NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ibrutinib for treating relapsed or refractory mantle cell lymphoma [ID753]

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

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD2)**

2. **Company response to ACD 2 submitted by Janssen**

3. **Consultee and commentator comments on the Appraisal Consultation Document 2 from:**
   - Lymphoma Association
   - Royal College of Physicians
   - Bloodwise
   - Department of Health – *no comment*

4. **ERG critique of company ACD 2 response**

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

SingleTechnology Appraisal

Ibrutinib for treating relapsed or refractory mantle cell lymphoma [ID753]

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	**Proposal for the Committee's consideration** Janssen thank the Committee for the invitation to submit a proposal for inclusion in the (new) CDF, however, we would like to respectfully decline this invitation. At this stage, having reviewed the draft recommendation in detail and with an understanding of current NHSE pricing policy, Janssen have re-visited the data presented to the Committee and respectfully request that the one-prior-line (1PL) subgroup of patients within the RR MCL population be considered ***for baseline commissioning*** for the following reasons: • Ibrutinib has become standard of care in England in the time it has been available via the (old) CDF and has alleviated an otherwise deep unmet need within RR MCL. • Ongoing data collection continues to support that better patient outcomes result from using ibrutinib earlier in the treatment pathway i.e. in the 1PL setting. • Clinical opinion advocates for earlier use of ibrutinib and this preference by clinicians is evidenced by the uptake data which shows high usage (i.e., market leadership) in the 1PL subgroup. • Ibrutinib meets the end-of-life criteria and bearing in mind the modifiers which would be considered as a result, it is a cost-effective option when the current PAS is applied.	Comments noted. After considering the updated RAY data and comments received in the response to the appraisal consultation document, the committee recommends ibrutinib as an option for treating relapsed or refractory mantle cell lymphoma in adults who have had only 1 previous line of therapy. Please see sections 1, 4.8, and 4.14 – 4.16 of the final appraisal determination (FAD) for the committee's recommendations and full considerations of this subgroup.

Consultee	Comment [sic]	Response
Janssen	**Unmet need addressed** The persisting unmet need in RR MCL has been discussed at length and the need for an effective and tolerable treatment was clearly recognised by the Committee given that without consideration of ibrutinib, "*…there is no standard of care for treating relapsed or refractory mantle cell lymphoma in England, and that treatment tends to combine rituximab with a range of chemotherapy options*" (Section 4.1, page 5). The drastic change to the unmet need since ibrutinib's availability on the (old) CDF from January 2015 has also been acknowledged by the Committee through the following statements from the patient and clinical experts: • "*It is taken orally and people value this highly because it can be taken in the privacy of their own home and reduces the need for hospital visits. It can be used by older and frail people and, unlike current chemotherapy options, patients do not usually need additional treatments to counter adverse reactions. For these reasons, the patient experts considered that ibrutinib is a life-transforming drug that results in a step change in the quality of life of patients with relapsed or refractory mantle cell lymphoma and their families and carers…*" (Section 4.2, page 6) • "*The Committee heard from the patient and clinical experts that ibrutinib is already widely used in clinical practice because of its availability through the Cancer Drugs Fund, and is welcomed by patients because it is highly effective compared with existing treatments and extremely well tolerated with very few adverse reactions*" (Section 4.2, page 6) To confirm and quantify these statements, in the nearly three years since availability via the (old) CDF, ibrutinib has become the standard of care in RR MCL overall and data as of August 2017 show that ibrutinib had [redacted]% uptake within the 1PL subgroup (QuintilesIMS, 2017) supporting the clinically-driven relevance of positioning ibrutinib in the 1PL setting.	Comments noted. The committee recognised the high unmet clinical need of people with relapsed or refractory mantle cell lymphoma.

Consultee	Comment [sic]	Response
Janssen	**Data clearly support the efficacy and tolerability of ibrutinib in 1PL subgroup** The Committee noted "*…results from the studies suggested greater efficacy in patients who had ibrutinib after 1 prior therapy compared with 2 or more therapies*" (Section 4.8, page 9) and acknowledged clinical opinion stating that *"[the committee] …heard from the clinical expert that ibrutinib is particularly beneficial after the first relapse*" (Section 4.8, page 9). Furthermore, "*The committee noted with interest that the final overall-survival results from RAY are expected in 2017*" (Section 4.4, page 7). The updated data from RAY, the phase 3 registrational trial for ibrutinib in RR MCL, based on median follow-up of 39 months (previous data cut had median follow-up of 20 months) was indeed presented in June 2017 at the International Conference on Malignant Lymphoma (ICML) and subsequently published in August 2017. Updated results are not only consistent with the primary analysis but also confirm that patients who had received ibrutinib after only 1PL had "the most durable and best PFS and OS outcomes" (Rule et al, 2017; abstract). Cross-over of 39% was reported in the update and despite this, the cross-over unadjusted median OS remains impressive with 42.1 months for ibrutinib (vs 27.0 months for temsirolimus) in the 1PL subgroup (Rule et al, 2017; presentation). Comparatively, the median OS in the overall RR MCL population was 30.3 months for ibrutinib (vs 23.5 months for temsirolimus) and it was 22.1 months for ibrutinib (vs 17.0 months for temsirolimus) in the >1PL subgroup; these data consistently support that there is a particular benefit in using ibrutinib in the 1PL subgroup. This is of considerable clinical importance as these patients otherwise face a life-expectancy of less than 12 months when treated with the pre-ibrutinib options of various rituximab-based chemotherapies, as per the audit data from the Haematological Malignancy Research Network (HMRN). Crucially, the 1PL data also validate the current modelled results for ibrutinib. Projected PFS for ibrutinib appears to track very closely to the updated trial results; this is arguably the key data from the modelling perspective as PFS is the determinant of treatment duration and therefore, cost. Projected OS for ibrutinib appears to be notably conservative compared to the trial results as the modelled median OS is approximately 31 months vs the trial median OS of 42.1 months.	Comments noted. Please see sections 4.8 and 4.14 of the final appraisal determination (FAD) for the committee's full considerations on the clinical and cost effectiveness of ibrutinib in the 1 previous therapy subgroup.

Consultee	Comment [sic]	Response
Janssen	The Committee's main objection to the consideration of the 1PL subgroup data was stated as "*…the subgroups had been defined post hoc and [the Committee] was therefore reluctant to draw any firm conclusions about the relative efficacy of ibrutinib in these groups*" (Section 4.8, page 9). Within the RAY study, analysis was pre-specified across one or two prior lines versus greater than three prior lines. The full list of the pre-specified analyses is provided in the Appendix (Table 2) and demonstrates that not many were predictors of PFS, however, based upon multivariate analysis, there was reason to further explore line of therapy as an independent predictor of efficacy. Consequently, with a clinical rationale to explore further, the one or two prior line population was further stratified post-hoc to 1PL vs two or more prior lines; baseline characteristics are provided in the Appendix (Tables 3 and 4). Results of the post-hoc analysis have since been published and presented at international congresses, concluding that "ibrutinib provided the greatest benefit when used at first relapse" (Rule et al, 2017; presentation). It should be noted that data showing ibrutinib provides a greater benefit when used earlier in the treatment pathway has also been reported in a different haematological indication (chronic lymphocytic lymphoma) and therefore there is wider evidence to support this argument at the molecule level (O'Brien et al, 2016). Janssen note that post-hoc analyses have been used in the past to inform decision making by NICE Appraisal Committees. These data were generally considered when they are found to have clinical relevance and there was strength in the evidence base; we believe both factors are met for ibrutinib and the 1PL subgroup. Should any reservation remain as to the validity or robustness of the RAY study's post-hoc analysis, Janssen would encourage the Committee to seek further clinical opinion on this as there is clear clinical interest and strong evidenced-based reasoning to support the use of ibrutinib in this specific subgroup.	Comments noted. Please see section 4.8 of the final appraisal determination (FAD) for the committee's full considerations.

Consultee	Comment [sic]	Response
Janssen	**Cost-effectiveness of the 1PL subgroup** As the Committee has concluded that "*…the company's model was in line with accepted NICE methods and was appropriate for decision-making*" (Section 4.12, page 12), the results of the cost-effectiveness analysis with the existing simple PAS of [redacted]% applied are presented in the table below; deterministic and probabilistic sensitivity analysis results are provided in the appendix. The Committee has further "*…agreed that this additional data [from the updated HMRN audit] provided some reassurance about the method of modelling the company had used, and reiterated that it considered the company's original model and base-case ICER to be acceptable for decision-making*" (Section 4.13, page 12). Therefore, given (a) the clinical relevance of the 1PL subgroup discussed above, (b) the updated trial data for ibrutinib which validates the benefits estimated by the model for ibrutinib, and (c) the previously-presented updated HMRN data which provide evidence for the PPS of the comparator arm to be adjusted such that survival on this arm is reflective of survival reported in UK real-world data (Janssen submitted this on 14th September 2016 as part of our response to the first ACD), results have been re-presented for this scenario along with results without the adjustment to the PPS of the comparator arm but using the original and the alternative PFS HR for the 1PL subgroup.	Comments noted.
Janssen	As discussed in the previous section, the updated data confirm PFS, and therefore treatment duration and cost, to be accurately modelled and highlight the conservative nature of the modelled OS for ibrutinib (Figure 1). Furthermore, the Committee agree that the end-of-life criteria have been met for the overall RR MCL population and this remains applicable in the 1PL subgroup as evidenced by (a) the trial data and clinical opinion supporting the extension to life criterion and (b) the later data-cut from the HMRN audit supporting a short life expectancy of less than 24 months (Figure 2). With these considerations and the PAS applied, use of ibrutinib in the 1PL subgroup is a cost-effective option.	Comments noted. Please see section 4.15 and 4.16 of the final appraisal determination (FAD) for the committee's full considerations.

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Bloodwise	Bloodwise are extremely disappointed and concerned by the conclusion in the draft guidance that Ibrutinib is not recommended for treating relapsed or refractory mantle cell lymphoma (MCL) in adults. The evidence from both patients and clinicians for the use of Ibrutinib for this purpose is overwhelmingly positive and we are concerned that the relevant evidence from patients has not been taken into account sufficiently. We reiterate the following key messages from our previous submission and would ask that these be taken into account before the Final Appraisal Determination is reached: Ibrutinib is regarded by patients as a step change in the way MCL is treated, significantly out-performing current treatments with no comparable treatments available. Patients report a rapid reduction in symptoms, such as swelling, pain and fatigue, allowing many to return to their normal life very quickly. As an oral treatment that can be taken at home, there are significant benefits for patients compared to current therapies, which involve multiple hospital visits. Patients usually receive intravenous chemotherapy with the numerous side effects that go with treatment, ongoing support and significant practical difficulties associated with multiple hospital visits. Treatment with Ibrutinib is therefore particularly beneficial for patients with mobility issues or without access to transport who cannot easily get to hospital appointments. The side effects of ibrutinib are mild and generally only last for around a couple of weeks. This is a significant improvement on current more invasive chemotherapy treatment. In conclusion, there are quite simply no other treatments available that rival Ibrutinib for its management of all the issues outlined above which MCL patients face and as such the medication is truly life changing for these patients. We would urge the committee to reassess their draft guidance and approve Ibrutinib for use in treating relapsed or refractory mantle cell lymphoma.	Comments noted. After considering the updated RAY data and comments received in the response to the appraisal consultation document, the committee recommends ibrutinib as an option for treating relapsed or refractory mantle cell lymphoma in adults who have had only 1 previous line of therapy. Please see sections 1, 4.8, and 4.14 – 4.16 of the final appraisal determination (FAD) for the committee's recommendations and full considerations for this subgroup.

NCRI-ACP-RCP-RCR	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments. Our experts were disappointed that the committee came to a negative decision with respect to this drug, however since the last meeting more evidence has emerged on the longer term efficacy of ibrutinib in MCL that may prove helpful. Firstly, there has been a further analysis of the RAY trial which was presented at the International Conference on Malignant Lymphoma (Rule et al ICML 2017). The RAY trial was a randomised study comparing temsirolimus with ibrutinib for relapsed refractory MCL and was the basis for registration of the agent in Europe. The primary end point of this study was PFS which was strongly positive in favour of ibrutinib. With 3 years of follow up, whilst PFS remains strongly positive, overall survival still shows no significant difference between arms. However a quarter of patients remain on ibrutinib and there are no patients still receiving temsirolimus. 39% of patients have subsequently crossed over to the ibrutinib arm which clearly confounds the overall survival endpoint. As a consequence it seems unlikely that longer follow up will lead to a significant OS advantage however the hazard ratio is 0.74 (p=0.06). In addition this study demonstrates a very strong correlation between when the drug is given and its efficacy as defined by progression free survival and overall survival. With respect to PFS when Ibrutinib is given at first relapse the median PFS is 25.4 months compared with 12.1 months when given later. For OS this translates to a median of 42.1 months compared with 22.1 months. Whilst this is a post hoc analysis, it seems clear that earlier use is highly beneficial and this is supported by a pooled analysis of the 3 trials that have included ibrutinib (Rule et al BJHaem 2017). In this study a clear association between efficacy (PFS and OS) and line of therapy is evident. The RAY trial is criticised as temsirolimus is not felt to be an appropriate comparator for UK practice. This is true but as this was a licensing study the EMA required a licensed drug as a comparator and this was the only licensed drug in Europe at that time. There will not be any further trials comparing ibrutinib with other more relevant agents although randomised	Comments noted. After considering the updated RAY data and comments received in the response to the appraisal consultation document, the committee recommends ibrutinib as an option for treating relapsed or refractory mantle cell lymphoma in adults who have had only 1 previous line of therapy. Please see sections 1, 4.8, and 4.14 – 4.16 of the final appraisal determination (FAD) for the committee's recommendations and full considerations for this subgroup.

Nominating organisation	Comment [sic]	Response
	trials in the front line are ongoing for elderly patients. It is without question that ibrutinib has transformed the treatment paradigm for MCL. It is the single most active agent in the relapsed setting and has an extremely modest side-effect profile when compared with conventional chemotherapy. As well as the trial data there is UK based unpublished population data on the use of Ibrutinib within an expanded access program. This was collected by an academic institution and is a totally independent dataset which is not supported by Janssen in any way. The data on over 60 patients appears identical that seen within existing clinical trials supporting the notion that these results do translate into a general trial population. This can be made available to the committee if requested. Ibrutinib is a highly active drug and will completely shift the treatment approach for MCL over the next few years. The earlier the drug is used the more efficacious it is and it will inevitably be part of front line therapy soon. It is oral, very well tolerated and can be given to patients with multiple co-morbidities making it ideal for the more elderly and frail patient who are often unable to access novel therapeutics. I would hope that you would re-consider your decision and make this drug available to all patients with MCL at relapse.	

Lymphoma association	It is disappointing to hear that NICE is proposing not to recommend ibrutinib for routine use for relapsed/refractory mantle cell lymphoma on the NHS in England. As the committee is well aware, those with relapsed/refractory mantle cell lymphoma represent a small patient population in extremely challenging circumstances, with low survival chances. As is acknowledged in the committee papers and by the appraisal committee, treatment options are very much determined by clinician choice, as there is no standard care. Despite this, via its current availability on the Cancer Drugs Fund, ibrutinib has in effect become the standard of care for relapsed/refractory mantle cell lymphoma patients, both because of its effectiveness and because it provides significant quality of life benefits for relapsed/refractory patients due to being less toxic, better tolerated and administered orally and at home. If ibrutinib is not available on the NHS, patients are in effect being condemned to choosing between a range of treatments with higher toxicity profiles, which will have a detrimental impact on their and their carers' lives and will be less effective, even though there is a more effective treatment on the market. Furthermore, we understand that part of the problem is NICE and/or NHS's reluctance to agree differential pricing systems for treatments that work across different indications. Most patients would find it hard to believe that such wrangling, among other reasons, is proving a block to approving an effective treatment for use on the NHS. Lymphoma has numerous subtypes with different characteristics, rates of incidences and prognoses, so that most patients would readily understand that the same treatment is going to have a different value depending on the subtype and how the treatment works on patients with those subtypes. From the evidential basis, it worth noting that when NICE appraises treatments for lymphoma subtypes, especially the rarer ones, all too often the complaint is that there isn't a randomised controlled clinical trial as part of the evidence base for the assessment. Yet, in this appraisal, when there is a Phase III trial, it's not the right one or it's not good enough. Patients and patient groups will really struggle to understand NICE's	Comments noted. After considering the updated RAY data and comments received in the response to the appraisal consultation document, the committee recommends ibrutinib as an option for treating relapsed or refractory mantle cell lymphoma in adults who have had only 1 previous line of therapy. Please see sections 1, 4.8, and 4.14 – 4.16 of the final appraisal determination (FAD) for the committee's recommendations and full considerations for this subgroup.

	approach to the evidence, especially in a disease where the outcomes are so poor, as is clearly highlighted by the evidence. While the trial evidence is based on temsirolimus, which may not be a relevant comparator given that it is not used in the UK, it is hard to understand why NICE's methodology cannot have some flexibility to allow it to be used as an indirect comparator, drawing on available clinical evidence for other treatments for relapsed/refractory patients. This is particularly so when temsirolimus is the only licensed treatment in this indication, and it's almost certain that NICE wouldn't accept evidence where unlicensed comparators are used. Again, the size of the patient population requires some flexibility on NICE's part, given the limitations of carrying out Phase III trials with these numbers of people. Recommending the treatment for the CDF is certainly better than it not being available at all, but it's hard to see what extra evidence would be gathered in the next two or three years that would meet NICE's exacting and arguably unrealistic standards, especially given the apparent dislike of real-world data. Furthermore, it's worth noting that the British Committee on Standards in Haematology (BCSH, 2012) MCL guidelines recommend that, where possible, patients should be managed within the context of a clinical trial: "there is no-gold standard therapy for relapsed MCL, and clinicians will choose the treatment most appropriate for the individual patient. The choice of therapy will be determined by patient age, performance status, initial therapy, bone marrow reserve and history of infections." The guidelines highlight rituximab, bortezomib, temsirolimus and combination chemotherapy as possible treatment options. Similarly, the European Society for Medical Oncology (ESMO, 2014) clinical practice guidelines recommend early relapsed patients or those who are refractory should be treated with combined targeted therapies (such as bortezomib, ibrutinib, temsirolimus, lenalidomide). Given the expert clinicians' inclusion of temsirolimus in their guidelines, it is simply incomprehensible to patients why NICE is not able to approve a treatment such as ibrutinib which has been shown in a Phase III clinical trial	

Nominating organisation	Comment [sic]	Response
	to be more effective than that treatment and makes major improvement in patients' quality of life. We sincerely hope that NICE will see sense and reverse its proposal	

Comments received from commentators - None

Comments received from members of the public - None

Response to the Appraisal Consultation Document (ACD)

Ibrutinib for treating mantle cell lymphoma [ID753]

19th October 2017

Janssen are appreciative of this opportunity to comment on the second draft recommendation made by the Appraisal Committee for ibrutinib in relapsed or refractory (RR) mantle cell lymphoma (MCL).

Despite the disappointing negative ACD, Janssen remain committed to finding a mutually agreeable way to achieve permanent baseline funding for ibrutinib for treating RR MCL patients within England and Wales. Of note, ibrutinib for the treatment of RR MCL has been available on the Cancer Drugs Fund (CDF) for nearly three years, and has since become the standard of care in this patient population. We are encouraged to note that regarding ibrutinib, the Committee *"…concluded that the availability of an effective oral therapy with a manageable adverse-reaction profile is highly valued by people, and addresses a high unmet need for people with relapsed or refractory mantle cell lymphoma. The committee accepted that ibrutinib has several benefits for people including oral administration, manageable adverse reactions and low toxicity. The committee concluded that ibrutinib could be considered a step change in managing relapsed or refractory mantle cell lymphoma.*" (Summary of appraisal committee's key conclusions, pages 16-17).

This response will focus on summarizing the situation to date which has led Janssen to propose a new consideration for the Committee that we believe will allow us to achieve our common goal of baseline NHS funding to this step-changing treatment in an area of high unmet need.

Background

Over the course of this appraisal, Janssen had [redacted] ensured that the full RR MCL population was a cost-effective option for NHSE. However, due to policy constraints, this offer was rejected by NHSE.

Proposal for the Committee's consideration

Janssen thank the Committee for the invitation to submit a proposal for inclusion in the (new) CDF, however, we would like to respectfully decline this invitation. At this stage, having reviewed the draft recommendation in detail and with an understanding of current NHSE pricing policy, Janssen have re-visited the data presented to the Committee and respectfully request that the one-prior-line (1PL) subgroup of patients within the RR MCL population be considered ***for baseline commissioning*** for the following reasons:

- Ibrutinib has become standard of care in England in the time it has been available via the (old) CDF and has alleviated an otherwise deep unmet need within RR MCL.
- Ongoing data collection continues to support that better patient outcomes result from using ibrutinib earlier in the treatment pathway i.e. in the 1PL setting.
- Clinical opinion advocates for earlier use of ibrutinib and this preference by clinicians is evidenced by the uptake data which shows high usage (i.e., market leadership) in the 1PL subgroup.
- Ibrutinib meets the end-of-life criteria and bearing in mind the modifiers which would be considered as a result, it is a cost-effective option when the current PAS is applied.

Relevance of the 1PL subgroup

The Committee commented that "*…the company had not suggested that it would be appropriate to only consider ibrutinib for a subgroup of patients who have had only 1 prior therapy*" (Section 4.11, page 11). Therefore, first and foremost, Janssen wish to clarify below the reasons why the Committee should appropriately consider ibrutinib for the 1PL subgroup.

Unmet need addressed

The persisting unmet need in RR MCL has been discussed at length and the need for an effective and tolerable treatment was clearly recognised by the Committee given that without consideration of ibrutinib, "*…there is no standard of care for treating relapsed or refractory mantle cell lymphoma in England, and that treatment tends to combine rituximab with a range of chemotherapy options*" (Section 4.1, page 5).

The drastic change to the unmet need since ibrutinib's availability on the (old) CDF from January 2015 has also been acknowledged by the Committee through the following statements from the patient and clinical experts:

- "*It is taken orally and people value this highly because it can be taken in the privacy of their own home and reduces the need for hospital visits. It can be used by older and frail people and, unlike current chemotherapy options, patients do not usually need additional treatments to counter adverse reactions. For these reasons, the patient experts considered that ibrutinib is a life-transforming drug that results in a step change in the quality of life of patients with relapsed or refractory mantle cell lymphoma and their families and carers…*" (Section 4.2, page 6)
- "*The Committee heard from the patient and clinical experts that ibrutinib is already widely used in clinical practice because of its availability through the Cancer Drugs Fund, and is welcomed by patients because it is highly effective compared with existing treatments and extremely well tolerated with very few adverse reactions*" (Section 4.2, page 6)

To confirm and quantify these statements, in the nearly three years since availability via the (old) CDF, ibrutinib has become the standard of care in RR MCL overall and data as of August 2017 show that ibrutinib had [redacted] uptake within the 1PL subgroup (QuintilesIMS, 2017) supporting the clinically-driven relevance of positioning ibrutinib in the 1PL setting.

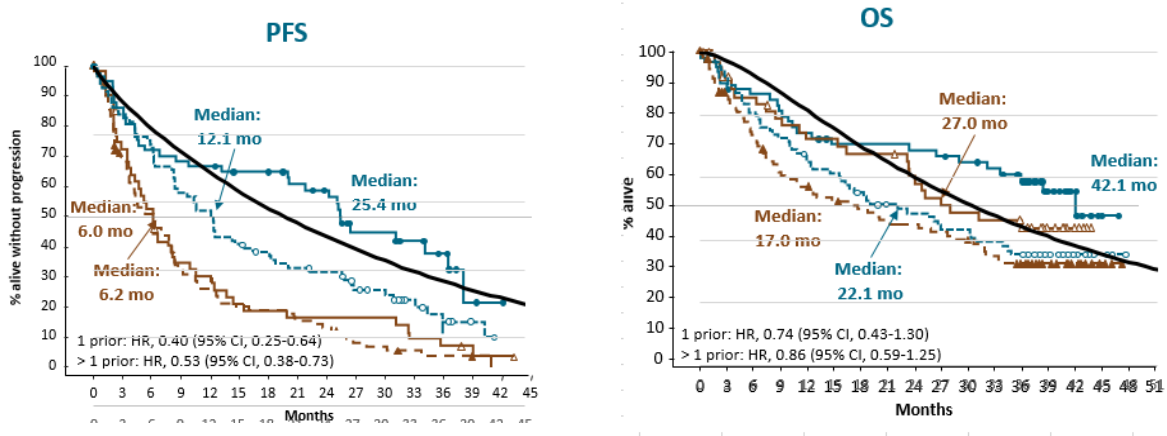
Data clearly support the efficacy and tolerability of ibrutinib in 1PL subgroup

The Committee noted "*…results from the studies suggested greater efficacy in patients who had ibrutinib after 1 prior therapy compared with 2 or more therapies*" (Section 4.8, page 9) and acknowledged clinical opinion stating that *"[the committee] …heard from the clinical expert that ibrutinib is particularly beneficial after the first relapse*" (Section 4.8, page 9). Furthermore, "*The committee noted with interest that the final overall-survival results from RAY are expected in 2017*" (Section 4.4, page 7).

The updated data from RAY, the phase 3 registrational trial for ibrutinib in RR MCL, based on median follow-up of 39 months (previous data cut had median follow-up of 20 months) was indeed presented in June 2017 at the International Conference on Malignant Lymphoma (ICML) and subsequently published in August 2017. Updated results are not only consistent with the primary analysis but also confirm that patients who had received ibrutinib after only 1PL had "the most durable and best PFS and OS outcomes" (Rule et al, 2017; abstract). Cross-over of 39% was reported in the update and despite this, the cross-over unadjusted median OS remains impressive with 42.1 months for ibrutinib (vs 27.0 months for temsirolimus) in the 1PL subgroup (Rule et al, 2017; presentation). Comparatively, the median OS in the overall RR MCL population was 30.3 months for ibrutinib (vs 23.5 months for temsirolimus) and it was 22.1 months for ibrutinib (vs 17.0 months for temsirolimus) in the >1PL subgroup; these data consistently support that there is a particular benefit in using ibrutinib in the 1PL subgroup. This is of considerable clinical importance as these patients otherwise face a life-expectancy of less than 12 months when treated with the pre-ibrutinib options of various rituximab-based chemotherapies, as per the audit data from the Haematological Malignancy Research Network (HMRN).

Crucially, the 1PL data also validate the current modelled results for ibrutinib (Figure 1). Projected PFS for ibrutinib (solid black line) appears to track very closely to the updated trial results (solid blue line); this is arguably the key data from the modelling perspective as PFS is the determinant of treatment duration and therefore, cost. Projected OS for ibrutinib (solid black line) appears to be notably conservative compared to the trial results (solid blue line) as the modelled median OS is approximately 31 months vs the trial median OS of 42.1 months.

Figure 1: Modelled vs updated trial KM PFS and OS data



Note: solid blue line – ibrutinib KM for 1PL; solid brown line – temsirolimus KM for 1PL; dashed blue line – ibrutinib KM for >1PL; dashed brown line – temsirolimus KM for >1PL; solid black line – ibrutinib model projection

The Committee's main objection to the consideration of the 1PL subgroup data was stated as "*…the subgroups had been defined post hoc and [the Committee] was therefore reluctant to draw any firm conclusions about the relative efficacy of ibrutinib in these groups*" (Section 4.8, page 9). Within the RAY study, analysis was pre-specified across one or two prior lines versus greater than three prior lines. The full list of the pre-specified analyses is provided in the Appendix (Table 2) and demonstrates that not many were predictors of PFS, however, based upon multivariate analysis, there was reason to further explore line of therapy as an independent predictor of efficacy. Consequently, with a clinical rationale to explore further, the one or two prior line population was further stratified post-hoc to 1PL vs two or more prior lines; baseline characteristics are provided in the Appendix (Tables 3 and 4). Results of the post-hoc analysis have since been published and presented at international congresses, concluding that "ibrutinib provided the greatest benefit when used at first relapse" (Rule et al, 2017; presentation). It should be noted that data showing ibrutinib provides a greater benefit when used earlier in the treatment pathway has also been reported in a different haematological indication (chronic lymphocytic lymphoma) and therefore there is wider evidence to support this argument at the molecule level (O'Brien et al, 2016).

Janssen note that post-hoc analyses have been used in the past to inform decision making by NICE Appraisal Committees. These data were generally considered when they are found to have clinical relevance and there was strength in the evidence base; we believe both factors are met for ibrutinib and the 1PL subgroup. Should any reservation remain as to the validity or robustness of the RAY study's post-hoc analysis, Janssen would encourage the Committee to seek further clinical opinion on this as there is clear clinical interest and strong evidenced-based reasoning to support the use of ibrutinib in this specific subgroup.

Cost-effectiveness of the 1PL subgroup

As the Committee has concluded that "*…the company's model was in line with accepted NICE methods and was appropriate for decision-making*" (Section 4.12, page 12), the results of the cost-effectiveness analysis with the existing simple PAS of [redacted] applied are presented in the table below; deterministic and probabilistic sensitivity analysis results are provided in the appendix.

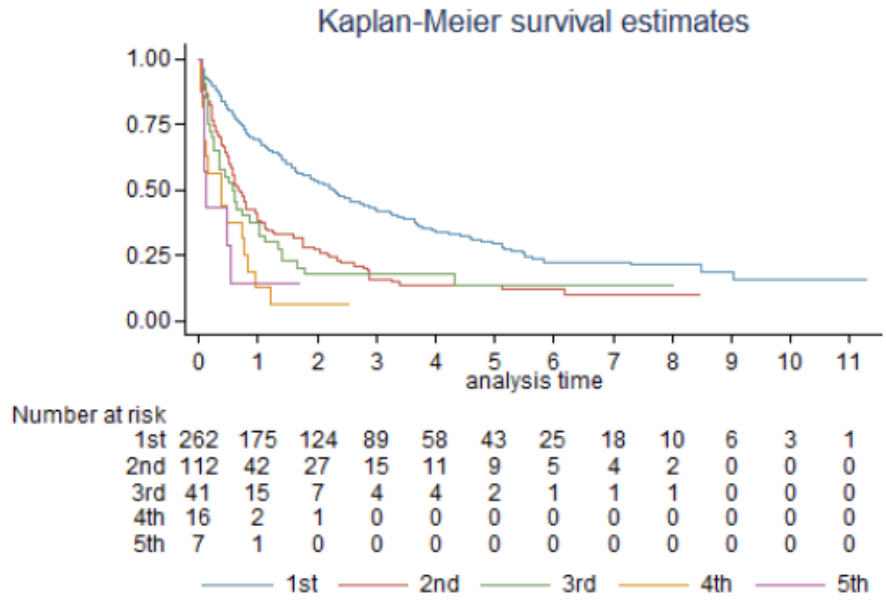
The Committee has further "*…agreed that this additional data [from the updated HMRN audit] provided some reassurance about the method of modelling the company had used, and reiterated that it considered the company's original model and base-case ICER to be acceptable for decision-making*" (Section 4.13, page 12). Therefore, given (a) the clinical relevance of the 1PL subgroup discussed above, (b) the updated trial data for ibrutinib which validates the benefits estimated by the model for ibrutinib, and (c) the previously-presented updated HMRN data which provide evidence for the PPS of the comparator arm to be adjusted such that survival on this arm is reflective of survival reported in UK real-world data (Janssen submitted this on 14th September 2016 as part of our response to the first ACD), results have been re-presented for this scenario along with results without the adjustment to the PPS of the comparator arm but using the original and the alternative PFS HR for the 1PL subgroup.

Table 1: Cost-effectiveness results for the 1PL subgroup versus R-CHOP, with PAS

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Subgroup results with original PFS HR (0.28) and with a differential PPS HR based on HMRN data as presented in Company Submission							
Ibrutinib	[redacted]	[redacted]	[redacted]	£93,196	2.64	1.87	**£49,849**
R-CHOP	[redacted]	[redacted]	[redacted]				
Subgroup results with original PFS HR (0.28) as presented in Company Submission							
Ibrutinib	[redacted]	[redacted]	[redacted]	£90,645	2.34	1.67	£54,150
R-CHOP	[redacted]	[redacted]	[redacted]				
Subgroup results with alternative PFS HR (0.24) based on HMRN data as presented in Company Response to ACD1							
Ibrutinib	[redacted]	[redacted]	[redacted]	£91,432	2.44	1.73	£52,791
R-CHOP	[redacted]	[redacted]	[redacted]				
ICER: incremental cost-effectiveness ratio, QALYs: quality-adjusted life years, R-CHOP: rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone							

As discussed in the previous section, the updated data confirm PFS, and therefore treatment duration and cost, to be accurately modelled and highlight the conservative nature of the modelled OS for ibrutinib (Figure 1). Furthermore, the Committee agree that the end-of-life criteria have been met for the overall RR MCL population and this remains applicable in the 1PL subgroup as evidenced by (a) the trial data and clinical opinion supporting the extension to life criterion and (b) the later data-cut from the HMRN audit supporting a short life expectancy of less than 24 months (Figure 2). With these considerations and the PAS applied, use of ibrutinib in the 1PL subgroup is a cost-effective option.

Figure 2: Overall Survival by Treatment Line, August 2016 updated HMRN audit



Concluding remarks

Janssen believes that the ICER for the 1PL subgroup is cost-effective for this end-of-life population when considering the new clinical data released this year; furthermore, it is crucial to note that the benefit ibrutinib offers to patients in terms of addressing a considerable unmet need is not one which is easily captured within the constraints of an economic model. With this in mind, it is highly likely that the base case ICER is a conservative estimate of the cost-effectiveness of this subgroup.

In the time since ibrutinib was first made available via the CDF nearly three years ago, it quickly became standard of care in RR MCL - the need for ibrutinib within the RR MCL treatment pathway has been, and remains clearly demonstrated. Trial data consistently demonstrate a consistent and unprecedented survival benefit and as such, clinical demand remains resolute and the preference to use ibrutinib in the 1PL subgroup is evident from current uptake data as well as the statements from the clinical experts. Janssen have an unwavering history of working collaboratively with NICE to ensure access to our treatments is secured for patients at a price that is acceptable to both NICE and the NHS; therefore, we respectfully ask that this proposal be considered by the Committee so that access can continue.

O'Brien S, Byrd J, Hillmen P, et al. (2016) Outcomes with ibrutinib by line of therapy in patients with CLL: Analyses from phase III data. Journal of Clinical Oncology 34:15_suppl, 7520-7520

QuintilesIMS. QuintilesIMS. Proprietary data (commercially confidential): CLL/ MCL Therapy Monitor UK June / July 2017

[I] Amongst patients who have been recently seen by specialists and that the specialists concerned have been screened based on passing a MCL patient workload threshold

Rule S, Jurczak W, Jerkeman M, et al. (2017) Ibrutinib vs temsirolimus: three-year follow-up of patients with previously treated mantle cell lymphoma from the phase 3, international, randomized, open-label RAY study. Hematological Oncology, 35(S2): 143–144 [Abstract and ICML 2017 Presentation]

APPENDIX:

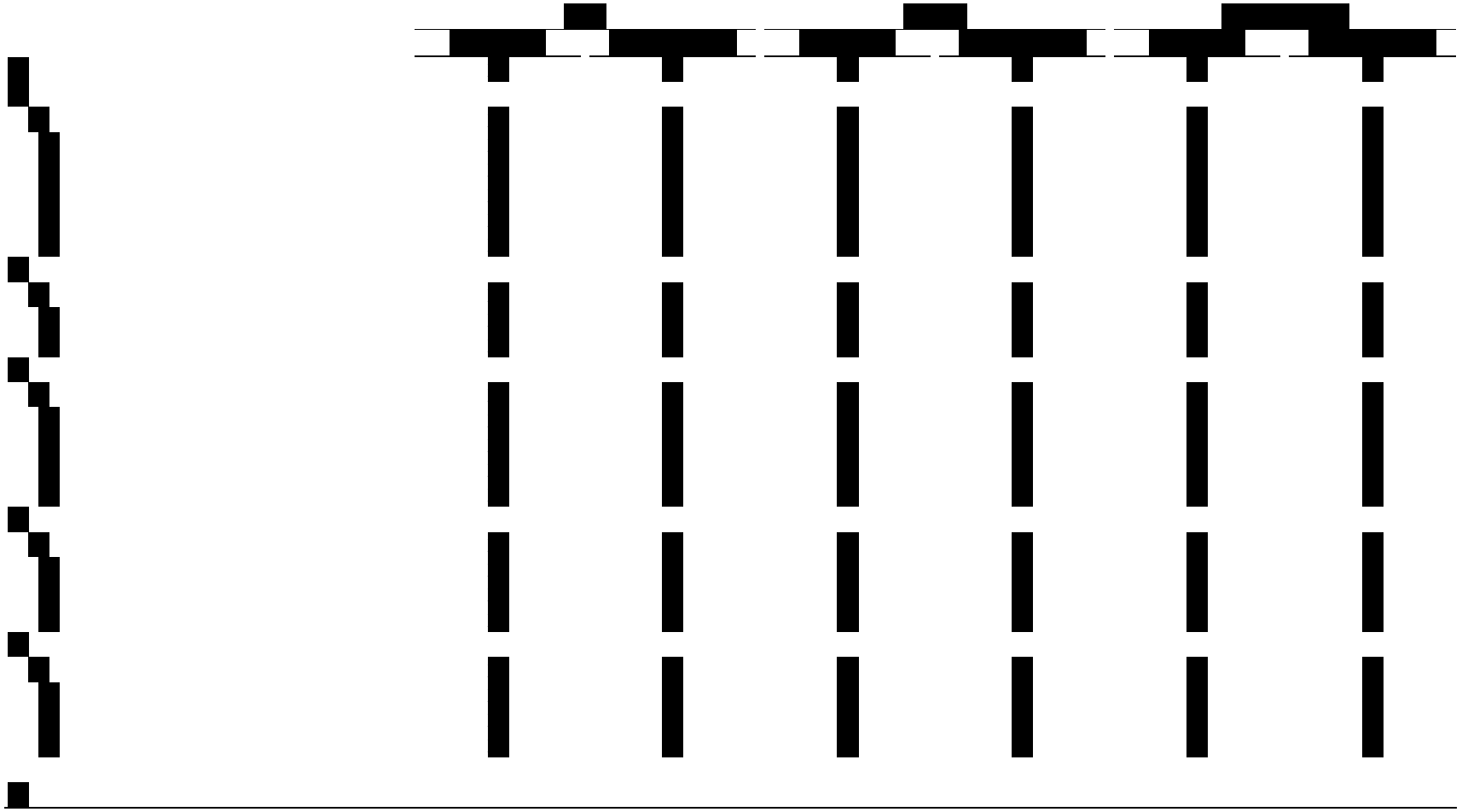
Table 2: RAY covariate-adjusted analysis for progression-free survival by independent review committee assessment

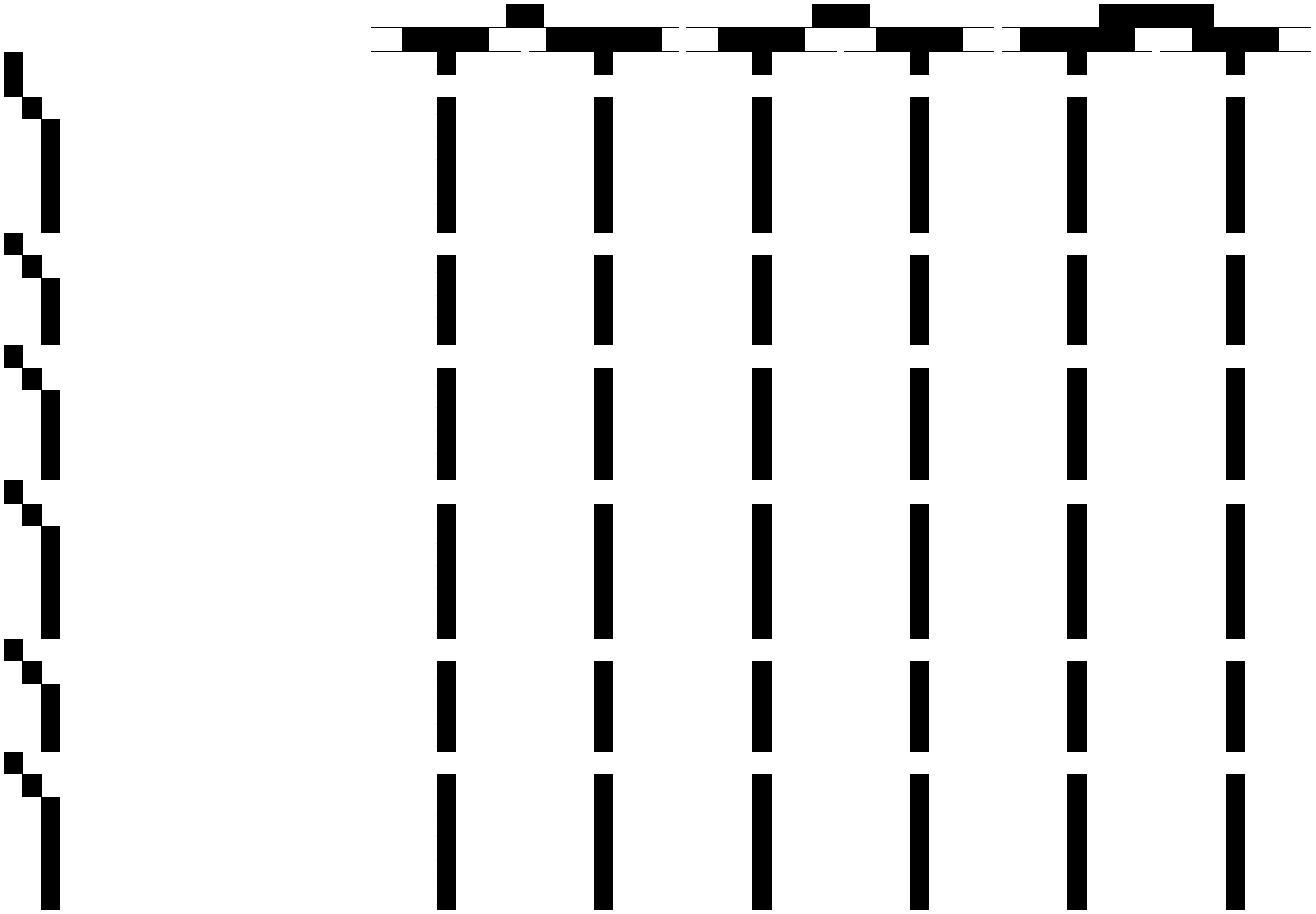
	HR	95% CI for HR	p value
Treatment (ibrutinib *vs* temsirolimus)	0·41	(0·30–0·57)	<0·0001
Sex (male *vs* female)	0·82	(0·57–1·18)	0·2812
Age group (≥65 *vs* <65 years)	1·08	(0·74–1·58)	0·6713
Race (Caucasian *vs* non-Caucasian)	1·05	(0·57–1·93)	0·8808
Baseline ECOG PS (1 *vs* 0)	1·56	(1·13–2·16)	0·0069
Region (Europe *vs* non-Europe)	0·84	(0·53–1·34)	0·4688
Baseline extranodal disease (yes *vs* no)	0·91	(0·62–1·33)	0·6225
MIPI score (intermediate *vs* low)*	1·36	(0·90–2·03)	0·1400
MIPI score (high *vs* low)*	2·51	(1·55–4·07)	0·0002
Prior lines of therapy (≥3 *vs* <3)*	1·58	(1·14–2·19)	0·0066
Stage of disease (IV *vs* I-III)	1·08	(0·61–1·91)	0·7902
Prior bortezomib (yes *vs* no)	1·03	(0·70–1·53)	0·8641
Tumour bulk (≥5 *vs* <5 cm)	0·96	(0·66–1·40)	0·8309
Tumour burden	1·00	(1·00–1·00)	0·8147
Histology (blastoid *vs* non-blastoid)	2·49	(1·60–3·86)	<0·0001
Refractory disease (yes *vs* no)	1·21	(0·86–1·71)	0·2680
Bone marrow involvement (yes *vs* no)	0·96	(0·67–1·40)	0·8509

HR=hazard ratio. CI=confidence interval. ECOG PS=Eastern Cooperative Oncology Group performance status. MIPI=mantle-cell lymphoma international prognostic index. *From interactive web response system (IWRS) assignment.

Source: Dreyling M, Jurczak W, Jerkeman M, et al. (2016). Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. The Lancet, 387(10020):770-778 Supplementary appendix. (http://www.sciencedirect.com/science/article/pii/S0140673615006674)

Table 3: Demographics and Baseline Characteristics for Prior Lines Subgroups (1 PL vs > 1 PL), Intent-to-treat Analysis Set (Study PCI-32765MCL3001)





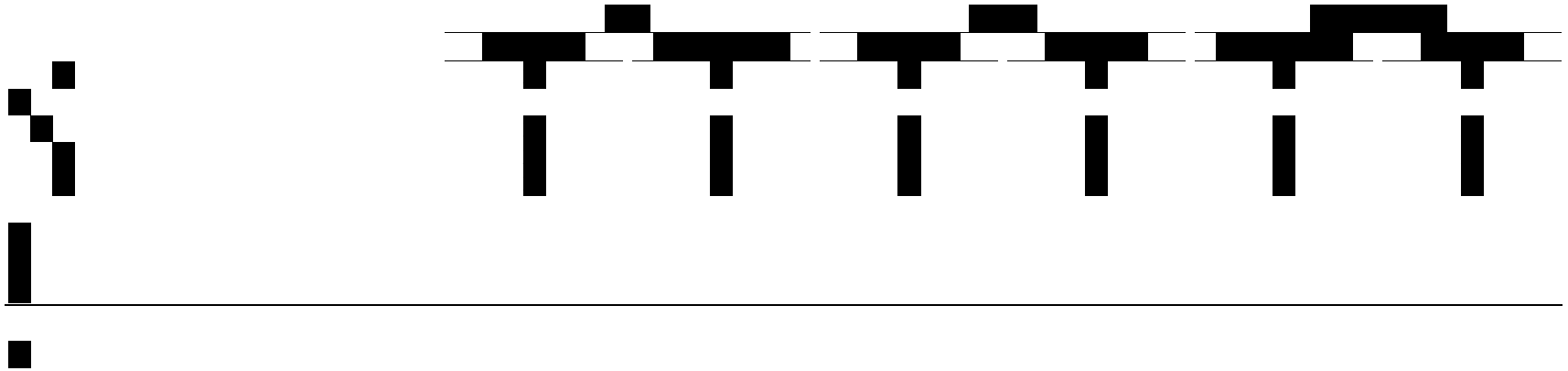


Figure 3: Tornado diagram of deterministic sensitivity analysis for the 1PL subgroup versus R-CHOP, with adjusted PPS HR, PAS, and PFS HR 0.28

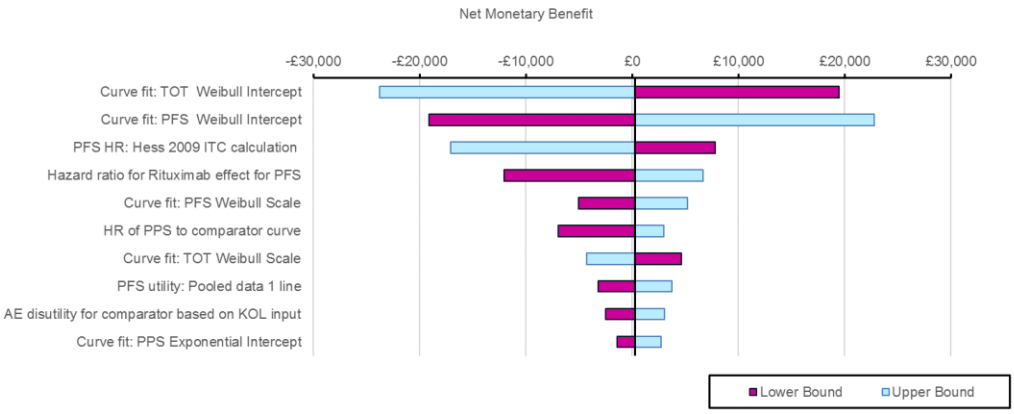


Figure 4: ICER scatter plot for the 1PL subgroup versus R-CHOP, with adjusted PPS HR, PAS, and PFS HR 0.28

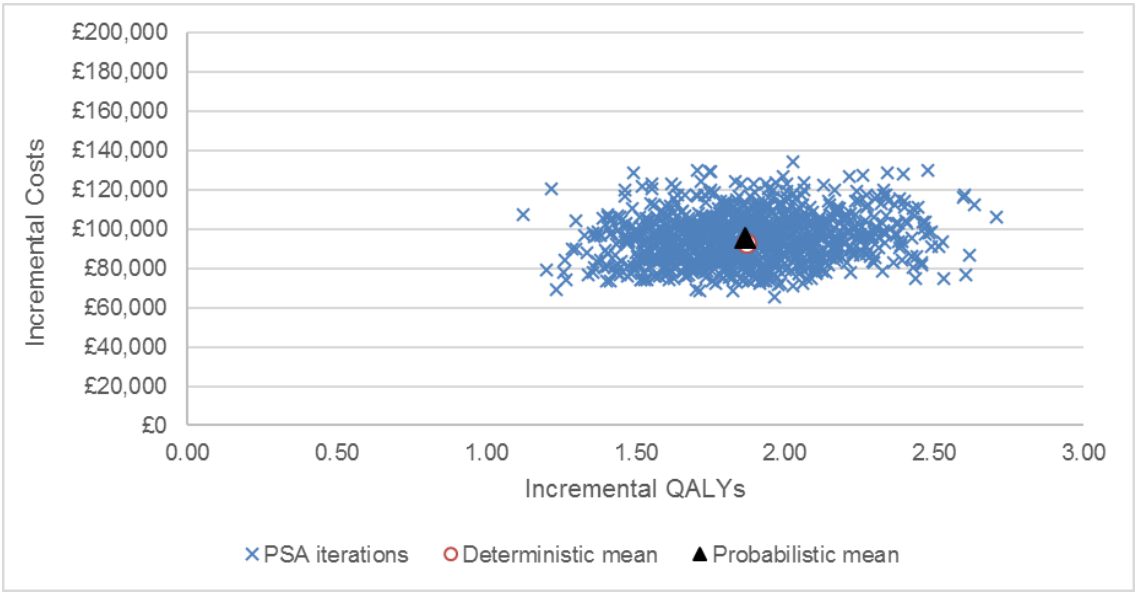


Figure 5: CE acceptability curve for the 1PL subgroup versus R-CHOP, adjusted PPS HR, PAS, and PFS HR 0.28

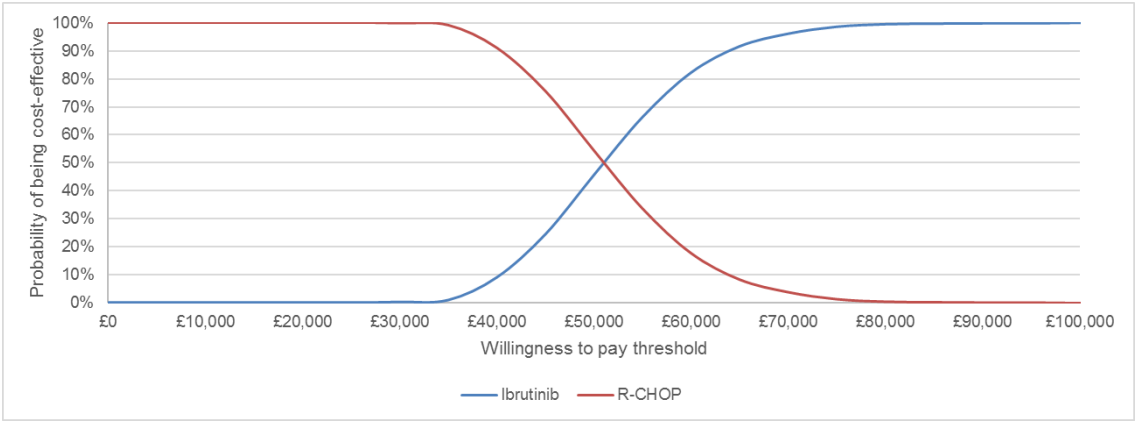


Figure 6: Tornado diagram of deterministic sensitivity analysis for the 1PL subgroup versus R-CHOP, with PAS and PFS HR 0.28

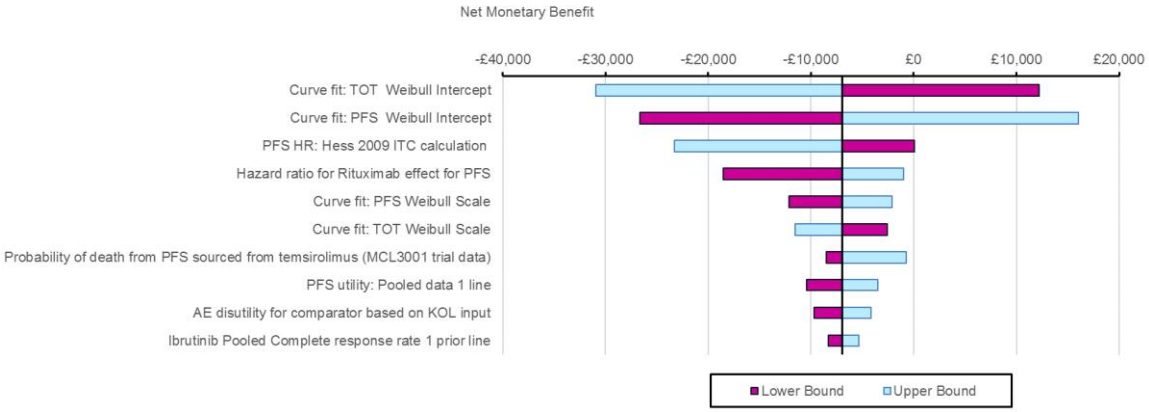


Figure 7: ICER scatter plot for the 1PL subgroup versus R-CHOP, with PAS and PFS HR 0.28

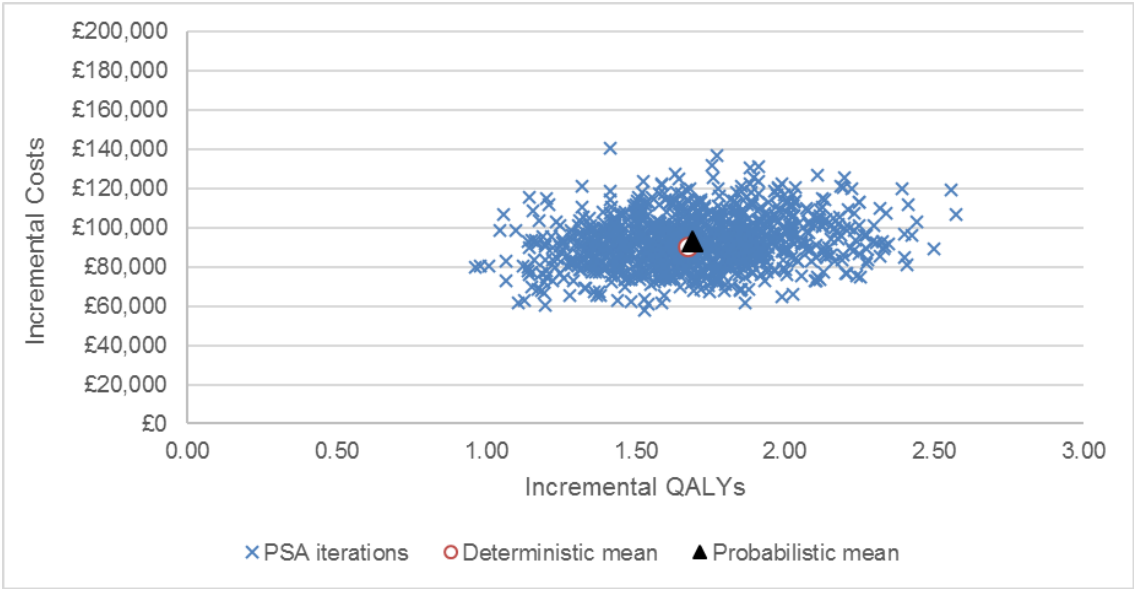


Figure 8: CE acceptability curve for the 1PL subgroup versus R-CHOP, with PAS and PFS HR 0.28

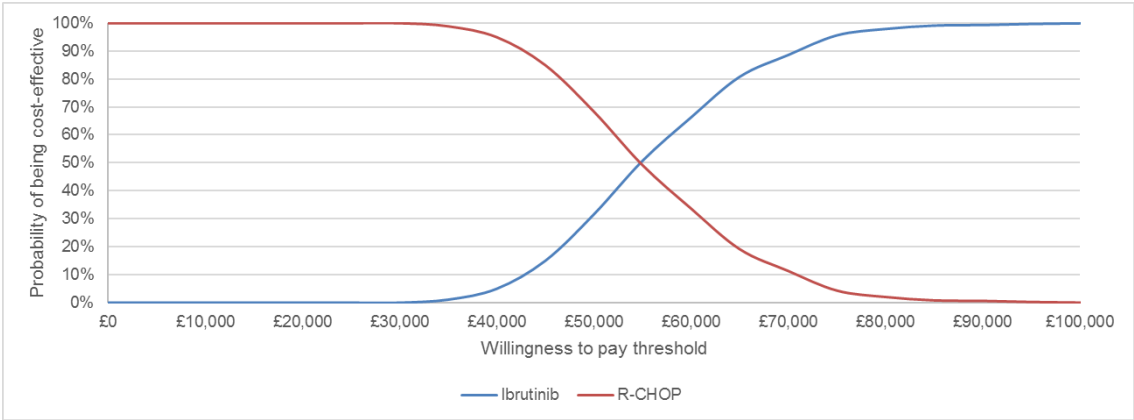


Figure 9: Tornado diagram of deterministic sensitivity analysis for the 1PL subgroup versus R-CHOP, with PAS and PFS HR 0.24

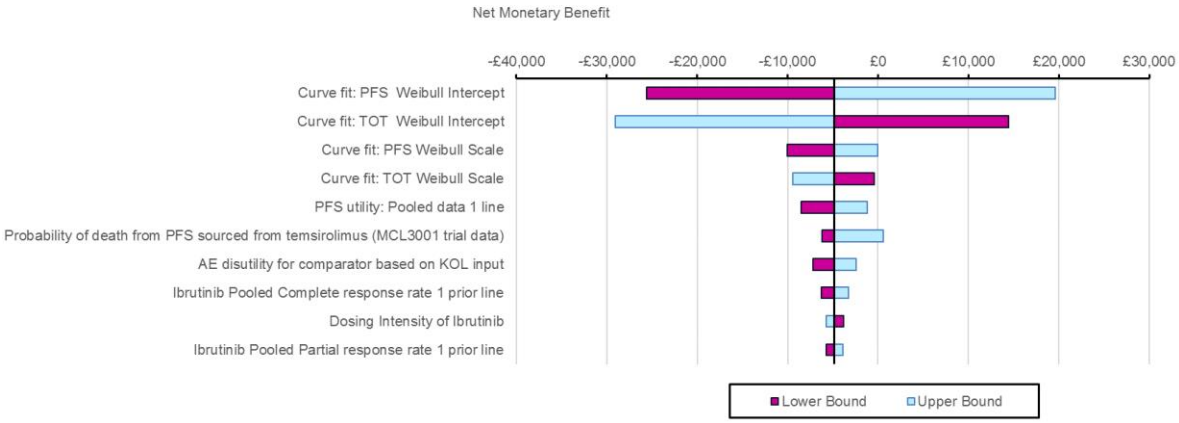


Figure 10: ICER scatter plot for the 1PL subgroup versus R-CHOP, with PAS and PFS HR 0.24

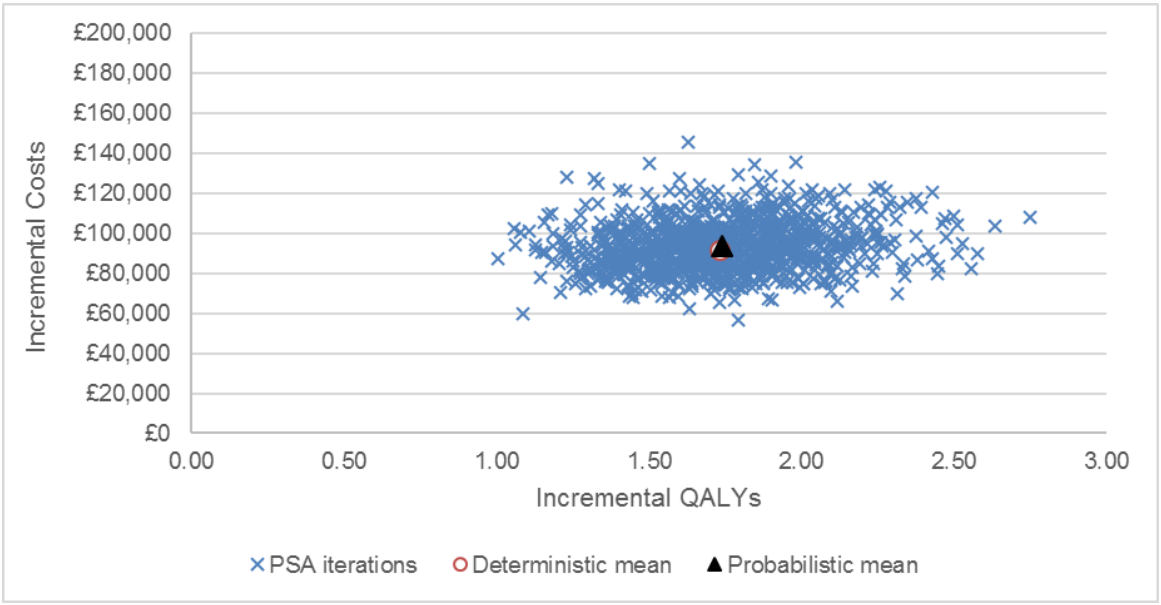


Figure 11: CE acceptability curve for the 1PL subgroup versus R-CHOP, with PAS and PFS HR 0.28

Lymphoma association

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enquiries@lymphomas.org.uk

While the trial evidence is based on temsirolimus, which may not be a relevant comparator given that it is not used in the UK, it is hard to understand why NICE's methodology cannot have some flexibility to allow it to be used as an indirect comparator, drawing on available clinical evidence for other treatments for relapsed/refractory patients. This is particularly so when temsirolimus is the only licensed treatment in this indication, and it's almost certain that NICE wouldn't accept evidence where unlicensed comparators are used.

Again, the size of the patient population requires some flexibility on NICE's part, given the limitations of carrying out Phase III trials with these numbers of people. Recommending the treatment for the CDF is certainly better than it not being available at all, but it's hard to see what extra evidence would be gathered in the next two or three years that would meet NICE's exacting and arguably unrealistic standards, especially given the apparent dislike of real-world data.

Furthermore, it's worth noting that the British Committee on Standards in Haematology (BCSH, 2012) MCL guidelines recommend that, where possible, patients should be managed within the context of a clinical trial: "there is no-gold standard therapy for relapsed MCL, and clinicians will choose the treatment most appropriate for the individual patient. The choice of therapy will be determined by patient age, performance status, initial therapy, bone marrow reserve and history of infections." The guidelines highlight rituximab, bortezomib, temsirolimus and combination chemotherapy as possible treatment options.

Similarly, the European Society for Medical Oncology (ESMO, 2014) clinical practice guidelines recommend early relapsed patients or those who are refractory should be treated with combined targeted therapies (such as bortezomib, ibrutinib, temsirolimus, lenalidomide).

Given the expert clinicians' inclusion of temsirolimus in their guidelines, it is simply incomprehensible to patients why NICE is not able to approve a treatment such as ibrutinib which has been shown in a Phase III clinical trial to be more effective than that treatment and makes major improvement in patients' quality of life.

We sincerely hope that NICE will see sense and reverse its proposal

Yours sincerely

Chief Executive

Supporting people affected by lymphatic cancer

Lymphoma association

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18 October 2017

Lymphoma Asssocation response to 2nd Appraisal Consultation Document

Ibrutinib for treating relapsed or refractory mantle cell lymphoma [ID753]

It is disappointing to hear that NICE is proposing not to recommend ibrutinib for routine use for relapsed/refractory mantle cell lymphoma on the NHS in England. As the committee is well aware, those with relapsed/refractory mantle cell lymphoma represent a small patient population in extremely challenging circumstances, with low survival chances. As is acknowledged in the committee papers and by the appraisal committee, treatment options are very much determined by clinician choice, as there is no standard care.

Despite this, via its current availability on the Cancer Drugs Fund, ibrutinib has in effect become the standard of care for relapsed/refractory mantle cell lymphoma patients, both because of its effectiveness and because it provides significant quality of life benefits for relapsed/refractory patients due to being less toxic, better tolerated and administered orally and at home. If ibrutinib is not available on the NHS, patients are in effect being condemned to choosing between a range of treatments with higher toxicity profiles, which will have a detrimental impact on their and their carers' lives and will be less effective, even though there is a more effective treatment on the market. Furthermore, we understand that part of the problem is NICE and/or NHS's reluctance to agree differential pricing systems for treatments that work across different indications. Most patients would find it hard to believe that such wrangling, among other reasons, is proving a block to approving an effective treatment for use on the NHS. Lymphoma has numerous subtypes with different characteristics, rates of incidences and prognoses, so that most patients would readily understand that the same treatment is going to have a different value depending on the subtype and how the treatment works on patients with those subtypes.

From the evidential basis, it worth noting that when NICE appraises treatments for lymphoma subtypes, especially the rarer ones, all too often the complaint is that there isn't a randomised controlled clinical trial as part of the evidence base for the assessment. Yet, in this appraisal, when there is a Phase III trial, it's not the right one or it's not good enough. Patients and patient groups will really struggle to understand NICE's approach to the evidence, especially in a disease where the outcomes are so poor, as is clearly highlighted by the evidence.

Supporting people affected by lymphatic cancer

Ibrutinib for treating relapsed or refractory mantle cell lymphoma [ID753]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 19 October 2017 upload to NICE Docs

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

Please return to: **[insert email address]** / NICE DOCS

Ibrutinib for treating relapsed or refractory mantle cell lymphoma [ID753]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 19 October 2017 upload to NICE Docs

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments. Our experts were disappointed that the committee came to a negative decision with respect to this drug, however since the last meeting more evidence has emerged on the longer term efficacy of ibrutinib in MCL that may prove helpful. Firstly, there has been a further analysis of the RAY trial which was presented at the International Conference on Malignant Lymphoma (Rule et al ICML 2017). The RAY trial was a randomised study comparing temsirolimus with ibrutinib for relapsed refractory MCL and was the basis for registration of the agent in Europe. The primary end point of this study was PFS which was strongly positive in favour of ibrutinib. With 3 years of follow up, whilst PFS remains strongly positive, overall survival still shows no significant difference between arms. However a quarter of patients remain on ibrutinib and there are no patients still receiving temsirolimus. 39% of patients have subsequently crossed over to the ibrutinib arm which clearly confounds the overall survival endpoint. As a consequence it seems unlikely that longer follow up will lead to a significant OS advantage however the hazard ratio is 0.74 (p=0.06). In addition this study demonstrates a very strong correlation between when the drug is given and its efficacy as defined by progression free survival and overall survival. With respect to PFS when Ibrutinib is given at first relapse the median PFS is 25.4 months compared with 12.1 months when given later. For OS this translates to a median of 42.1 months compared with 22.1 months. Whilst this is a post hoc analysis, it seems clear that earlier use is highly beneficial and this is supported by a pooled analysis of the 3 trials that have included ibrutinib (Rule et al BJHaem 2017). In this study a clear association between efficacy (PFS and OS) and line of therapy is evident. The RAY trial is criticised as temsirolimus is not felt to be an appropriate comparator for UK practice. This is true but as this was a licensing study the EMA required a licensed drug as a comparator and this was the only licensed drug in Europe at that time. There will not be any further trials comparing ibrutinib with other more relevant agents although randomised trials in the front line are ongoing for elderly patients. It is without question that ibrutinib has transformed the treatment paradigm for MCL. It is the single most active agent in the relapsed setting and has an extremely modest side-effect profile when compared with conventional chemotherapy. As well as the trial data there is UK based unpublished population data on the use of Ibrutinib within an expanded access program. This was collected by an academic institution and is a totally independent dataset which is not supported by Janssen in any way. The data on over 60 patients appears identical that seen within existing clinical trials supporting the notion that these results do translate into a general trial population. This can be made available to the committee if requested. Ibrutinib is a highly active drug and will completely shift the treatment approach for MCL over the next few years. The earlier the drug is used the more efficacious it is and it will inevitably be part of front line therapy soon. It is oral, very well tolerated and can be given to patients with

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	multiple co-morbidities making it ideal for the more elderly and frail patient who are often unable to access novel therapeutics. I would hope that you would re-consider your decision and make this drug available to all patients with MCL at relapse.

Insert extra rows as needed

Checklist for submitting comments

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

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

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

Comments on the ACD received through the NICE Website

Name	[redacted]
Role	Policy Officer
Other role	
Organisation	Bloodwise
Location	England
Conflict	The manufacturer, Janssen fund an unrelated project we are working on patient experience.
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Bloodwise are extremely disappointed and concerned by the conclusion in the draft guidance that Ibrutinib is not recommended for treating relapsed or refractory mantle cell lymphoma (MCL) in adults. The evidence from both patients and clinicians for the use of Ibrutinib for this purpose is overwhelmingly positive and we are concerned that the relevant evidence from patients has not been taken into account sufficiently. We reiterate the following key messages from our previous submission and would ask that these be taken into account before the Final Appraisal Determination is reached: Ibrutinib is regarded by patients as a step change in the way MCL is treated, significantly out-performing current treatments with no comparable treatments available. Patients report a rapid reduction in symptoms, such as swelling, pain and fatigue, allowing many to return to their normal life very quickly. As an oral treatment that can be taken at home, there are significant benefits for patients compared to current therapies, which involve multiple hospital visits. Patients usually receive intravenous chemotherapy with the numerous side effects that go with treatment, ongoing support and significant practical difficulties associated with multiple hospital visits. Treatment with Ibrutinib is therefore particularly beneficial for patients with mobility issues or without access to transport who cannot easily get to hospital appointments. The side effects of ibrutinib are mild and generally only last for around a couple of weeks. This is a significant improvement on current more invasive chemotherapy treatment. In conclusion, there are quite simply no other treatments available that rival Ibrutinib for its management of all the issues outlined above which MCL patients face and as such the medication is truly life changing for these patients. We would urge the committee to reassess their draft guidance and approve Ibrutinib for use in treating relapsed or refractory mantle cell lymphoma.
Section 2 (The technology)	
Section 3	

(The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Ibrutinib for treating relapsed or refractory mantle cell lymphoma: Additional information provided by the ERG

Paul Tappenden, ScHARR-TAG

01/11/2017

Additional information provided by the ERG

The company's response to the ACD presents an ICER of £49,849 per QALY gained within the 1 prior line of therapy (LOT) subgroup.[1] The ERG notes that this analysis is equivalent to the analysis presented in the company's original scenario analyses (Table 82 of the original company submission,[2] last row), but includes an updated Patient Access Scheme. The ERG has some concerns about this analysis because:

- The subgroup was defined *post hoc*
- The company's model does not provide a good fit to the observed PFS or OS data for the 1 prior LOT subgroup
- The analysis assumes an additional survival advantage (slower rate of death) for patients in the ibrutinib group even after they have discontinued treatment compared with the R-CHOP group. This may be optimistic and is difficult to judge due to the presence of censoring and treatment switching in the trial data, and due to the poor fit of the model.
- The results should be considered to be highly uncertain.

The ERG's original exploratory analysis in the 1 prior LOT subgroup produced a more favourable ICER than the company's analysis due to the use of observed Kaplan-Meier curves for time to treatment discontinuation/death rather than a parametric function. Using the new PAS for ibrutinib, this ERG exploratory analysis gives an ICER of £37,318 per QALY gained. This analysis assumes the same post-progression survival curve for both treatment groups. The ERG notes however that the ACD states that the Committee *"was minded not to accept the results of the ERG's amendments because these represented the extreme (lowest) end of the ERG's wide estimate of possible ICERs, depending on the model and parameters used."*

References

1. Janssen. Response to the Appraisal Consultation Document (ACD): Ibrutinib for treating mantle cell lymphoma. 19th October 2017.
2. Janssen Ltd. Ibrutinib for the treatment of relapsed or refractory mantle cell lymphoma. Company's evidence submission to the National Institute for Health and Care Excellence. Janssen: High Wycombe, Buckinghamshire; 2016.
3. Tappenden P, Simpson E, Sanderson J, Pollard D, Clowes M, Kaltenthaler E, Meiklejohn D, Morley N. Ibrutinib for treating relapsed or refractory mantle cell lymphoma: A Single Technology Appraisal. School of Health and Related Research (ScHARR), 2016.