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 (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Janssen

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

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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	Additional data from the HMRN audit was provided to validate the methodology applied to inform the effectiveness of R-chemo in the cost-effectiveness analysis.	The committee noted that additional data presented by the company and agreed that this additional data 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 (see section 4.12)
Janssen	ACD section 4.8 states that "*the committee was concerned that subgroups had been defined post hoc and were based on a small number of patients (57 patients had 1 prior therapy and 82 patients had 2 or more prior therapies)"*. The company wishes to clarify that the numbers above are based on the ibrutinib arm of the RAY study, whereas the cost-effectiveness analyses were based on data from the pooled dataset of the 3 ibrutinib trials (99 patients had1 prior therapy and 271 patients had 2 or more prior therapies	Comment noted. The final appraisal determination has been amended to reflect this (see section 4.8)

Comments received from clinical experts and patient experts - None

Comments received from commentators - None

Comments received from members of the public - None

Response to the Appraisal Consultation Document (ACD) Ibrutinib for treating relapsed or refractory mantle cell lymphoma [ID753]

September 14th 2016

Janssen is grateful for the opportunity to comment on the ACD related to ibrutinib for treating relapsed or refractory mantle cell lymphoma (R/R MCL).

Overall Janssen would like to thank the Committee for their fair approach to this appraisal, in recognising that not only is ibrutinib a step change in the treatment of R/R MCL, but also that ibrutinib offers benefits beyond the standard QALY estimations.

We have structured this response based on two aspects of the ACD document:

1. First, we recognise that there is uncertainty in relation to the comparative effectiveness evidence available (ibrutinib vs R-chemo) based on the ACD "*The committee concluded that there is considerable uncertainty associated with the indirect comparisons and that the benefit of ibrutinib compared with R-chemo is unclear, although it accepted that the available evidence and experience from clinical practice strongly suggest that ibrutinib is more effective*" [para 4.7]. We therefore present additional analyses informed by Haematological Malignancy Research Network (HMRN) registry data on R-chemo. We use this information to validate the results of the cost-effectiveness analyses presented in the submission
2. Secondly, we go on to address a one minor factual inaccuracy presented within the ACD.

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

1. Additional information on comparative effectiveness

As acknowledged within the submission and throughout this appraisal, there is very limited evidence available to inform the effectiveness of R-chemo regimens. Additional HMRN data are now available from newly diagnosed patients with MCL between 1st September 2004 and 31st August 2015 across the Yorkshire and Humber & Yorkshire Coast Cancer Networks. The new data included a later data cut up to August 2015 (the initial audit included data until August 2012) and specific R/R MCL data as opposed to the initial audit, which covered the wider MCL setting. The data covered 112 patients over several treatment lines (176 lines of treatment in total, meaning that some patients received more than one line of treatment). Throughout this section we use this information to provide validation of the methodology applied to inform the effectiveness of R-chemo in the cost-effectiveness analysis presented in the submission.

Effectiveness of R-chemo regimens based on latest HMRN data

Updated HMRN data reiterate the premise that there is no evidence that R-chemo regimens have different effectiveness in the treatment of R/R MCL. Table 1 reports the hazard ratios (HRs) of different R-chemo treatments (R-CHOP, R-CVP and FCR) and the associated 95% confidence intervals. R-CVP and FCR are compared to R-CHOP (R-CHOP HR = 1).

The confidence intervals for alternative R-chemo regimens are very wide and all overlap with R-CHOP. This indicates that there is no evidence to suggest that treatment with R-chemo differs between regimens. Although sample sizes of each individual R-chemo regimes are very small, these findings support the economic case presented in the submission, which assumed equivalent efficacy of R-chemo regimens.

Table 1: PFS adjusted HR of R-chemo regimens

Treatment	N	Adjusted PFS HR* (95% CI)
R-CHOP	[redacted]	[redacted]
R-CVP	[redacted]	[redacted]
FCR	[redacted]	[redacted]

R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone, R-CVP: rituximab + cyclophosphamide + vincristine + prednisone, FCR: fludarabine + cyclophosphamide + rituximab

* The HR was adjusted by age at diagnosis and sex

Progression-free survival and overall survival based on latest HMRN data

Table 2 reports median PFS for different R-chemo regimens from the latest HMRN data. As shown in the table, there are a very small number of patients in each of these treatment groups, as such there is a considerable degree of uncertainty associated with these results.

Nonetheless the weighted median PFS for R-CHOP, R-CVP and FCR ([redacted] patients) is [redacted] years ([redacted] months). The cost-effectiveness model produces very similar results with median PFS for R-chemo of [redacted] years ([redacted] months).

The weighted median OS for R-CHOP, R-CVP and FCR is [redacted] years ([redacted] months). The cost-effectiveness model produces similar results with median OS for R-chemo of [redacted] years ([redacted] months).

Table 2: Median PFS and OS for different treatments from latest HMRN data

	N	Median PFS (years)	Median OS (years)
R-CHOP	[redacted]	[redacted]	[redacted]
R-CVP	[redacted]	[redacted]	[redacted]
FCR	[redacted]	[redacted]	[redacted]
Rituximab Containing Regimens	[redacted]	[redacted]	[redacted]
Weighted average (R-CHOP, R-CVP and FCR)	[redacted]	[redacted]	[redacted]

R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone, R-CVP: rituximab + cyclophosphamide + vincristine + prednisone, FCR: fludarabine + cyclophosphamide + rituximab

Rituximab effect based on latest HMRN data

The base case for the cost-effectiveness analysis included in the submission used a HR from an indirect treatment comparison (HR1=0.19) plus a HR to account for the effect of adding rituximab (HR2=0.69) to finally estimate a PFS HR for ibrutinib vs R-chemo (Overall HR=0.28). The HR2 (0.69) was based on the initial HMRN audit. The latest HMRN data indicate that when this PFS HR is estimated only for the relapsed/refractory patients, this HR2 is equal to 0.80 (adjusted for age at diagnosis and gender). This indicates that the base case model may have been conservative and slightly overestimated the effect of adding rituximab, therefore overestimating the overall treatment effect of R-chemo.

When re-evaluating the overall PFS HR of ibrutinib vs R-chemo, the estimate is decreased from 0.28 to 0.24, which favours ibrutinib. The base case results at list price using the revised HR are presented in Table 3. The ICER decreased from £101,709 in the original basecase to £99,448.

Table 3: Base case discounted results at list price, ibrutinib versus R-CHOP, PFS HR=0.24

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Ibrutinib	[redacted]	[redacted]	[redacted]	£95,959	1.29	0.96	£99,448
R-CHOP	[redacted]	[redacted]	[redacted]				

ICER: incremental cost-effectiveness ratio, QALYs:, quality-adjusted life years, R-CHOP: rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone

2. Minor factual inaccuracy:

The ACD states in section 4.8 "*the committee was concerned that the subgroups had been defined post hoc and were based on a small number of patients (57 patients had 1 prior therapy, and 82 patients had 2 or more lines of therapy)*".

Janssen understand the Committee's concern and wanted to clarify that the numbers above are based on the ibrutinib arm of the RAY study. The cost-effectiveness analyses in our submission were based on data from the pooled dataset of the three ibrutinib trials, with patients receiving one prior therapy = 99 and more than one prior therapy = 271.