fully; however, in doing so and having the model artefact of "post-progression" which was then further sub-divided, certain 'logical inconsistencies', as labelled by the ERG, appeared. Janssen aim to further explain these and provide alternative approaches in the sub-sections which follow.	
Janssen	Modelling of pre-progression mortality – PC arm Returning to discussion of the initial health state (i.e., "2L") and the PC arm specifically, three inputs are required to capture possible transitions: probability to remain progression-free, probability of death while progression free (i.e., pre-progression mortality), and probability of progression. The IDC is used to inform remaining progression-free. Probability of progression is derived from probability to remain progression-free minus probability of death while progression-free (i.e., pre-progression mortality). In order to inform pre-progression mortality associated with PC, the matched CR cohort dataset (n = 175, comprising of patients who had experienced one to four prior lines of treatment; see Section	The committee concluded that the company's revised approach to modelling pre-progression mortality in the comparator arm was acceptable for decision making (FAD section, 4.10)

Consultee	Comment [sic]	Response
	2.1) was deemed the best source of data because the efficacy input for this health state (i.e., remaining progression-free; PFS HR) was also derived from this dataset. In the original CS, patients were sampled at the last line of active treatment for which they had an observation in the dataset (i.e., at study cut-off date). Pre-progression mortality was estimated based on deaths that occurred during the full observation period - from start of the last line of treatment until the end of follow-up (i.e., cut-off date). Therefore, pre-progression deaths could have included those that occurred during a “watch and wait” period (a death during the time when a patient has stopped e.g. third line treatment because they have progressed but not yet commenced next e.g. fourth line treatment); these deaths could alternatively be considered post-progression deaths. The uncertainty associated with pre-progression mortality (whether in the PC or in the ibrutinib arm, which is discussed further below), is one that can be alleviated relatively easily with further real-world data collection should ibrutinib in the WM setting be considered for the CDF. In the interim, to address the Committee and the ERG’s present concerns about whether the available data were used appropriately, Janssen present an alternative derivation of pre-progression mortality for the PC arm. This approach has a relatively minor impact on model ICERs. In the revised model, pre-progression mortality for PC was derived using a narrower observation window where the point of progression (and not the start of next line of treatment) was used as the ‘cut-off’ point for collecting pre-progression mortality data. As a consequence, death occurring after patients have progressed but whilst they are in the “watch and wait” period (i.e., not yet commenced the next line of treatment) is no longer used to derive the pre-progression risk of death.	

Consultee	Comment [sic]	Response
	The revised estimate reflected slightly lower mortality than in the original CS (see Figure 2 for a comparison of the two pre-progression mortality curves).	
Janssen	Modelling of pre-progression mortality – ibrutinib arm Section 4.12 Janssen firmly disagrees with the scenario described by the Committee (scenario analysis #7 presented by the ERG in its report assuming "equivalent pre-progression mortality for the ibrutinib and comparator groups"), as it is clinically implausible given the potency of ibrutinib. This scenario analysis was presented by the ERG itself in its report as a "pessimistic" scenario to test extreme ICER values (Section 5.4.1 on page 138 of the ERG report) and was by no means included in the ERG's "preferred base-case scenario" (i.e., scenario #4). This assumption that pre-progression mortality would be equivalent between ibrutinib and PC, while labelled an extreme scenario by the ERG, is simply unreasonable and without clinical basis. With a median of 14.8 months of follow-up from Study 1118E, only three deaths had occurred in ibrutinib-treated patients, which is markedly different from the observed data for PC (see Figure 3). Differences in the populations between Study 1118E and the matched CR cohort cannot explain such substantial differences in mortality rates, strongly indicating treatment as the key differentiator. Therefore, the alternative assumption explored by the ERG (scenario #3), and subsequently Janssen, that pre-progression mortality for patients on ibrutinib would be equivalent to that of the general population can hold and has been supported by clinical experts (see Appendix 4 of the original company submission, response to Question 3).	The committee accepted that there is uncertainty associated with estimating pre-progression mortality in the ibrutinib arm because of limitations in the data available. (FAD, section 4.11)

Consultee	Comment [sic]	Response
	Janssen considers this approach presented by the ERG (scenario #3) to be plausible as an alternative to the original company base case assumption of general population mortality. Under this alternative, pre-progression mortality for ibrutinib is based on a constant hazard of projected Study 1118E OS data until this projection intersects with that of the general population mortality, at which point the general population mortality is applied. Note that the 3 deaths reported in Study 1118E were all pre-progression deaths and therefore, OS data are fully representative of pre-progression mortality. In summary, Janssen strongly believe that there is sufficient evidence to discredit the extreme scenario is which pre-progression mortality is assumed equal between the two treatments and is pleased that the ERG have also not considered it within their preferred base-case. Should any doubt remain, as highlighted in the discussion on data pertaining to pre-progression mortality for PC, this parameter is one that can be easily addressed through additional data collected as part of the CDF. In the interim, the data presented above supports that differentiation clearly exists.	
Janssen	Clarifications Firstly, there was some discussion with respect to the definition of treatment naïve chemo-immunotherapy intolerable patients, a population which is within the ibrutinib label. The Committee concluded that as there were no data available in patients who have not received prior therapy and for whom chemo-immunotherapy is unsuitable, ibrutinib could not be recommended in this setting. Janssen wished to explore this further and define both the patient type and potential numbers. WM is a rare	These comments have been noted.

Consultee	Comment [sic]	Response
	disease, which the Committee acknowledged, and this can limit the extent of data collection which can be achieved. However, for these patients where chemo-immunotherapy is not an option, there remains a significant unmet need. Patient numbers are anticipated to be small in the treatment-naïve setting, approximated at 10% during expert consultation. These may be older patients, with co-morbidities, where there is a need to give treatment to control disease rapidly but the intensity of chemo-immunotherapy prohibits the dose intensity that is required to achieve satisfactory disease control. Additional factors may include rituximab intolerance (which is a part of all chemo-immunotherapy regimens) defined as infusion-related reaction or tumour flare in response to receipt; or further disease or clinical-related factors such as poor renal function or the presence of peripheral neuropathy which prohibit the choice of certain options such as purine analogues, vinca alkaloids and/or proteasome inhibitors. It was highly valued by the patient representative submissions that ibrutinib is a generally well tolerated option and as such offers an option where other avenues are limited. Consequently, Janssen would ask the Committee to reconsider the treatment naïve chemo-immunotherapy cohort in this context. Secondly, the ERG expressed concerns related to the inconsistency between PFS data for ibrutinib used in the curve-fitting and the KM data presented in the company's clarification response (see ERG report, Figure 19). The PFS data presented in the clarification response does indeed appear inconsistent with what was used in the model. Janssen apologizes for this confusion and provides the correct information here. Furthermore, it also appeared that in the CS, Janssen used PFS data from the clinical study report (CSR) for which the clinical cut-off date (CCO) was 28 February 2014, as opposed to the PFS data from the 12 December	

Consultee	Comment [sic]	Response
	2014 CCO and on which the Treon 20152 publication was based. Janssen therefore incorporated data from the latest CCO in the revised model (please see Section 4.3). For completeness of information, the Kaplan-Meier (KM) PFS with the latest CCO is presented below (Figure 4). The associated long-term projections for these data are presented in Figure 5.	
Janssen	Corrections Janssen wish to correct an error in relation to the drug acquisition cost of FCR, a component of PC. The error, a mismatch between the FCR dosing regimen described in the CS (which was correct) and the implementation of this for costing purposes in the cost-effectiveness model originally submitted (which was incorrect), was addressed in the revised model. The revised model now aligns with what is correctly stated within the company submission. The ERG expressed concern that modelling errors may be present as listed below. Janssen have thoroughly investigated each of the ERG's concerns and found no such errors in the model. It is possible that the model calculations were not clear to follow and a misunderstanding has occurred.; therefore, clarity is provided here: □ The costs of 3L & 4L in PC arm are discounted twice: A misinterpretation by the ERG has likely occurred. Janssen confirm the costs were not discounted twice. Therefore, no revisions were required. The calculation of lower follow-up costs in the 3L and 4L PFS states are not explained in the CS, nor do they follow any obvious logic. Clinical advisors to the ERG suggested that follow-up costs would remain constant or increase with each consecutive line of therapy: A misinterpretation by the ERG has likely occurred. The	This comment has been noted. The ERG noted that they consider the errors identified still exist and have not been resolved (ERG commentary on the company's response to the ACD, page 4) The committee was mindful of the limitations within the model structure but concluded that it was acceptable for decision making. (FAD, section 4.9)

Consultee	Comment [sic]	Response
	schedule of follow-up costs (types and frequencies of use) remain the same across all lines of treatment. The follow-up costs appear lower in later lines due to the fact that fewer patients remain alive in later lines and because patients progress faster. Therefore, no revisions were required. The CS notes that AEs that were not reported in some of the studies (denoted "NR" in Table 38) were assumed to be 0% in the model and that this is a "conservative" assumption: This pertains not to an error, but to a modelling assumption where Janssen assumed that if an AE was not reported, it did not occur i.e., 0%. Changing the model to exclude these inputs completely has a negligible impact on results (<£5 change in the final ICER) and as such, no revisions to the model have been made.	
Janssen	Conclusion The Committee has made an initial decision to not recommend ibrutinib for WM and to not consider it for inclusion in the CDF. Furthermore, the Committee cites a lack of clarity regarding the size of ibrutinib's treatment benefit and uncertainty regarding survival, with a particular emphasis on a lack of clarity related to inputs used for pre-progression mortality, as the key reasons for not being able to arrive at a most likely ICER. Janssen urges the Committee to consider the additional information presented in this response to the ACD, which strongly supports the following: • The treatment effect of ibrutinib in terms of PFS has been consistently demonstrated across scenarios using rigorous and commonly-used approaches that utilise two patient-level data sets in a space where clinical	The comments have been noted.

Consultee	Comment [sic]	Response
	data are severely limited as well as across trials as evidenced by the additional data that has recently been presented. • The opportunity to collect additional data (e.g., PFS) through the CDF would be an invaluable opportunity to further confirm ibrutinib's treatment effect and to fully discount the most extreme scenarios tested by the ERG. Data collection on the CDF would add to the dearth of evidence in this rare patient population, about which little has been studied or published, thereby broadening the clinical evidence base. • A revised economic analysis in which reasonable alternative approaches towards informing pre-progression mortality for the PC and ibrutinib arms does not result in significantly different health outcomes. Janssen would like to thank the Committee again for the opportunity to comment on the ACD and ask that the Committee consider the additional information shared within the response. Janssen also ask that the Committee consider inclusion of ibrutinib on the CDF, under the commercial conditions (i.e. at zero cost) that we have proposed to NHSE. This is an area of high unmet need and we would like to make ibrutinib available to patients in the UK as soon as possible.	
Lymphoma Association	It is extremely disappointing that NICE is opposing not to recommend the use of ibrutinib within its marketing authorisation for Waldenstrom's Macroglobulinaemia (WM). This is despite NICE's conclusions that: • The therapy could be considered a step change in managing WM (ACD, para 4.14) • WM is a rare and debilitating disease that is associated with a high unmet clinical need for new effective therapies (ACD, para 4.3); and	This comment has been noted. The committee's conclusion on the nature of Waldenstrom's Macroglobulinaemia and innovative quality of ibrutinib can be found in sections 4.3 and 4.14 of the FAD.

Consultee	Comment [sic]	Response
	• The trial evidence showed an overall response rate f 90.5% at 24 months follow up (ACD para 4.7)	
Lymphoma Association	Furthermore, there appears to be overwhelming support from patients, patient groups and practicing clinicians for not only the use of its treatment, but its clinical effectiveness and the dramatic changes it males to living with WM. On top of that, it appears that the manufacturer was offering a discounted price for the treatment that would apparently have achieved an acceptable ICER.	This comment has been noted. The committee can only appraise the price relevant to the NHS. "When there are nationally available price reductions… the reduced price should be used in the reference-case analysis to best reflect the price relevant to the NHS" (Methods guide 5.5.2).
Lymphoma Association	Looked at more widely, if this is the way technology appraisals are going to be handled for new, innovative, targeted treatments for particular subtypes of lymphoma (which are in effect a collection of rare cancers with small patient numbers and difficulties in collecting Phase III trial data due to those numbers), then it is hard to see how lymphoma patients in England will ever be able to benefit from these treatments. Yet other nations within the UK seem able to approve at least some of these treatments for routine use. Lymphoma patients, their carers and families, simply do not understand how this happened in a public system that is paid for out of their taxes; and find it hard to fathom why NICE, the NHS and relevant pharmaceutical companies cannot reach mutually acceptable arrangements to bring new treatments into routine NHS practice expeditiously despite the vast sums of money and industry that is spent on their assessment and appraisal. Elsewhere in the world, ibrutinib is also funded or reimbursed within healthcare systems, but not in the UK – why is this?	This comment has been noted.

Consultee	Comment [sic]	Response
Lymphoma Association	We have seen the ACD response that WMUK has submitted to NICE and would like to indicate our support in general for the points it has raised. In particular, we would like to highlight the following areas of its submission: **Health economics** – the ERG's use of a comparison model suited to conventional single chemotherapy intervention, followed by relapse, is completely inappropriate for the treatment world in which we now live and which will only expand and develop further in this respect. With advances in precision medicine treatment comparisons will become harder and harder to make in the way that NICE currently approaches them. It's akin to insisting that hard copy publications such as books are the only way to consume information, and ignoring the invention and use of the internet as a means of communicating and disseminating knowledge.	This comment has been noted. The model was a de novo model submitted by the company. The ERG's role was to critically evaluate the evidence submission (Process guide, section 3.3.9). The ERG did note several issues with the model structure.
Lymphoma Association	**The ERG view of the Dana Farber "pivotal trial" data** – given the low patient numbers for WM in the UK, it is inevitable that clinical trials must work internationally. This doesn't mean that the patients in this trial were "less damaged" than the average UK patient.	This comment has been noted. The committee concluded that the study was of a reasonable quality, generalisable to UK clinical practice and suitable for decision making, but was limited by the lack of a comparison against a treatment used in the UK (FAD, section 4.6)"

Consultee	Comment [sic]	Response
Lymphoma Association	**Uncertainty** – with rarer forms of cancer, such as WM, and with smaller population, there are always likely to be higher levels of uncertainty. However, to work with thresholds of uncertainty that might be acceptable for common cancers mean reduced opportunities for the approval of rare cancer treatments	This comment has been noted. "There are always likely to be deficiencies in the evidence base available for health technology assessment…Therefore, analyses should be explicit about the limitations of the evidence, and attempts to overcome these, and quantify as fully as possible how the limitations of the data are reflected in the uncertainty in the results of the analysis" Methods Guide 3.2.2
Lymphoma Association	**Cost impact** - for this relatively small group of patients who would benefit from this clinical effective treatment, the overall cost to the NHS will be modest, particularly when set against the saving in conventional chemotherapy treatments and the economic and other benefits to the individual patients and wider society.	This comment has been noted. "The potential budget impact of the adoption of a new technology does not determine the Appraisal Committee's decision. The Committee does take account of how its advice may enable the more efficient use of available healthcare resources" Methods guide 6.2.14

Consultee	Comment [sic]	Response
Waldenstrom's Macroglobulinaemia UK	WMUK warmly welcomes the positive acceptance by the committee that: a) Ibrutinib provides a first genetically targeted therapy and a step change in treatment in this orphan disease. b) Was welcomed by expert clinicians and patients alike as providing a new treatment paradigm, turning an incurable disease into a chronic one for >90% relapsed patients and those unsuitable for chemo-immunotherapy.	This comment has been noted.
Waldenstrom's Macroglobulinaemia UK	**Administration concerns**: problems with committee administration, including late distribution of documents, missing pages, and patient expert marginalisation suggests that committee and experts had too little time to consider 934 pages of complex evidence. Despite the Chair's apology, this casts some doubt over the NICE's resolve to be patient-centric, raising concerns that neither cost, nor clinical effectiveness nor patient welfare, was the committee's focus.	This comment has been noted. NICE acknowledge that on this occasion errors were made in the distribution of papers to the experts attending the meeting
Waldenstrom's Macroglobulinaemia UK	**Health economics**: ERG output with complex health economic calculations was used in a comparison model suited to conventional single chemotherapy intervention and relapse, rather than one based on transformation into a chronic disease. This, in our opinion, exaggerated the actual financial impact of this targeted type of treatment; minimising chemotherapy savings to the NHS and the economic value to patients, carers and society in transforming patients into economically active citizens.	This comment has been noted. The model was a de novo model submitted by the company. The ERG's role was to critically evaluate the evidence submission (Process guide, section 3.3.9) For the reference case, the perspective on outcomes should be all direct health effects, whether for patients or other people. The perspective adopted on costs should be that of the NHS and personal and social services. (Methods guide, 5.1.7)

Consultee	Comment [sic]	Response
Waldenstrom's Macroglobulinaemia UK	**Expert clinician support**, as reported, is muted compared with actual meeting comments and statements. This contrasts with effusive ACD praise for patients. In several places in the text mentioning patient support we would have expected 'and clinicians' to be added. 22 of the most eminent WM clinicians and all main blood cancer charities expressed their unreserved open support the Ibrutnib WM indication, but the former was hidden from the Committee's sight by redaction. The 280 UK treatment questionnaire results showing unmet patient need and Ibrutinib tolerability received no comment.	This comment has been noted. The committee has noted the clinical experts support (throughout the FAD). The committee received the full and unreacted letter of support from the 22 WM clinicians.
Waldenstrom's Macroglobulinaemia UK	**WM genetic targets for BTK not represented in the ACD summary**: there is no mention of the specific genetic targets in WM (MYD88 L256P, CXCR4 discussed by the committee and in main text), targeted by BTK inhibitors in WM, making it the first, and only, genetically targeted therapy for this indication, thus more efficacious in WM, compared with other B Cell malignancies (ie. CLL, MCL) which do not generally share these mutations).	This comment has been noted. The committee accepted the genetically targeting properties of ibrutinib (ACD, section 4.4). This is also now acknowledged in the Summary table (FAD, page 15)
Waldenstrom's Macroglobulinaemia UK	**Limitations of existing treatments**: Whilst side effects of conventional chemotherapy are well presented in 4.3 it needs to be stressed that most responses are VGPR at best. There is also concern to patients of long term transformations (such as Richter's transformation to DBCL) after use of purine analogues such as Fludabarine. There is also the need to use irradiated blood products for those who have had such treatments. Stem cell treatments have been withheld pending review, and IFRs are now generally rejected at screening as cohort requests.	This comment has been noted. The committee conclusions on the current treatment options can be found in section 4.2 of the FAD.

Consultee	Comment [sic]	Response
Waldenstrom's Macroglobulinaemia UK	**Treatment-naïve patient concerns**: The ERG and thus the ACD worry extensively and repeatedly about uncertainty. BTK inhibitors working at the genetic level can be expected to be as least as effective on treatment-naïve patients, as confirmed by Dana Farber (Oct 2016, IWWM9, Amsterdam, personal communication). Older Patients with existing comorbidities will particularly benefit. This oft-repeated ERG suggestion is unjustified and has not been raised as a problem elsewhere in reimbursement discussions. The EMA dealt with it in licensing simply saying: "The restricted indication was considered acceptable as there is no reason to expect inferior efficacy or a worse safety profile in the first line setting, and for the group of patients unsuitable for chemo-immunotherapy, limited treatment options are currently available ……..The assessment of ibrutinib in naïve patients was based only on historical comparisons. However, the observed ORR of 87.3%, as reported in the 1118E study, is reassuring in terms of activity, and numerically superior in inter-study comparisons with most published studies investigating other monotherapy agents in previously treated and/or naive patients. Furthermore, the presence of the MYD88 L265P mutation in both untreated and previously treated WM patients, supporting the mechanistic rationale for treatment with ibrutinib in the treatment-naive setting". (EMA, CHMP 21st May 2015, 2.4.3)	Comment noted. The committee appreciated that patients who have not received prior therapy and for whom chemo-immunotherapy is unsuitable have a particularly high unmet clinical need and considered that the current lack of trial data for this group of patients was a limitation of the evidence base. (FAD. section 4.5)

Consultee	Comment [sic]	Response
Waldenstrom's Macroglobulinaemia UK	**Over-negative ERG View of Dana Farber** (D F) 'Pivotal Trial' Data: Whilst accepting the trial was well conducted, ERG seems intent in impressing on the committee of much data uncertainty in a trial acclaimed as 'pivotal' worldwide. The ACD makes no concessions to the rareness of the disease and difficulty assembling rare disease trials. It states incorrectly that there were no UK patients and infers D F patients may be less damaged than the average UK patient. D F is a tertiary referral centre, effectively the USA's specialist centre for WM and trialists were generally referred patients with no options following multiple relapses and thus likely to be more heavily treated cases than in routine UK Ibrutinib use. The data has already been used to support licensing and reimbursement in USA, Canada and most European Countries, including Greece (most recently the Irish Republic). German patients were reimbursed two days after licensing in June 2015. Why are we last in the reimbursement queue?	This comment has been noted. The committee understood that Waldenstrom's macroglobulinaemia meets the European Medicines Agency's prevalence criteria for rare disease (FAD, section 4.3) The committee heard from the company that there is some difficulty in collecting data in such a small population of patients. (FAD, section 4.5)
Waldenstrom's Macroglobulinaemia UK	Pricing/ICER discussion opportunity wasted: The committee spent a majority of the meeting listening to ERG calculations on a list price with discount when a lower price offer was apparently on the table at NICE. This would supposedly achieve an acceptable ICER result. This occasioned yet further delay and expense, 17 months on from Licensing. There was obvious doubt on pricing – the main focus of the ERG – so common sense would indicate that the meeting should have been postponed until price confirmation, to avoiding wasting the committee's time.	This comment has been noted. The committee appraises the value proposition presented by the company. This should represent the price at which the technology is available to the NHS. When there are nationally available price reductions… the reduced price should be used in the reference-case analysis to best reflect the price relevant to the NHS.(Methods guide 5.5.2)

Consultee	Comment [sic]	Response
Waldenstrom's Macroglobulinaemia UK	**Uncertainty exaggerated**: Whilst all accept uncertainty to a degree, particularly in rare disease trials, there are inherent contradictions in both ERG and ACD reports. On the one hand the trial, "provided convincing evidence of clinical efficacy" (EMA, CHMP May 2105 2.5.5) and follow up data to 37 months shown at IWWM9 (Oct 2106, Treon etc al IWWM9 Amsterdam) confirms how good the results continued to be, (OS of 90% at 95%CI); yet uncertainty by ERG is stressed repeatedly, whilst the ERG is somehow certain that the CDF+ registry route will not reduce uncertainty.	This comment has been noted. "There are always likely to be deficiencies in the evidence base available for health technology assessment…Therefore, analyses should be explicit about the limitations of the evidence, and attempts to overcome these, and quantify as fully as possible how the limitations of the data are reflected in the uncertainty in the results of the analysis" Methods Guide 3.2.2
Waldenstrom's Macroglobulinaemia UK	End of life and rareness criteria: Under Scottish Medicines Consortium rules Ibrutinib would probably be classed as an end of life treatment (death within 3 years) and would get special consideration with far more patient input under their PACE regime. Relapse in heavily treated patients is not necessarily indolent, and may be rapid if not treated.	This comment has been noted. The committee concluded that ibrutinib did not meet the criteria to be considered a life-extending, end-of-life treatment.(FAD, section 4.13)

Consultee	Comment [sic]	Response
Waldenstrom's Macroglobulinaemia UK	**The critical importance of the Clinical Data Registry and CDF route is overlooked**: Public Health England has admitted it can provide no accurate statistics for rare blood cancers. WMUK, trusts, private donors and a wide range of pharma have financed the setting up of the innovative Rory Morrison Clinical Data Registry to address this. It is professionally hosted, NHS IT compatible, with inbuilt data mining tools to reduce treatment uncertainty in this rare disease and is up and running with 300+ patients already entered. This includes EQ5D and later with real time patient reported outcome layers. It will be vital in studying the variability of WM outcomes in targeted medicine related to CXCR4 and MYD88 mutations. We are concerned that clinical need for this study did not feature during the abrupt dismissal of the CDF route of funding by ERG. In addition we do not accept that WM is always indolent in heavily treated patients, and thus no progress could be expected in the two year period. If this criteria were to be strictly applied it is difficult to see any effective pharmaceutical being admitted to the CDF.	This comment has been noted. The committee heard from the clinical experts that the registry currently includes over 300 patients and is able to record patient level data on progression, survival, response, quality of life, and genomic markers, both for treatment naïve and previously treated patients. The committee considered that this data would be a valuable addition to the clinical evidence base and may resolve some of the uncertainties identified. (FAD, section 4.16)
Waldenstrom's Macroglobulinaemia UK	Wider observations regarding reimbursement **a) Previous lack of focus on WM by NICE**: WM patients and clinicians in this orphan disease, using hand me down/off label/orphan use from other lymphomas, have suffered further by withdrawal of interventions such as Bortezomib and recently Stem Cell Transplantation. Widely used Bendamustine is still CDF only. Newly published NICE non Hodgkin lymphoma guidelines (NG52, 2016) ignored WM whilst dealing with other rarer NHLs. There is no NICE pathway for WM or treatment algorithm. This discriminates further against WM, where treatment options have actually reduced in the last 2 years.	This comment has been noted. However, this is beyond the scope of the appraisal committee.

Consultee	Comment [sic]	Response
Waldenstrom's Macroglobulinaemia UK	**Lack of allowance for Rareness:** The Chair stated that she had no instructions to make allowance for rareness, despite public statements by Sir Andrew Dillon to the contrary, and NICE now proposes to allow ICERS up to £100k for ultra-rare diseases: Ethically and clinically, why should £30k be the upper limit for 'just' rare diseases? Where is the RD/URD boundary set? In correspondence, Professor Carole Longson gave WMUK some comfort "we have many examples in the technology appraisals programme demonstrating that it is possible to make a reasonable case for pharmaceuticals with a limited evidence base and a small population".	This comment has been noted. The £100,000 per QALY level, at the time of the appraisal, is a consultation proposal for highly specialised technologies and as such cannot be taken into consideration for this appraisal.
Waldenstrom's Macroglobulinaemia UK	**Use of Ibrutinib in other B cell cancers**. We are concerned that NICE's/NHS increasing focus on cost reduction may be linking the WM STA to a wider discussion over Ibrutinib pricing in other blood cancers. The pre-meeting briefing slides seem to indicate this. We hope the committee completely agree that the needs of clinicians and patients in this specific indication should be treated entirely on merit.	This comment has been noted. The committee has only considered the evidence submitted in this appraisal.
Waldenstrom's Macroglobulinaemia UK	**The cost impact to the NHS will be very modest.** In year 1 at the price given, cost impact would be less than £6m, less the saving in conventional chemotherapy and disregarding all economic benefits to patients and society. A further discount would reduce this pro rata. This falls well within the NICE proposed 'budget impact threshold' of £20m. (NICE, Oct 2016 "to better manage the introduction of treatments that are deemed cost effective but have a very high cost"). However we are very encouraged by Andrew Dillon's Times 31st October statement "NICE isn't going to take affordability into account in deciding whether the NHS should use a new treatment".	This comment has been noted. The £20m affordability threshold is currently a proposal and cannot be considered in this appraisal.

Consultee	Comment [sic]	Response
Waldenstrom's Macroglobulinaemia UK	Can NICE deliver its promise to make innovative medicines rapidly available for rarer diseases? The UK lags substantially behind most of Europe in overall WM survival. Preliminary new data (Prof C. Buske at IWWM9, Pan European Data Platform WM Study, Amsterdam 2016. #1) for 2000- 2015 showed the UK had the lowest OS in WM compared with any major EU country, and below Eastern Europe. For instance 10 year survival probability for UK was 0.50, Italy 0.85. Buske (again, from pan European WM study) stated: "Several studies have shown appreciable differences in the uptake of new cancer drugs across Europe…they have also shown Germany and France among the European countries with the highest access to cancer medicines and the United Kingdom among those with the lowest"	This comment has been noted.
Leukaemia CARE	At present there are limited treatment options available for WM patients, creating a severe unmet need, which could be addressed by the availability of ibrutinib. It is important to have numerous lines of therapy available, as without effective treatment the likely outcome is death.	This comment has been noted. The committee's conclusions on the current management of Waldenstrom's Macroglobulinaemia can be found in section 4.2 of the FAD
Leukaemia CARE	WM is a rare and chronic condition, with a severe and debilitating symptom burden. Patients have reported that ibrutinib can rapidly address this symptom burden and often allow them to return to their normal lives. As such, this is a key quality of life benefit that should not be overlooked.	This comment has been noted. The committee's conclusions on the nature of Waldenstrom's Macroglobulinaemia can be found in section 4.13 of the FAD

Consultee	Comment [sic]	Response
Leukaemia CARE	Ibrutinib is an innovative treatment and the first therapy to be licensed specifically for the treatment of WM. It is also considered to be a step change in the treatment of WM, with a different mechanism of action to other treatments. As such, the availability of ibrutinib would be strongly welcomed by patients as an effective and tolerable therapy.	This comment has been noted. The committee's conclusions on the innovative qualities of ibrutinib can be found in section 4.13 of the FAD
Leukaemia CARE	Whilst ibrutinib is associated with high responses rates and improved survival (normal or near-normal), we acknowledge that the data is uncertain. However, this uncertainty is due to the innovative nature of ibrutinib and the fact that WM is both a rare and chronic condition.	This comment has been noted. The committee's conclusions on the innovative qualities of ibrutinib can be found in section 4.13 of the FAD
Leukaemia CARE	We take objection to the comment that ibrutinib should not be included in the Cancer Drugs Fund because two years is "unlikely to be long enough to collect meaningful progression or survival data because of the long natural history of the disease.". To do so would discriminate against rare and chronic conditions, where there is often the greatest uncertainty. Ibrutinib for the treatment of WM is a prime example of this. Aleviating this uncertainty and enabling access to innovative treatments was central to the recent changes to the Cancer Drugs Fund.	This comment has been noted. The committee's conclusions on ibrutinib's inclusion in the CDF can be found in sections 4.15-4.17 of the FAD

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Clinical expert A	**Has all of the relevant evidence been taken into account?** Yes, and I would like to commend the robustness of the evidence review, which I find to be fair, accurate and representative.	This comment has been noted.

Nominating organisation	Comment [sic]	Response
Clinical expert A	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Yes, I believe that they are. However, the clinical entity of Waldenström's macroglobulinaemia is disadvantaged by its size (patient numbers) and the methodology used in pivotal trials, (which are typically performed in the United States where the clinical agenda is different to that of countries with state-funded healthcare systems), which makes the task of demonstrating clinical and cost effectiveness very difficult. Nevertheless the effectiveness of this drug in this condition is beyond doubt so it is the economics that are proving prohibitive.	This comment has been noted.
Clinical expert A	**Are the recommendations sound and a suitable basis for guidance to the NHS?** No, I believe that Ibrutinib should be available for patients with relapsed and refractory Waldenström's to address a significant unmet clinical need, which was further deepened by the removal of Bortezomib from the CDF.	This comment has been noted.
Clinical expert A	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** I believe that the importance of low toxicity cannot be underestimated in this patient group, many of who are older (median age is close to 70 years for this condition). This treatment represents a step-change in this regard, as evidenced by patient testimony at the initial meeting as well as the WMUK patient survey earlier this year that highlighted underappreciated chemotherapy-related side effects.	This comment has been noted. The committee noted that ibrutinib is highly effective compared with existing treatments, and very well tolerated with a lower toxicity profile. (ACD, section 4.4)

Clinical expert A	Cancer Drugs Fund (ACD, page 12) 4.15 " It concluded that ibrutinib for treating Waldenstrom's macroglobulinaemia does not have the plausible potential to be cost effective in routine commissioning and cannot be recommended for inclusion in the Cancer Drugs Fund." Within the didactic constraints of a 2 year period, meaningful survival data is unlikely to be forthcoming, but it is very likely that important PFS data would be accrued, as well as valuable QOL, adverse events and relevant real-life UK data on patients with WM. This is a 'small disease' with manageable numbers for effective data collection, and an existing Registry already in place. Given that the methodology for data collection to inform the new CDF is in development, we stakeholders await clear guidance on exactly how it will look. Consequently, we were relatively ill-prepared to answer detailed questions about the kind of data we can capture in the Registry, but we will be in a position to offer a more detailed breakdown of the proposed data collection model at the second meeting. We believe that the inclusion of a data collection exercise would be informative for this indication as well as others going forwards. The 9th International Workshop on WM has just taken place in Amsterdam, and further data regarding the various genomic profiles of WM entities were presented. Incorporating a genomic profile into the data collection process will provide an amazing opportunity to interrogate subgroups of WM patients who would benefit from this drug through a national data capture exercise. We would like to discuss this further at the second discussion meeting. This may not immediately translate into a more favourable cost-effectiveness estimate, but will help to provide a valuable snap shot in the era of novel biological agents.	This comment has been noted. The committee's conclusions on ibrutinib's inclusion in the CDF can be found in sections 4.15-4.17 of the FAD

Nominating organisation	Comment [sic]	Response
Clinical expert A	ACD 4.4 “The committee concluded that there is no standard of care for treating Waldenstrom’s macroglobulinaemia and that targeted therapy is highly valued by patients and addresses a significant unmet need.” I attach a recently published meta-analysis for information (Santos-Lozano et al 2016)	This comment has been noted.
Clinical expert A	ACD 4.4 “The committee heard that ibrutinib would be particularly valuable for people with disease that is refractory to first line treatment or who relapsed following successful first line therapy. “ This point cannot be underestimated. There are very few agents available for the treatment of UK patients with WM, who lag behind their counterparts in Europe as far as accessibility to treatment options is concerned.	This comment has been noted.
Clinical expert A	ACD 4.6 “The committee concluded that PCYC-1118E is of a reasonable quality and generalisable to UK clinical practice, but is limited by the lack of a comparison against a treatment used in the UK.” It is probably useful for the comparator to be “Rituximab + chemo (either alkyltators, purine analogues or bendamustine, which has a mechanism of action that straddles these)”.	This comment has been noted.
Clinical expert A	ACD 4.9, 4.10 “The committee was mindful of the limitations within the model structure but concluded that it was acceptable for decision making.” This is reassuring but what does it mean in practice?	This comment has been noted. The committee was satisfied that it could make a decision based on the results of the economic model.

Nominating organisation	Comment [sic]	Response
Clinical expert A	ACD “The committee made no specific recommendations for any subgroups.” I think it is hard to accurately capture the material benefits of this treatment in older age groups (which accounts for the majority of patients with WM), but I believe there would be a clinically significant advantage for older patients in particular. For example, a high proportion of older and less fit patients need hospital transport to attend appointments for chemotherapy, as well as management of complications. Frequent attendances in clinics for blood tests and review all add up to QOL costs for the patients and financial costs for the NHS. The toxicities of conventional chemotherapy can also lead to the need for blood transfusions, growth factor injections, intravenous immunoglobulin infusions to treat secondary hypogammaglobulinaemia and so forth.	This comment has been noted.

Nominating organisation	Comment [sic]	Response
Clinical expert B	It is disappointing that ibrutinib has not been recommended for treatment of patients with Waldenstrom's macroglobulinaemia (WM). In my view ibrutinib represents a real paradigm shift in disease management and is an exemplar for precision / personalised medicine. It was pleasing to note that the committee recognised that WM was • a debilitating and life limiting disorder • an unmet clinical need due to limited available therapies with significant toxicities and short durations of response • disadvantaged by removal of bortezomib from the Cancer Drugs Fund and uncertainty surrounding funding for autologous stem cell transplantation Similarly the committee concluded that ibrutinib was • a novel therapy which targets the MYD88 L265P gene mutation present in the majority of WM patients • associated with high response rates and excellent survival outcomes at 2 years • likely more effective than existing treatments • associated with an excellent toxicity profile The committee concluded, correctly in my view, that ibrutinib represented a truly innovative approach to treatment of WM and a "step change" in management strategies. It was unable to recommend its use largely on the basis of cost-effectiveness issues. I have a number of comments on this	This comment has been noted.

Nominating organisation	Comment [sic]	Response
Clinical expert B	**Overall survival assumptions** It is, in my opinion, based on the efficacy data from the PCYC-118E study along with comparisons from the European chart review cohort that ibrutinib will result in significant overall survival (OS) benefits for WM patients. It is agreed that both sources of data are satisfactory for evaluation in the current context. It is clearly inappropriate and likely unethical to wait for definitive OS data to emerge from PCYC-118E study. I have little or no expertise in cost effectiveness analyses but note the debate regarding pre-progression mortality assumptions made in the application by the company and raised by the ERG. On reflection, I think that it is not unreasonable to think that pre-progression survival may be better in ibrutinib treated patients as a result of the greater long and short term haematological and infectious complications that can occur with conventional chemotherapy particularly in the relapsed / refractory setting. Quantifying this potential effect is clearly very challenging. I agree that it is not possible at present to perform a cost-effectiveness analysis for treatment naïve patients.	This comment has been noted. The committee heard from the clinical experts that it was not unreasonable to expect pre-progression survival to be better in ibrutinib treated patients because of the greater long and short term haematological and infectious complications that can occur with conventional chemotherapy.(FAD section 4.11)
Clinical expert B	**Most plausible incremental cost-effectiveness ratio.** Uncertainties with respect to mortality modelling and on-going negotiations regarding drug cost preclude any further meaningful comment.	This comment has been noted.

Nominating organisation	Comment [sic]	Response
Clinical expert B	**Cancer Drugs Fund (CDF).** The committee has concluded that ibrutinib should not be included in the CDF. The committee felt that over the 2-year period it was unlikely that additional survival data will be forthcoming and there was limited likelihood of the cost-effectiveness outcome improving to a level that would allow routine use. On reflection, I believe there are a number reasons to challenge these conclusions • Cost effectiveness should be reviewed when survival modelling has been agreed and a formal decision regarding drug costing made. • Additional survival data from PCYC-118E as well the INNOVATE study will become available during this time period. This will include data from treatment naïve patients in addition to the relapse / refractory group. • Whilst it is appreciated that formal progression free and overall survival data are unlikely to become available within 2 years of CDF access. Appropriately collected response data would be valuable. If M protein and haemoglobin responses (as well toxicities) are similar to those seen PCYC-118E and INNOVATE it would not be unreasonable to assume similar survival outcomes. The availability of an existing national registry as well as a proactive patient group provides an excellent opportunity to collect real world response data as well as patient reported outcomes in real time. This could potentially provide a model and route of approval for other rare disorders where conventional phase 3 data are lacking	This comment has been noted. The committee's conclusions on ibrutinib's inclusion in the CDF can be found in sections 4.15-4.17 of the FAD

Nominating organisation	Comment [sic]	Response
Clinical expert B	**Equality issues.** Whilst there are no definite concerns it should be noted that WM is disease of older people and is more common in men than women.	This comment has been noted. The committee acknowledged that access to ibrutinib may be particularly beneficial for older people (FAD, section 4.18)
Clinical expert B	**Conclusions.** Ibrutinib represents a real paradigm shift in disease management. Ibrutinib should be available for patients with relapsed / refractory WM. It has unprecedented single agent activity and excellent toxicity profile. It specifically targets the biological effect of MYD88 mutations and as such is an exemplar for precision medicine. Access could potentially be limited to those patients with demonstrable mutations. Access via the CDF seems most appropriate at this time. Access to a national registry along with a proactive patient group represents a real opportunity to develop a process and model for other rare disorders. There is no evidence to support the use of ibrutinib in treatment naïve patients. This is not, in my opinion, an area of unmet need and should be formally addressed with further trials.	This comment has been noted.

Comments received from commentators

Commentator	Comment [sic]	Response
	None	

Comments received from members of the public

Role*	Section	Comment [sic]	Response
		None	

Summary of comments received from members of the public

Theme	Response
NA	NA

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Response to the Appraisal Consultation Document (ACD)

Ibrutinib for treating Waldenström's macroglobulinaemia [ID884]

November 2nd 2016

Contents

1. Overview

Janssen welcomes the opportunity to comment on the preliminary recommendation made by the Appraisal Committee detailed in the appraisal consultation document (ACD). We are disappointed the Appraisal Committee's preliminary decision is that ibrutinib is not recommended within its marketing authorisation for treating Waldenström's macroglobulinaemia (WM) in adults who have had at least one prior therapy or as first-line treatment when chemo-immunotherapy is unsuitable; however, we are committed to working with NICE and this response aims to address the Appraisal Committee's key concerns as outlined in the ACD.

Ibrutinib, with its unprecedented efficacy and well tolerated safety profile, represents the first technology licensed for treating this rare condition, offering a step-change to National Health Service (NHS) patients who are offered limited and ever-decreasingly effective treatment options – as evidenced by the Cancer Drugs Fund (CDF) delisting of bortezomib in 2015 and the recent decommissioning of stem cell transplant in this population.

In this light and with a commitment to find a way forward for ibrutinib in WM, the main points we wish to address are as follows:

- **Comparative effectiveness**: Given the rarity of WM, an ultra-orphan condition, there is a recognised scarcity of clinical data. Within this constraint, Janssen have used the most complete data available in WM and applied the most robust evidence synthesis approach possible for establishing ibrutinib's relative efficacy versus Physician's Choice (PC): a multivariate Cox regression analysis utilising patient-level data from Study 1118E and a pan-European chart review. To test uncertainty in the results, several approaches to the analysis were evaluated to create a matched (i.e., comparable) population for comparison. The resulting estimates of ibrutinib's relative efficacy remain robust and consistent across scenarios, as do model results.
- **Modelling of pre-progression mortality – PC arm**: Given concerns raised by the ERG, a revised approach towards estimating pre-progression mortality for PC is provided to address the Committee's concerns. The revision results in similar mortality inputs without significant impact to model results.
- **Modelling of pre-progression mortality – ibrutinib arm**: The assumption that patients treated with ibrutinib would have an equivalent mortality risk as the general population is supported by clinical experts and the available clinical data. An alternative scenario in which the OS data from Study 1118E is projected directly does not have significant impact on model results. The Committee's consideration of the ERG's extreme assumption that pre-progression mortality would be equivalent between ibrutinib and PC is unsound and contradicts the available clinical evidence and input from clinical experts.
- **Additional data**: With agreement from NICE, Janssen summarise additional clinical evidence that has become available since the initial company submission (CS) made in June 2016. These data pertain to updated results from Study 1118E and to additional preliminary results from arm C of an ongoing trial (iNNOVATE) in rituximab-refractory WM patients. The preliminary data from iNNOVATE report a 12-month PFS of 93%. These results not only support the data seen thus far from Study 1118E but further demonstrate the step-changing nature of ibrutinib in WM.
- **Clarifications and model revisions**: The model and results have been updated to reflect certain comments from the ERG; other such comments were reviewed but did not necessarily result in any changes required to the model. These are discussed in further detail along with additional clarifications offered by Janssen.

A detailed response to each of these key issues is provided on the following pages.

2. Comparative effectiveness (multivariate Cox regression)

"The committee understood that the analysis suggested a substantial reduction in the risk of disease progression with ibrutinib compared with existing Waldenström's macroglobulinaemia therapies however it was also aware that the ERG had several concerns with the company's approach, including that the methods used to select patients in the matched cohort were unclear and that an alternative matched cohort produced a smaller reduction in the risk of progression for ibrutinib compared with existing treatments. The committee concluded, based on the testimonies from patients and clinical experts, that ibrutinib appears to be more clinically effective than existing treatments but there is considerable uncertainty about the size of the benefit." (Section 4.8)

The Committee concluded that there is uncertainty around the magnitude of relative clinical benefit associated with ibrutinib vs existing treatment (physician choice [PC]). The Committee suggests that this uncertainty may stem from the approach followed by Janssen to conduct the indirect comparison (IDC) and more specifically, in line with the ERG report, from the methods used to select patients from the pan-European chart review (CR) study and create the "matched" cohort. Janssen aim to address each point in turn beginning with the "matching" process.

2.1. Rationale and methods used to select patients in the "matched" cohort

In order to estimate relative clinical efficacy, Janssen utilised two sources of patient-level data (Study 1118E and the pan-European CR) to conduct a multivariate Cox regression model, which is a robust and flexible methodology allowing adjustment for differences between data sources that cannot be linked via common comparators. As described in the Company Submission (CS) and acknowledged during the public session of the first appraisal committee meeting, due to the rare nature of WM, neither additional nor alternative data sources are available to inform the estimate of relative clinical efficacy and comparative trial data in WM is understandably limited.

In the CS, Janssen explained that in order to apply the Cox regression method based on patient-level data, a "matched" cohort was required and it was therefore created by selecting a subset (n = 175) of the overall pan-European CR cohort (n = 454) that had received similar prior lines of therapy as Study 1118E. Matching is a commonly-used technique to adjust for confounding variables when there is a small overlap between treatment and control arms in these variables.[1] Regression analyses are shown to perform poorly in terms of adjusting for residual confounding when there are large imbalances in confounding variables between treatment groups. The matching approach was used to create a balanced population prior to estimation of the treatment effect. In Study 1118E, the distribution of the prior lines of treatment (Study 1118E enrolled patients that had received up to nine lines of prior treatment) was substantially different from that in the overall pan-European CR cohort (CR cohort had received up to four lines of prior treatment). To match the number of prior treatments between the ibrutinib and the PC arms,[1] each patient from the CR was randomly sampled following two constraints:

i) the same patient from the CR was not allowed to be in two lines at the same time
ii) the distribution across lines of therapy of the final subset of patients selected from the CR matched the distribution of patients from Study 1118E as follows: 38% with one prior line, 30% with two prior lines, 17% with three prior lines and 15% with four prior lines.

As a result, a total of 175 patients were selected from the CR to create this matched cohort. Janssen acknowledges the limitation to this approach, namely that the CR cohort did not capture heavily treated patients – i.e., patients who received five or more lines of treatment; therefore, the

[1] Data Analysis Using Regression and Multilevel/Hierarchical Models. Andrew Gelman, Columbia University, New York Jennifer Hill, Columbia University, New York. DATE PUBLISHED: December 2006

distribution across lines of therapy of the matched cohort can only reflect the distribution of the subset of the Study 1118E population who received no more than four lines of prior treatment (74.5% of the ITT population).

2.2. Primary and scenario IDC analyses

The Committee questioned the magnitude of the treatment benefit conferred by ibrutinib in the WM setting. It is for this reason that, in addition to the primary analysis, Janssen provided two sensitivity analyses in the CS (i.e., no imputation of missing data and alternative imputation methods for imputing missing data) as well as a further analysis in response to the clarification question B30 (alternative sampling method). Overall, four PFS HR point estimates and their 95% confidence intervals have been presented by Janssen using different regression techniques and together these data provide the strongest available evidence of a consistent treatment benefit associated with ibrutinib when compared with PC. These data allow the Committee to observe that the minimum treatment benefit associated with ibrutinib remains notable and reflects the step-change nature of this treatment, which aims to not simply address the symptoms of the disease, but rather targets the disease itself.

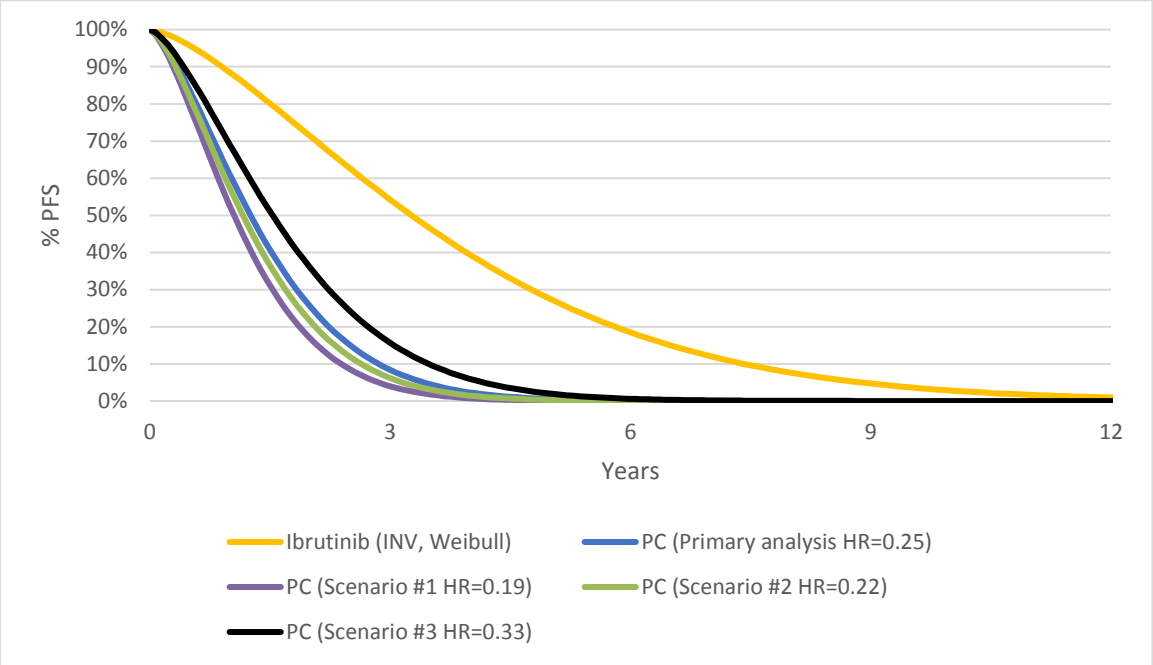
The methods and reasoning behind these four estimates based on a multivariate Cox regression model are detailed in full in the CS and the clarification responses. These estimates demonstrate clearly that multiple approaches were taken, all resulting in a clinically and statistically significant benefit that cannot be ignored. Furthermore, the ERG's specific critique that no "unique matched cohort" could be established (ERG Report, Section 4.4) could be made against any statistical analysis in which sampling is required and therefore reflects sampling variability, and not a weakness in the specific analyses used in this submission.

In conclusion, Table 1 summarises the HRs which vary from [redacted] to [redacted] and all 95% confidence intervals (CI) remain significant. These data reflect a consistent finding regarding ibrutinib's relative clinical efficacy in terms of PFS and supports the assertion that the probabilistic sensitivity analysis using 95% CI accurately captured the variation in the HR of PFS. Figure 1 below further presents the impact of implementing each of the four point estimates for PFS in the model, illustrating that the PFS HR of PC remains relatively consistent across scenarios and consequently, the treatment benefit of ibrutinib remains notable even in the most unfavourable scenario.

Table 1. PFS HRs and 95% CIs Derived from IDC

Analysis	Description	PFS HR (95% CI)
Primary analysis (CS)	Missing characteristics imputed	[redacted]
Scenario analysis #1 (CS)	Excluded patients with missing characteristics	[redacted]
Scenario analysis #2 (CS)	Missing characteristics imputed using risk categories only	[redacted]
Scenario analysis #3 (in response to clarification question B30)	Missing characteristics imputed	[redacted]

Figure 1. Comparison of projected PFS based on different HR estimates



3. Modelling of pre-progression mortality

"The committee considered the estimates of pre-progression mortality and noted the ERG's comments that the company had potentially used unsuitable data to inform the pre-progression mortality for the comparator group (physician's choice). It heard from the ERG that it was unclear whether the model used data on all deaths, or only those occurring before progression, to model pre-progression mortality in the comparator arm. The committee was not satisfied that this issue was resolved following the explanation given by the company in the meeting. The committee understood that if there was an inflated risk of death prior to progression in the comparator arm when compared with ibrutinib, this would lead to an overestimate of the relative effectiveness of ibrutinib and an underestimate of the incremental cost effectiveness ratio (ICER). It concluded that it could not determine how pre-progression mortality in the comparator arm was estimated, and that this uncertainty impacted on the cost-effectiveness estimates produced in the economic model." (Section 4.11)

The Committee felt that the dataset used to model PC pre-progression mortality was not clearly described and that as a result, the survival benefit assumed in the base-case analyses submitted by Janssen could be overestimated, leading to uncertainty in the true ICER.

Janssen wish to clarify fully the data used to estimate the PC pre-progression mortality. In order to do so, it is important to first clarify the model health states as this may have caused undue confusion and second, to clarify and revise the approach used to estimate pre-progression mortality of PC in the model.

3.1. Health states in model

First, Janssen wish to clarify that post-progression within the model (i.e., the health states currently referred to as 3L, 4L, and BSC) is an artefact of modelling that does not exist in the real world in exact form. WM patients, like most cancer patients, move from one treatment to the next, to palliation, and then to death. Patients are theoretically in post-progression from one treatment while at the same time in pre-progression on the next. Therefore, dividing the pan-European CR data

into an artificial modelling construct of “post-progression” does not work perfectly and there are intrinsic issues which will arise regardless of the method by which the data are divided.

In the model construct (see Figure 19, page 76 of the CS), the health state patients first enter is labelled as “2L” but can be considered as the relapsed or refractory (R/R) setting because this first health state makes use of as much data from Study 1118E as possible, bearing in mind the matching required for the IDC (i.e., data from patients with a mixed number of prior treatments ranging from 1 to 4 as discussed in Section 2.1). While the data from Study 1118E could have been sub-divided by prior line of therapy and then assigned to associated health states, the sample size was too small to do so without severely compromising the analysis.

Next, because the ibrutinib data applied in this initial health state ultimately consisted of patients with a heterogeneous number of prior treatments, the data for the PC comparator arm used in this initial health state were applied (matched) in a similar way to ensure the data were comparing like for like, in terms of patients with a heterogeneous number of prior lines of treatment. For example, the CR data could have been sub-divided by prior line of therapy and then applied into associated health states because the sample size may well have allowed for this without compromising the analysis (unlike with the Study 1118E data); however, the ibrutinib arm and PC arm data would then be mis-matched.

The subsequent health states labelled as “3L”, “4L”, and “BSC” together ultimately represent the modelling artefact of “post-progression” from the initial health state, i.e. those patients who progress from ibrutinib or PC based on progression probabilities taken from Study 1118E and the IDC, less the respective pre-progression mortality (discussed in the next sub-section). The reason why “post-progression” has been sub-divided into three health states (3L, 4L, and BSC) is strictly to ensure the full burden of costs borne by the NHS were considered because it is clear from available data (whether the CR, Study 1118E, or expert clinical opinion) that patients with WM go through multiple treatment options and as such, the cost implications of this need to be captured. In order to populate these health states (with the same data whether patients progress from ibrutinib or PC), cost data were based on a distribution of treatments typically used in these health states as informed by UK clinical opinion; clinical data were from the CR and used for progression (from “3L” and from “4L”) and pre-progression mortality. Importantly, these CR data are taken from a *different, but overlapping, pool* of patients (n = 454) than those used to populate the PC arm for the initial health state (n = 175). More specifically, these data were taken from the CR patients who had failed third line (n = 60 of the 454 CR patients). This “cut-off” to subdivide patients in order to assign data for “post-progression” was selected based on the fact that patients in Study 1118E had a median of 2 prior lines of treatment.

In summary, every effort was made to use the full range of available data, to align patients (and data) to various health states as best as possible in a logical way, and to ensure the burden of costs faced by the NHS was considered fully; however, in doing so and having the model artefact of “post-progression” which was then further sub-divided, certain ‘logical inconsistencies’, as labelled by the ERG, appeared. Janssen aim to further explain these and provide alternative approaches in the sub-sections which follow.

3.2. Modelling of pre-progression mortality – PC arm

Returning to discussion of the initial health state (i.e., “2L”) and the PC arm specifically, three inputs are required to capture possible transitions: probability to remain progression-free, probability of death while progression free (i.e., pre-progression mortality), and probability of progression.

The IDC is used to inform remaining progression-free. Probability of progression is derived from probability to remain progression-free minus probability of death while progression-free (i.e., pre-progression mortality). In order to inform pre-progression mortality associated with PC, the matched CR cohort dataset (n = 175, comprising of patients who had experienced one to four prior lines of

treatment; see Section 2.1) was deemed the best source of data because the efficacy input for this health state (i.e., remaining progression-free; PFS HR) was also derived from this dataset.

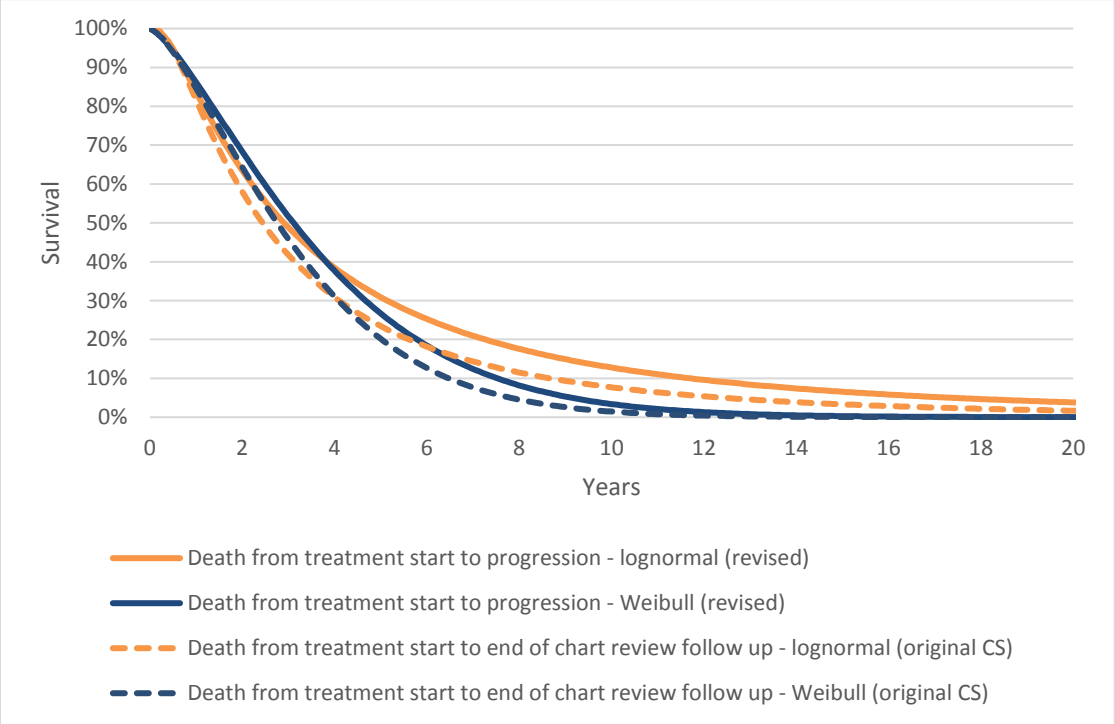
In the original CS, patients were sampled at the last line of active treatment for which they had an observation in the dataset (i.e., at study cut-off date). Pre-progression mortality was estimated based on deaths that occurred during the full observation period - from start of the last line of treatment until the end of follow-up (i.e., cut-off date). Therefore, pre-progression deaths could have included those that occurred during a "watch and wait" period (a death during the time when a patient has stopped e.g. third line treatment because they have progressed but not yet commenced next e.g. fourth line treatment); these deaths could alternatively be considered post-progression deaths.

The uncertainty associated with pre-progression mortality (whether in the PC or in the ibrutinib arm, which is discussed further below), is one that can be alleviated relatively easily with further real-world data collection should ibrutinib in the WM setting be considered for the CDF. In the interim, to address the Committee and the ERG's present concerns about whether the available data were used appropriately, Janssen present an alternative derivation of pre-progression mortality for the PC arm. This approach has a relatively minor impact on model ICERs.

In the revised model, pre-progression mortality for PC was derived using a narrower observation window where the point of progression (and not the start of next line of treatment) was used as the 'cut-off' point for collecting pre-progression mortality data. As a consequence, death occurring after patients have progressed but whilst they are in the "watch and wait" period (i.e., not yet commenced the next line of treatment) is no longer used to derive the pre-progression risk of death.

The revised estimate reflected slightly lower mortality than in the original CS (see Figure 2 for a comparison of the two pre-progression mortality curves).

Figure 2. Comparison of pre-progression mortality curves for PC



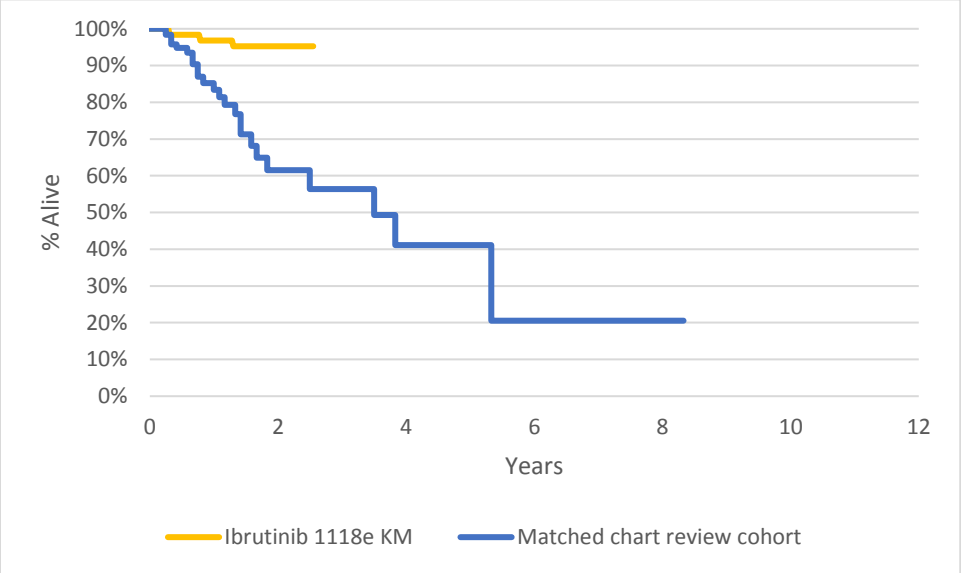
3.3. Modelling of pre-progression mortality – ibrutinib arm

"The committee recalled that median overall survival had not been reached in PCYC-1118E and it noted comments from the clinical experts that pre-progression mortality estimates were unclear, because almost half of patients with WM die from unrelated causes. In the clinical expert's view, death in the progression-free state is most likely to be from an unrelated cause. The committee noted the ERG's concern that the assumption used by the company could bias the ICER in favour of ibrutinib. One of the ERG's exploratory analyses incorporated an assumption of equivalent pre-progression mortality for the ibrutinib and comparator groups, which resulted in a substantially higher ICER than presented by the company. The committee appreciated that there was considerable uncertainty around the estimation of overall survival but concluded that the issue of pre-progression mortality was a concern that merited further consideration." (Section 4.12)

Janssen firmly disagrees with the scenario described by the Committee (scenario analysis #7 presented by the ERG in its report assuming "equivalent pre-progression mortality for the ibrutinib and comparator groups"), as it is clinically implausible given the potency of ibrutinib. This scenario analysis was presented by the ERG itself in its report as a "pessimistic" scenario to test extreme ICER values (Section 5.4.1 on page 138 of the ERG report) and was by no means included in the ERG's "preferred base-case scenario" (i.e., scenario #4).

This assumption that pre-progression mortality would be equivalent between ibrutinib and PC, while labelled an extreme scenario by the ERG, is simply unreasonable and without clinical basis. With a median of 14.8 months of follow-up from Study 1118E, only three deaths had occurred in ibrutinib-treated patients, which is markedly different from the observed data for PC (see Figure 3). Differences in the populations between Study 1118E and the matched CR cohort cannot explain such substantial differences in mortality rates, strongly indicating treatment as the key differentiator.

Figure 3. Comparison of pre-progression mortality of ibrutinib versus PC



Therefore, the alternative assumption explored by the ERG (scenario #3), and subsequently Janssen, that pre-progression mortality for patients on ibrutinib would be equivalent to that of the general population can hold and has been supported by clinical experts (see Appendix 4 of the original company submission, response to Question 3).

Janssen considers this approach presented by the ERG (scenario #3) to be plausible as an alternative to the original company base case assumption of general population mortality. Under this alternative, pre-progression mortality for ibrutinib is based on a constant hazard of projected Study

1118E OS data until this projection intersects with that of the general population mortality, at which point the general population mortality is applied. Note that the 3 deaths reported in Study 1118E were all pre-progression deaths and therefore, OS data are fully representative of pre-progression mortality.

In summary, Janssen strongly believe that there is sufficient evidence to discredit the extreme scenario is which pre-progression mortality is assumed equal between the two treatments and is pleased that the ERG have also not considered it within their preferred base-case. Should any doubt remain, as highlighted in the discussion on data pertaining to pre-progression mortality for PC, this parameter is one that can be easily addressed through additional data collected as part of the CDF. In the interim, the data presented above supports that differentiation clearly exists.

4. Minor clarifications, corrections, and revised economic analyses

Janssen would like to take this opportunity to clarify a few points of confusion, address corrections that were suggested by the ERG, and finally, present revised results based on proposed changes to the company base-case.

4.1. Clarifications

Firstly, there was some discussion with respect to the definition of treatment naïve chemo-immunotherapy intolerable patients, a population which is within the ibrutinib label.

The Committee concluded that as there were no data available in patients who have not received prior therapy and for whom chemo-immunotherapy is unsuitable, ibrutinib could not be recommended in this setting. Janssen wished to explore this further and define both the patient type and potential numbers. WM is a rare disease, which the Committee acknowledged, and this can limit the extent of data collection which can be achieved. However, for these patients where chemo-immunotherapy is not an option, there remains a significant unmet need. Patient numbers are anticipated to be small in the treatment-naïve setting, approximated at 10% during expert consultation. These may be older patients, with co-morbidities, where there is a need to give treatment to control disease rapidly but the intensity of chemo-immunotherapy prohibits the dose intensity that is required to achieve satisfactory disease control. Additional factors may include rituximab intolerance (which is a part of all chemo-immunotherapy regimens) defined as infusion-related reaction or tumour flare in response to receipt; or further disease or clinical-related factors such as poor renal function or the presence of peripheral neuropathy which prohibit the choice of certain options such as purine analogues, vinca alkaloids and/or proteasome inhibitors. It was highly valued by the patient representative submissions that ibrutinib is a generally well tolerated option and as such offers an option where other avenues are limited. Consequently, Janssen would ask the Committee to reconsider the treatment naïve chemo-immunotherapy cohort in this context.

Secondly, the ERG expressed concerns related to the inconsistency between PFS data for ibrutinib used in the curve-fitting and the KM data presented in the company's clarification response (see ERG report, Figure 19). The PFS data presented in the clarification response does indeed appear inconsistent with what was used in the model. Janssen apologizes for this confusion and provides the correct information here. Furthermore, it also appeared that in the CS, Janssen used PFS data from the clinical study report (CSR) for which the clinical cut-off date (CCO) was 28 February 2014, as opposed to the PFS data from the 12 December 2014 CCO and on which the Treon 2015[2] publication was based.

[2] Treon, S.P., Tripsas, C.K., et al. (2015). Ibrutinib in previously treated Waldenstrom's macroglobulinemia. N Engl J Med. 372(15): 1430-40.

Janssen therefore incorporated data from the latest CCO in the revised model (please see Section 4.3). For completeness of information, the Kaplan-Meier (KM) PFS with the latest CCO is presented below (Figure 4). The associated long-term projections for these data are presented in Figure 5.

[redacted]

[redacted]

4.2. Corrections

Janssen wish to correct an error in relation to the drug acquisition cost of FCR, a component of PC. The error, a mismatch between the FCR dosing regimen described in the CS (which was correct) and the implementation of this for costing purposes in the cost-effectiveness model originally submitted

(which was incorrect), was addressed in the revised model. The revised model now aligns with what is correctly stated within the company submission.

The ERG expressed concern that modelling errors may be present as listed below. Janssen have thoroughly investigated each of the ERG's concerns and found no such errors in the model. It is possible that the model calculations were not clear to follow and a misunderstanding has occurred.; therefore, clarity is provided here:

- The costs of 3L & 4L in PC arm are discounted twice: A misinterpretation by the ERG has likely occurred. Janssen confirm the costs were not discounted twice. Therefore, no revisions were required.

- The calculation of lower follow-up costs in the 3L and 4L PFS states are not explained in the CS, nor do they follow any obvious logic. Clinical advisors to the ERG suggested that follow-up costs would remain constant or increase with each consecutive line of therapy: A misinterpretation by the ERG has likely occurred. The schedule of follow-up costs (types and frequencies of use) remain the same across all lines of treatment. The follow-up costs appear lower in later lines due to the fact that fewer patients remain alive in later lines and because patients progress faster. Therefore, no revisions were required.

- The CS notes that AEs that were not reported in some of the studies (denoted "NR" in Table 38) were assumed to be 0% in the model and that this is a "conservative" assumption: This pertains not to an error, but to a modelling assumption where Janssen assumed that if an AE was not reported, it did not occur i.e., 0%. Changing the model to exclude these inputs completely has a negligible impact on results (<£5 change in the final ICER) and as such, no revisions to the model have been made.

4.3. Revised results

Janssen have revised the economic model following the concerns raised by the Committee and changes suggested by the ERG, and with consideration to the main points discussed in the preceding sections. The revised base case incorporates the following major changes:

- Revision to the pre-progression mortality of PC to reflect the mortality from treatment start to progression (see Section 3.1)
- Revision to the pre-progression mortality of ibrutinib to assume constant hazard based on Study 1118E observation until the general population mortality exceeds the constant hazard, and then switch to general population mortality (see Section 3.2)
- Revision to the ibrutinib PFS projection to reflect the PFS reported in the 12 December 2014 dataset and used in Treon 2015 publication[3] (see Section 4.1)
- Correction to PC drug acquisition costs to reflect the regimens described in the CS (see Section 4.2)

With the amendments as described above, the model results in an ICER of £87,934 for ibrutinib at the list price (Table 2) and £54,141 with the PAS applied (Table 3, results based on the current Department of Health approved simple PAS of [redacted]).

[redacted]

[3] Treon, S.P., Tripsas, C.K., *et al.* (2015). Ibrutinib in previously treated Waldenstrom's macroglobulinemia. *N Engl J Med*. 372(15): 1430-40.

Table 2: Revised Janssen base case results in R/R WM population at list price

Comparator	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (LYG)	ICER (QALYs)
Ibrutinib	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Physician's Choice	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	66,242	87,934

Table 3: Revised Janssen base case results in R/R WM population with PAS

Comparator	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (LYG)	ICER (QALYs)
Ibrutinib	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Physician's Choice	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	40,785	54,141

Table 4: Revised Janssen base case results in R/R WM population [redacted]

Comparator	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (LYG)	ICER (QALYs)
Ibrutinib	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Physician's Choice	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5. Additional clinical evidence

With permission from NICE, Janssen share with the Committee additional clinical evidence that has become available since the initial CS was made in June 2016.

As acknowledged in the CS, there is limited information to inform the effectiveness of ibrutinib in WM. Additional data are now available from studies PCYC-1118E (Study 1118E) and PCYC-1127, which are consistent with the earlier data provided in our submission; these are presented below.

37-month follow-up from PCYC-1118E presented at IWWM-9 2016 (Palomba et al., 2016) [4, 5]

As of 31st July this year, the median follow-up for the 63 patients was 37 months. All patients completed the planned 40 cycles of treatment with an estimated rate of progression-free survival of 82.0% (95% CI, 69.1 to 89.9). The estimated rate of overall survival was 90.0% (95% CI, 77.4 to 95.8).

Twenty-five of the 63 patients enrolled are now off study. Of these 25 patients, three withdrew consent and are now on commercial supply. Reasons for discontinuation for the remaining 22 patients varied and are detailed in Table 5 below. Of note, 11 patients discontinued ibrutinib due to disease progression.

[4] Palomba et al. (2016), Long-term follow-up of a pivotal phase II trial of ibrutinib for relapsed Waldenström's Macroglobulinemia, IWWM-9 (slide deck)
[5] Palomba et al. (2016), Long-term follow-up of a pivotal phase II trial of ibrutinib for relapsed Waldenström's Macroglobulinemia, IWWM-9 (abstract - Session 9, October 7, 2016)

No new drug-related serious events have emerged with longer follow-up and severe toxicities such as atrial fibrillation and major bleeding were not observed as late events.

Table 5. Reasons for discontinuation

Events	N = 22
Progression of Disease	11
DLBCL transformation	2
MDS	1
Rectal Carcinoma	1
Endocarditis	1
Thrombocytopenia	1
Hematoma	1
Amyloidosis	1
Death	1
Pneumonia due to influenza	1
Atrial fibrillation	1

DLBCL: Diffuse large B-cell lymphoma; MDS: Myelodysplastic syndrome

Arm C PCYC-1127 poster presentation at EHA 2016

Arm C in PCYC-1127 is a non-randomised arm of the Phase III study containing patients refractory to their prior-rituximab containing regimen, and therefore represents a subset of patients from Study 1118E. Further to the earlier poster presentations at ASH 2015 (Dimopoulos et al) and BSH 2016 (Dimopoulos et al), the update at EHA 2016 (Dimopoulos et al)[6,7] included updated response data and the first progression-free survival data. At a median follow-up of 17.1 months (previously 7.7 months) the overall response rate was reported as 90%, with a major response rate of 71%. Progression-free survival at 1-year was 93%, supporting trends observed in Study 1118E.

6. Conclusion

The Committee has made an initial decision to not recommend ibrutinib for WM and to not consider it for inclusion in the CDF. Furthermore, the Committee cites a lack of clarity regarding the size of ibrutinib's treatment benefit and uncertainty regarding survival, with a particular emphasis on a lack of clarity related to inputs used for pre-progression mortality, as the key reasons for not being able to arrive at a most likely ICER. Janssen urges the Committee to consider the additional information presented in this response to the ACD, which strongly supports the following:

- The treatment effect of ibrutinib in terms of PFS has been consistently demonstrated across scenarios using rigorous and commonly-used approaches that utilise two patient-level data sets in a space where clinical data are severely limited as well as across trials as evidenced by the additional data that has recently been presented.

[6] Dimopoulos et al. (2016), Single-agent ibrutinib in rituximab-refractory patients with Waldenström's Macroglobulinemia (WM): updated results from a multicenter, open-label Phase 3 Substudy (iNNOVATE™), abstract P652, 21st congress EHA

[7] Dimopoulos et al. (2016), Single-Agent ibrutinib in rituximab-refractory patients with Waldenström's Macroglobulinemia (WM): updated results from a multicenter, open-label Phase 3 Substudy (iNNOVATE™), poster P652, 21st congress EHA

- The opportunity to collect additional data (e.g., PFS) through the CDF would be an invaluable opportunity to further confirm ibrutinib's treatment effect and to fully discount the most extreme scenarios tested by the ERG. Data collection on the CDF would add to the dearth of evidence in this rare patient population, about which little has been studied or published, thereby broadening the clinical evidence base.
- A revised economic analysis in which reasonable alternative approaches towards informing pre-progression mortality for the PC and ibrutinib arms does not result in significantly different health outcomes.

Janssen would like to thank the Committee again for the opportunity to comment on the ACD and ask that the Committee consider the additional information shared within the response. Janssen also ask that the Committee consider inclusion of ibrutinib on the CDF, under the commercial conditions [redacted]. This is an area of high unmet need and we would like to make ibrutinib available to patients in the UK as soon as possible.

30 August 2017

Re: Ibrutinib for treating Waldenström's macroglobulinaemia [ID884]

Dear NICE Technology Appraisal Committee A,

We have had the opportunity to review the appraisal consultation document for ibrutinib for treating Waldenström's macroglobulinaemia [ID884] and would like to stress the following points:

1. At present there are limited treatment options available for WM patients, creating a severe unmet need, which could be addressed by the availability of ibrutinib. It is important to have numerous lines of therapy available, as without effective treatment the likely outcome is death.
2. WM is a rare and chronic condition, with a severe and debilitating symptom burden. Patients have reported that ibrutinib can rapidly address this symptom burden and often allow them to return to their normal lives. As such, this is a key quality of life benefit that should not be overlooked.
3. Ibrutinib is an innovative treatment and the first therapy to be licensed specifically for the treatment of WM. It is also considered to be a step change in the treatment of WM, with a different mechanism of action to other treatments. As such, the availability of ibrutinib would be strongly welcomed by patients as an effective and tolerable therapy.
4. Whilst ibrutinib is associated with high responses rates and improved survival (normal or near-normal), we acknowledge that the data is uncertain. However, this uncertainty is due to the innovative nature of ibrutinib and the fact that WM is both a rare and chronic condition.
5. We take objection to the comment that ibrutinib should not be included in the Cancer Drugs Fund because two years is "unlikely to be long enough to collect meaningful progression or survival data because of the long natural history of the disease.". To do so would discriminate against rare and chronic conditions, where there is often the greatest uncertainty. Ibrutinib for the treatment of WM is a prime example of this. Aleviating this uncertainty and enabling access to innovative treatments was central to the recent changes to the Cancer Drugs Fund.

As such, we urge you to reconsider your recommendation and make ibrutinib available to those who could benefit from it.

Yours Sincerely,

[redacted]

Leukaemia CARE

Lymphoma association

PO Box 386, Aylesbury,
Bucks HP20 2GA
Freephone helpline 0808 808 5555
Administration 01296 619400
Fundraising 01296 619419
www.lymphomas.org.uk
information@lymphomas.org.uk

28 October 2016

Lymphoma Association response to NICE single technology appraisal ACD on Ibrutinib for relapsed/refractory Waldenström's Macroglobulinaemia (ID884)

It is extremely disappointing that NICE is proposing not to recommend the use of ibrutinib within its marketing authorisation for Waldenström's Macroglobulinaemia (WM). This is despite NICE's conclusions that:

- the therapy "could be considered a step change in managing WM" (ACD para 4.14);
- WM is a "rare and debilitating disease that is associated with high unmet clinical need for new effective therapies" (ACD, para 4.3); and
- the trial evidence showed an overall response rate of 90.5% at 24 months follow up (ACD para 4.7).

Furthermore, there appears to be overwhelming support from patients, patient groups and practising clinicians for not only the use of its treatment, but its clinical effectiveness and the dramatic changes it makes to living with WM. On top of that, it appears that the manufacturer was offering a discounted price for the treatment that would apparently have achieved an acceptable ICER.

Looked at more widely, if this is the way technology appraisals are going to be handled for new, innovative, targeted treatments for particular subtypes of lymphoma (which are in effect a collection of rare cancers with small patient numbers and difficulties in collecting Phase III trial data due to those numbers), then it is hard to see how lymphoma patients in England will ever be able to benefit from these treatments. Yet other nations within the UK seem able to approve at least some of these treatments for routine use. Lymphoma patients, their carers and families, simply do not understand how this happens in a public system that is paid for out of their taxes; and find it hard to fathom why NICE, the NHS and relevant pharmaceutical companies cannot reach mutually acceptable arrangements to bring new treatments into routine NHS practice expeditiously, despite the vast sums of money and industry that is spent on their assessment and appraisal. Elsewhere in the world, ibrutinib is also funded or reimbursed within healthcare systems, but not in the UK – why is this?

We have seen the ACD response that WMUK has submitted to NICE and would like to indicate our support in general for the points it has raised. In particular, we would like to highlight the following areas of its submission:

- **Health economics** – the ERG's use of a comparison model suited to conventional single chemotherapy intervention, followed by relapse, is completely inappropriate for the treatment world in which we now live and which will only expand and develop further in this respect. With advances in precision medicine, treatment comparisons will become harder and harder to make in the way that NICE currently approaches them. It's akin to insisting that hard copy publications such as books are the only way to consume information, and ignoring the invention and use of the internet as a means of communicating and disseminating knowledge.

- **The ERG view of the Dana Farber "pivotal trial" data** – given the low patient numbers for WM in the UK, it is inevitable that clinical trials must work internationally. This doesn't mean that the patients in this trial were "less damaged" than the average UK patient.

- **Pricing** – it's been clear from the outset that pricing is an issue, so why can't this be dealt with in more detail earlier in the appraisal process, before all the time, investment and costs involved in carrying out an appraisal.

- **Uncertainty** – with rarer forms of cancer, such as WM, and with smaller populations, there are always likely to be higher levels of uncertainty. However, to work with thresholds of uncertainty that might be acceptable for common cancers means reduced opportunities for the approval of rare cancer treatments.

- **Cost impact** – for this relatively small group of patients who would benefit from this clinically effective treatment, the overall cost to the NHS will be modest, particularly when set against the savings in conventional chemotherapy treatments and the economic and other benefits to individual patients and wider society.

We hope NICE will consider changing its proposed recommendation.

Chief Executive, Lymphoma Association

WMUK
UK Point of Contact for Waldenström's Macroglobulinaemia

Ibrutinib in WM ID 884 STA,
WMUK response to ACD

General Comments

WMUK warmly welcomes the positive acceptance by the committee that:
a) Ibrutinib provides a first genetically targeted therapy and a step change in treatment in this orphan disease. b) Was welcomed by expert clinicians and patients alike as providing a new treatment paradigm, turning an incurable disease into a chronic one for >90% relapsed patients and those unsuitable for chemo-immunotherapy. **Administration concerns:** problems with committee administration, including late distribution of documents, missing pages, and patient expert marginalisation suggests that committee and experts had too little time to consider 934 pages of complex evidence. Despite the Chair's apology, this casts some doubt over the NICE's resolve to be patient-centric, raising concerns that neither cost, nor clinical effectiveness nor patient welfare, was the committee's focus.

1) **Health economics:** ERG output with complex health economic calculations was used in a comparison model suited to conventional single chemotherapy intervention and relapse, rather than one based on transformation into a chronic disease. This, in our opinion, exaggerated the actual financial impact of this targeted type of treatment; minimising chemotherapy savings to the NHS and the economic value to patients, carers and society in transforming patients into economically active citizens.

2) **Expert clinician support, as reported, is muted compared with actual meeting comments and statements.** This contrasts with effusive ACD praise for patients. In several places in the text mentioning patient support we would have expected 'and clinicians' to be added. 22 of the most eminent WM clinicians and all main blood cancer charities expressed their unreserved open support the Ibrutnib WM indication, but the former was hidden from the Committee's sight by redaction. The 280 UK treatment questionnaire results showing unmet patient need and Ibrutinib tolerability received no comment.

3) **WM genetic targets for BTK not represented in the ACD summary**: there is no mention of the specific genetic targets in WM (MYD88 L256P , CXCR4 discussed by the committee and in main text), targeted by BTK inhibitors in WM, making it the first, and only, genetically targeted therapy for this indication, thus more efficacious in WM, compared with other B Cell malignancies (ie. CLL, MCL) which do not generally share these mutations).

4) **Limitations of existing treatments:** Whilst side effects of conventional chemotherapy are well presented in 4.3 it needs to be stressed that most responses are VGPR at best. There is also concern to patients of long term transformations (such as Richter's transformation to DBCL) after use of purine analogues such as Fludabarine. There is also the need to use irradiated blood products for those who have had such treatments. Stem cell treatments have been withheld pending review, and IFRs are now generally rejected at screening as cohort requests.

5) **Treatment-naïve patient concerns**: The ERG and thus the ACD worry extensively and repeatedly about uncertainty. BTK inhibitors working at the genetic level can be expected to be as least as effective on treatment-naïve patients, as confirmed by Dana Farber (Oct 2016, IWWM9, Amsterdam, personal communication). Older Patients with existing comorbidities will particularly benefit. This oft-repeated ERG suggestion is unjustified and has not been raised as a problem elsewhere in reimbursement discussions. The

EMA dealt with it in licensing simply saying: ***"The restricted indication was considered acceptable as there is no reason to expect inferior efficacy or a worse safety profile in the first line setting, and for the group of patients unsuitable for chemo-immunotherapy, limited treatment options are currently available .....The assessment of ibrutinib in naïve patients was based only on historical comparisons. However, the observed ORR of 87.3%, as reported in the 1118E study, is reassuring in terms of activity, and numerically superior in inter-study comparisons with most published studies investigating other monotherapy agents in previously treated and/or naive patients. Furthermore, the presence of the MYD88 L265P mutation in both untreated and previously treated WM patients, supporting the mechanistic rationale for treatment with ibrutinib in the treatment-naive setting".*** (EMA, CHMP 21st May 2015, 2.4.3)

6) **Over-negative ERG View of Dana Farber (D F) 'Pivotal Trial' Data**: Whilst accepting the trial was well conducted, ERG seems intent in impressing on the committee of much data uncertainty in a trial acclaimed as 'pivotal' worldwide. The ACD makes no concessions to the rareness of the disease and difficulty assembling rare disease trials. It states incorrectly that there were no UK patients and infers D F patients may be less damaged than the average UK patient. D F is a tertiary referral centre, effectively the USA's specialist centre for WM and trialists were generally referred patients with no options following multiple relapses and thus likely to be more heavily treated cases than in routine UK Ibrutinib use. The data has already been used to support licensing and reimbursement in USA, Canada and most European Countries, including Greece (most recently the Irish Republic). German patients were reimbursed two days after licensing in June 2015. Why are we last in the reimbursement queue?

7) **Pricing/ICER discussion opportunity wasted:** The committee spent a majority of the meeting listening to ERG calculations on a list price with discount when a lower price offer was apparently on the table at NICE. This would supposedly achieve an acceptable ICER result. This occasioned yet further delay and expense, 17 months on from Licensing. There *was* obvious doubt on pricing – the main focus of the ERG – so common sense would indicate that the meeting should have been postponed until price confirmation, to avoiding wasting the committee's time.

8) **Uncertainty exaggerated:** Whilst all accept uncertainty to a degree, particularly in rare disease trials, there are inherent contradictions in both ERG and ACD reports. On the one hand the trial, **"provided convincing evidence of clinical efficacy"** (EMA, CHMP May 2105 2.5.5) **and follow up data to 37 months** shown at IWWM9 (Oct 2106, Treon etc al IWWM9 Amsterdam) confirms how good the results continued to be, (OS of 90% at 95%CI); yet **uncertainty** by ERG is stressed repeatedly, whilst the ERG is somehow ***certain*** that the CDF+ registry route will not reduce **uncertainty**.

9) **End of life and rareness criteria**: Under Scottish Medicines Consortium rules Ibrutinib would probably be classed as an end of life treatment (death within 3 years) and would get special consideration with far more patient input under their PACE regime. Relapse in heavily treated patients is not necessarily indolent, and may be rapid if not treated.

10) **The critical importance of the Clinical Data Registry and CDF route is overlooked**: Public Health England has admitted it can provide no accurate statistics for rare blood cancers. WMUK, trusts, private donors and a wide range of pharma have financed the setting up of the innovative Rory Morrison Clinical Data Registry to address this. It is professionally hosted, NHS IT compatible, with inbuilt data mining tools to reduce treatment uncertainty in this rare disease and is up and running with 300+ patients already entered. This includes EQ5D and later with real time patient reported outcome layers. It will be vital in studying the variability of WM outcomes in targeted medicine related to CXCR4 and MYD88 mutations. We are concerned that clinical need for this study did not feature during the abrupt dismissal of the CDF route of funding by ERG. In addition we do not accept that WM is always indolent in heavily treated patients, and thus no progress could be expected in the two year period. If this criteria were to be strictly applied it is difficult to see any effective pharmaceutical being admitted to the CDF.

Wider observations regarding reimbursement

a) **Previous lack of focus on WM by NICE:** WM patients and clinicians in this orphan disease, using hand me down/off label/orphan use from other lymphomas, have suffered further by withdrawal of interventions such as Bortezomib and recently Stem Cell Transplantation. Widely used Bendamustine is still CDF only. Newly published NICE non Hodgkin lymphoma guidelines (NG52, 2016) ignored WM whilst dealing with other rarer NHLs. There is no NICE pathway for WM or treatment algorithm. This discriminates further against WM, where treatment options have actually reduced in the last 2 years.

b) **Lack of allowance for Rareness:** The Chair stated that she had no instructions to make allowance for rareness, despite public statements by Sir Andrew Dillon to the contrary, and NICE now proposes to allow ICERS up to £100k for ultra rare diseases: Ethically and clinically, why should £30k be the upper limit for 'just' rare diseases? Where is the RD/URD boundary set? In correspondence, Professor Carole Longson gave WMUK some comfort *"we have many examples in the technology appraisals programme demonstrating that it is possible to make a reasonable case for pharmaceuticals with a limited evidence base and a small population".*

c) **Use of Ibrutinib in other B cell cancers**. We are concerned that NICE's/NHS increasing focus on cost reduction may be linking the WM STA to a wider discussion over Ibrutinib pricing in other blood cancers. The pre-meeting briefing slides seem to indicate this. We hope the committee completely agree that the needs of clinicians and patients in this specific indication should be treated entirely on merit.

d) **The cost impact to the NHS will be very modest**. In year 1 at the price given, cost impact would be less than £6m, *less* the saving in conventional chemotherapy and *disregarding all* economic benefits to patients and society. A further discount would reduce this pro rata. This falls well within the NICE proposed 'budget impact threshold' of £20m. (NICE, Oct 2016 "to better manage the introduction of treatments that are deemed cost effective but have a very high cost"). However we are very encouraged by Andrew Dillon's *Times* 31st October statement **"NICE isn't going to take affordability into account in deciding whether the NHS should use a new treatment".**

e) **Can NICE deliver its promise to make innovative medicines rapidly available for rarer diseases?** The UK lags substantially behind most of Europe in overall WM survival. Preliminary new data (Prof C. Buske at IWWM9, Pan European Data Platform WM Study, Amsterdam 2016. #1) for 2000- 2015 showed the UK had the lowest OS in WM compared with any major EU country, and below Eastern Europe. For instance 10 year survival probability for UK was 0.50, Italy 0.85. Buske (again, from pan European WM study) stated: ***"Several studies have shown appreciable differences in the uptake of new cancer drugs across Europe...they have also shown Germany and France among the European countries with the highest access to cancer medicines and the United Kingdom among those with the lowest"***

The committee has an unique opportunity to remedy the historic treatment inequity of WM

Yours truly, Roger Brown
Chair, WMUK 31/10/16

#1 IWWM9= 9th International Workshop on Waldenström's Macroglobulinemia, Amsterdam 5-8th October 2016.

Dr Shirley D'Sa Response to ACD:

Has all of the relevant evidence been taken into account?

Yes, and I would like to commend the robustness of the evidence review, which I find to be fair, accurate and representative.

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

Yes, I believe that they are. However, the clinical entity of Waldenström's macroglobulinaemia is disadvantaged by its size (patient numbers) and the methodology used in pivotal trials, (which are typically performed in the United States where the clinical agenda is different to that of countries with state-funded healthcare systems), which makes the task of demonstrating clinical and cost effectiveness very difficult. Nevertheless the effectiveness of this drug in this condition is beyond doubt so it is the economics that are proving prohibitive.

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

No, I believe that Ibrutinib should be available for patients with relapsed and refractory Waldenström's to address a significant unmet clinical need, which was further deepened by the removal of Bortezomib from the CDF.

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

I believe that the importance of low toxicity cannot be underestimated in this patient group, many of who are older (median age is close to 70 years for this condition). This treatment represents a step-change in this regard, as evidenced by patient testimony at the initial meeting as well as the WMUK patient survey earlier this year that highlighted underappreciated chemotherapy-related side effects.

Cancer Drugs Fund (page 12)

4.15 The committee considered whether it would be appropriate to recommend ibrutinib for inclusion in the Cancer Drugs Fund. If an appraisal committee concludes that the uncertainty in the clinical and cost-effectiveness data is too great to recommend the drug for routine use, it can consider a recommendation for use within the Cancer Drugs Fund if the ICERs presented have the plausible potential for satisfying the criteria for routine use, and if it is possible that the clinical uncertainty can be addressed through collection of outcome data from patients treated in the NHS, normally within 2 years. The committee noted that the ICER presented by the company in its base case was well above the level which could be accepted as a cost-effective use of NHS resources, and did not have the plausible potential for satisfying the criteria for routine use. The committee considered the potential for additional data collection and understood that there is an ongoing trial (iNNOVATE) in people with Waldenstrom's macroglobulinaemia that includes a small open-label sub-study of ibrutinib monotherapy, with interim results

expected in early 2017. It also understood that the company intends to collect additional efficacy and resource-use data as an add-on to an existing national registry of people with Waldenstrom's macroglobulinaemia. The committee welcomed the efforts being made to collect data on this rare condition and its treatment. However it heard from the clinical experts that although an additional 2 years of data collection would provide more robust data on response rates, and further genomic information, it was unlikely to be long enough to collect meaningful progression or survival data because of the long natural history of the disease. The committee therefore accepted that it was unlikely that further data collection would lead to a more favourable cost-effectiveness estimate for ibrutinib. It concluded that ibrutinib for treating Waldenstrom's macroglobulinaemia does not have the plausible potential to be cost effective in routine commissioning and cannot be recommended for inclusion in the Cancer Drugs Fund.

Within the didactic constraints of a 2 year period, meaningful survival data is unlikely to be forthcoming, but it is very likely that important PFS data would be accrued, as well as valuable QOL, adverse events and relevant real-life UK data on patients with WM. This is a 'small disease' with manageable numbers for effective data collection, and an existing Registry already in place.

Given that the methodology for data collection to inform the new CDF is in development, we stakeholders await clear guidance on exactly how it will look. Consequently, we were relatively ill-prepared to answer detailed questions about the kind of data we can capture in the Registry, but we will be in a position to offer a more detailed breakdown of the proposed data collection model at the second meeting.

We believe that the inclusion of a data collection exercise would be informative for this indication as well as others going forwards. The 9th International Workshop on WM has just taken place in Amsterdam, and further data regarding the various genomic profiles of WM entities were presented. Incorporating a genomic profile into the data collection process will provide an amazing opportunity to interrogate subgroups of WM patients who would benefit from this drug through a national data capture exercise. We would like to discuss this further at the second discussion meeting. This may not immediately translate into a more favourable cost-effectiveness estimate, but will help to provide a valuable snap shot in the era of novel biological agents.

Current practice (page 14)

Clinical need of patients, including the availability of alternative treatments	The committee concluded that there is no standard of care for treating Waldenstrom's macroglobulinaemia and that targeted therapy is highly valued by patients and addresses a significant unmet need.	4.2, 4.4

I attach a recently published meta-analysis for information (Santos-Lozano et al 2016)

What is the position of the treatment in the pathway of care for the condition?	The committee heard that ibrutinib would be particularly valuable for people with disease that is refractory to first line	4.4

	treatment or who relapsed following successful first line therapy.	

This point cannot be underestimated. There are very few agents available for the treatment of UK patients with WM, who lag behind their counterparts in Europe as far as accessibility to treatment options is concerned.

Relevance to general clinical practice in the NHS	The committee concluded that PCYC-1118E is of a reasonable quality and generalisable to UK clinical practice, but is limited by the lack of a comparison against a treatment used in the UK.	4.6

It is probably useful for the comparator to be "Rituximab + chemo (either alkyltators, purine analogues or bendamustine, which has a mechanism of action that straddles these)".

Page 17

Availability and nature of evidence	The committee understood that the company's model included patients with relapsed or refractory Waldenstrom's macroglobulinaemia who had received one prior therapy, and not treatment naïve patients in whom chemo-immunotherapy was considered unsuitable. It concluded that, because no evidence had been presented, it could not reliably assess the cost effectiveness of ibrutinib in this group of patients. The committee was mindful of the limitations within the model structure but concluded that it was acceptable for decision making.	4.9, 4.10

This is reassuring but what does it mean in practice?

Page 18

Are there specific groups of people for whom the technology is particularly cost effective?	The committee made no specific recommendations for any subgroups.	-

I think it is hard to accurately capture the material benefits of this treatment in older age groups (which accounts for the majority of patients with WM), but I believe there would be a clinically significant advantage for older patients in particular. For example, a high proportion of older and less fit patients need hospital transport to attend appointments for chemotherapy, as well as management of complications. Frequent attendances in clinics for blood tests and review all add up to QOL costs for the patients and financial costs for the NHS. The toxicities of conventional chemotherapy can also lead to the need for blood transfusions, growth factor injections, intravenous immunoglobulin infusions to treat secondary hypogammaglobulinaemia and so forth.

Dr Roger Owen,
Consultant Haematologist,
St James's University Hospital, Leeds
Comments made on behalf of the Royal College of Pathologists.

Re: ACD for ibrutinib for treating Waldenstrom's macroglobulinaemia.

It is disappointing that ibrutinib has not been recommended for treatment of patients with Waldenstrom's macroglobulinaemia (WM).

In my view ibrutinib represents a real paradigm shift in disease management and is an exemplar for precision / personalised medicine.

It was pleasing to note that the committee recognised that WM was

- a debilitating and life limiting disorder
- an unmet clinical need due to limited available therapies with significant toxicities and short durations of response
- disadvantaged by removal of bortezomib from the Cancer Drugs Fund and uncertainty surrounding funding for autologous stem cell transplantation

Similarly the committee concluded that ibrutinib was

- a novel therapy which targets the MYD88 L265P gene mutation present in the majority of WM patients
- associated with high response rates and excellent survival outcomes at 2 years
- likely more effective than existing treatments
- associated with an excellent toxicity profile

The committee concluded, correctly in my view, that ibrutinib represented a truly innovative approach to treatment of WM and a "step change" in management strategies. It was unable to recommend its use largely on the basis of cost-effectiveness issues. I have a number of comments on this

Overall survival assumptions

It is, in my opinion, based on the efficacy data from the PCYC-118E study along with comparisons from the European chart review cohort that ibrutinib will result in significant overall survival (OS) benefits for WM patients. It is agreed that both sources of data are satisfactory for evaluation in the current context. It is clearly inappropriate and likely unethical to wait for definitive OS data to emerge from PCYC-118E study. I have little or no expertise in cost effectiveness analyses but note the debate regarding pre-progression mortality assumptions made in the application by the company and raised by the ERG. On reflection, I think that it is not unreasonable to think that pre-progression survival may be better in ibrutinib treated patients as a result of the greater long and short term haematological and infectious complications that can occur with conventional chemotherapy particularly in the relapsed / refractory setting. Quantifying this potential effect is clearly very challenging.

I agree that it is not possible at present to perform a cost-effectiveness analysis for treatment naïve patients.

Most plausible incremental cost-effectiveness ratio.
Uncertainties with respect to mortality modelling and on-going negotiations regarding drug cost preclude any further meaningful comment.

Cancer Drugs Fund (CDF).
The committee has concluded that ibrutinib should not be included in the CDF. The committee felt that over the 2-year period it was unlikely that additional survival data will be forthcoming and there was limited likelihood of the cost-effectiveness outcome improving to a level that would allow routine use.

On reflection, I believe there are a number reasons to challenge these conclusions

- Cost effectiveness should be reviewed when survival modelling has been agreed and a formal decision regarding drug costing made.
- Additional survival data from PCYC-118E as well the INNOVATE study will become available during this time period. This will include data from treatment naïve patients in addition to the relapse / refractory group.
- Whilst it is appreciated that formal progression free and overall survival data are unlikely to become available within 2 years of CDF access. Appropriately collected response data would be valuable. If M protein and haemoglobin responses (as well toxicities) are similar to those seen PCYC-118E and INNOVATE it would not be unreasonable to assume similar survival outcomes.
- The availability of an existing national registry as well as a proactive patient group provides an excellent opportunity to collect real world response data as well as patient reported outcomes in real time. This could potentially provide a model and route of approval for other rare disorders where conventional phase 3 data are lacking.

Equality issues.
Whilst there are no definite concerns it should be noted that WM is disease of older people and is more common in men than women.

Conclusions.
- Ibrutinib represents a real paradigm shift in disease management.
- Ibrutinib should be available for patients with relapsed / refractory WM. It has unprecedented single agent activity and excellent toxicity profile. It specifically targets the biological effect of MYD88 mutations and as such is an exemplar for precision medicine. Access could potentially be limited to those patients with demonstrable mutations.
- Access via the CDF seems most appropriate at this time. Access to a national registry along with a proactive patient group represents a real opportunity to develop a process and model for other rare disorders.
- There is no evidence to support the use of ibrutinib in treatment naïve patients. This is not, in my opinion, an area of unmet need and should be formally addressed with further trials.

RG Owen
Consultant Haematologist.
1st-Nov-2016.

Ibrutinib for treating Waldenström's macroglobulinaemia: A Single Technology Appraisal

ERG commentary on the company's response to the ACD

Produced by School of Health and Related Research (ScHARR), The University of Sheffield, UK

Authors Paul Tappenden, Reader in Health Economic Modelling, ScHARR, University of Sheffield, UK
Praveen Thokala, Research Fellow, ScHARR, University of Sheffield, UK
Jean Sanderson, Research Associate, ScHARR, University of Sheffield, UK

Correspondence to Paul Tappenden, Reader in Health Economic Modelling, ScHARR, University of Sheffield, UK

8th November 2016

Amendments made in the company's revised model

The Evidence Review Group (ERG) has reviewed the company's response to the Appraisal Consultation Document (ACD) and their revised model. The ERG confirms that the following amendments have been made within the company's revised model:

- The survivor function for progression-free survival (PFS) for the ibrutinib group has been replaced with data relating to the 12th December 2014 data cut-off (DCO) of Study 1118E.
- Pre-progression mortality in the ibrutinib group is now modelled using an exponential survivor function derived from Study 1118E; this function subsequently reverts to the general population mortality hazard once the general population hazard rate exceeds that of the exponential function.
- Pre-progression mortality in the rituximab/chemotherapy group is modelled using an alternative survivor function derived from a re-analysis of the European chart review. The ERG still has some concerns regarding this analysis (detailed below).
- Chemotherapy drug cost calculations have been amended. These are not the same as the revised estimates used in the ERG's base case analysis. The impact of this on the incremental cost-effectiveness ratio (ICER) for ibrutinib is however minor.
- The Patient Access Scheme (PAS) price discount has been changed from [redacted] to [redacted].

The ERG can confirm that removing these model amendments results in the same ICER as that reported in the original company's submission (CS). The ERG's concerns about likely programming errors relating to the costs of follow-up (see ERG report, page 121) have not been incorporated into the company's revised model, however, the impact of this on the ICER is minor.

Additional concerns

The ERG has two concerns regarding the company's ACD response and the revised model. These relate to: (i) the amended approach to modelling pre-progression mortality, and; (ii) errors in the company's original and revised models.

(i) Pre-progression mortality

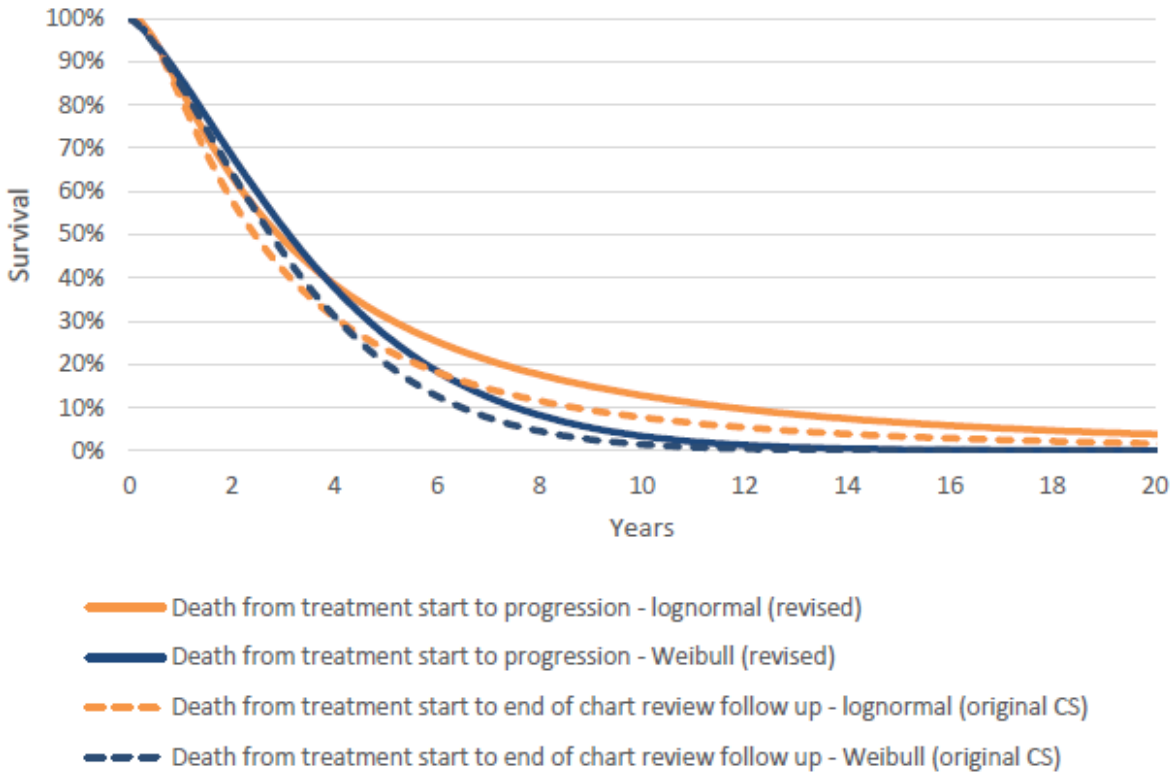
The ERG remains concerned regarding the company's approach to modelling pre-progression mortality in the rituximab/chemotherapy group. The company's ACD response is not clear about how the analysis of pre-progression mortality was originally undertaken or how this approach has been altered for use in the revised model. The company's ACD response states:

"Pre-progression mortality was estimated based on deaths that occurred during the full observation period - from start of the last line of treatment until the end of follow-up (i.e., cut-off date)… In the

revised model, pre-progression mortality for PC was derived using a narrower observation window where the point of progression (and not the start of next line of treatment) was used as the 'cut-off' point for collecting pre-progression mortality data"

Whilst not entirely clear from the text above, it appears that the company's original modelling included deaths occurring up to the end of follow-up (i.e. including post-progression). This is inappropriate and will exaggerate the mortality rate in the rituximab/chemotherapy group, thereby improving the cost-effectiveness profile for ibrutinib. The correct approach to modelling pre-progression mortality would have involved counting deaths occurring prior to disease progression on the current line of therapy as events and censoring patients who experienced progression before death. On the basis of the wording of the company's ACD response, it appears that the revised analysis still does not adopt this approach. It is also noteworthy that the pre-progression mortality curves presented in the company's ACD response do not appear to be substantially different to their original curves (see Figure 1). In most instances, one would expect pre-progression mortality curves to reach a steady plateau as a consequence of censoring due to progression events occurring before death; the exception would be if the majority of death events occurred before progression. This pattern is not evident in the company's revised analysis. Further, within the rituximab/chemotherapy group of the company's model, only around 10% of patients are still in the PFS state at 3 years. Given that the original and revised modelled death risks are similar up to this timepoint, the impact of using the revised curve on the ICER is small.

Figure 1: Comparison of company's original and revised pre-progression mortality functions



Without access to the original individual patient dataset used to undertake the analysis of pre-progression mortality, the ERG is unable to verify whether the company's revised approach for modelling pre-progression mortality is appropriate, but notes that this aspect of the model has the propensity to dramatically increase the ICER for ibrutinib versus rituximab/chemotherapy, as previously shown in ERG exploratory analysis #7 (excluding survival benefit ICER=£390,432 per QALY gained).

(ii) Errors in the company's original and revised models

The original ERG report highlighted a number of errors pertaining to the double-discounting of third/fourth-line treatment, follow-up costs and chemotherapy acquisition costs. The company's ACD response suggests that the first two of these reflect misinterpretations by the ERG. For the sake of clarity, these issues are drawn out more fully below.

Drug cost discounting

The company's ACD response states: "*The costs of 3L & 4L in PC arm are discounted twice: A misinterpretation by the ERG has likely occurred. Janssen confirm the costs were not discounted twice. Therefore, no revisions were required."*

The company's response is incorrect. In the worksheet "drug cost calc", the drug acquisition and administration costs for third- and fourth-line treatment are discounted first using the discount multipliers in column DZ. These discounted costs are then summed in cells ES8:ET8 and EU8:EV8. These total discounted costs are then fed through the "parameters" worksheet and are discounted again in worksheet "Markov RR (Ibr)" in columns CR:CS using discount multipliers provided in column CL. As noted in the original ERG report, the impact of this error on the ICER for ibrutinib is minor.

Follow-up costs

The company's ACD response states *"The schedule of follow-up costs (types and frequencies of use) remain the same across all lines of treatment. The follow-up costs appear lower in later lines due to the fact that fewer patients remain alive in later lines and because patients progress faster. Therefore, no revisions were required."*

The company's response is inaccurate. In the worksheet "parameters" cells F151:153 and F156:158, the follow-up costs for third- and fourth-line treatment for year 6+ are subtracted from the costs for years 1-2 and years 3-5. As noted in the original ERG report, this does not follow any obvious logic and appears to be a programming error. Again, the ERG notes that the impact of this error on the ICER for ibrutinib is minor.