National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Bortezomib for previously untreated mantle cell lymphoma

You are asked to check the ERG report from KSR to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **10th September 2015** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Statistically significant outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG note that: *"For the overall population, most efficacy outcomes favoured VR-CAP, but analyses were only statistically significant for progression free survival, duration of response and time to new treatment."* (pg 13, 127) A statistically significant difference favouring VR-CAP was also observed for time to disease progression, treatment free interval, complete response, time to response, durable overall response, durable complete overall response. Between group difference was not analysed for duration of response.	We propose the statement be amended to correctly reflect trial data. For example: *"For the overall population, most efficacy outcomes favoured VR-CAP, and analyses were statistically significant for progression free survival, time to disease progression, treatment free interval, time to new treatment, complete response, time to response, durable overall response and durable complete overall response."*	The current statement does not accurately reflect trial data and could result in incorrect conclusions regarding statistical significance of additional outcomes analyses.	We focused on the outcomes defined in the final scope. Therefore, the revised version reads: *"For the overall population, most efficacy outcomes defined in the final scope favoured VR-CAP, but analyses were only statistically significant for progression free survival, duration of response and time to new treatment. Statistically significant differences favouring VR-CAP were also observed for time to disease progression, treatment free interval, complete response, time to response, durable overall response, and durable complete overall response. For the Western Europe and North America…"*

Issue 2 Utility measurements

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG note that: *"According to the company, this method likely underestimates the*	We propose the statement be amended to correctly reflect trial data. For example: *"According to the company, this method*	The current statement does not accurately reflect trial data and could result in incorrect conclusions regarding what has been captured	Although this is a further clarification and not a factual inaccuracy, the ERG incorporated the suggested

impact of progression on QoL since utilities were only assessed whilst patients were on treatment." (pg 86-87) Utilities were assessed during treatment and at the end-of treatment visit, which was performed 30 days after the last dose of investigational product was administered	*likely underestimates the impact of progression on QoL since utilities were only assessed at short term, with the latest assessment being at the end-of-treatment visit, which was performed 30 days after the last dose of investigational product was administered."*	in the utility measurements performed in the trial.	amendment.

Issue 3 Western Europe and North America subgroup

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
A number of inaccuracies arise in the ERG's description of the Western Europe and North America subgroup:	We propose the following amends:	Clarity of the nature of the available regional subgroup data.	Thanks for highlighting these issues. They were addressed as follows:
Pg 13: the ERG notes the sample size of the Western Europe and North America subgroup is n=150, whereas this is in fact n= 91 (n=150 reflect the total number of patients in the EU and North America subgroups).	Replace n=150 with n=91		Changed as suggested
Pg 13; table 2.1 and pg44; table 5.25: the ERG reports overall survival data for Western European patients only (HR=0.83 [95%CI: 0.34, 2.02] as overall survival data for Western European and North American patients	Definition should be amended to Western European or data replaced with overall survival data for the Western European and North American subgroup (HR=1.09 [95%CI: 0.47, 2.52]).		Changed to present the overall survival data for Western European and North American participants
Pg 13; table 2.1: the footnote ‡ to the ERG table notes that the ERG's calculated relative risk are for a subgroup described as "*Europe* and USA/Canada (emphasis added)". We believe that the ERG has combined the data for the European Union subgroup and the North America subgroup, but this is not clear.	Reword the footnote to "data calculated from European Union and North America subgroups combined".		Changed as suggested to ensure consistency. Number of participants added. The previous wording reflected the wording used by the company (see table 3 of the response to request for clarification)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
Pg 13: the ERG states that only four outcomes were reported for the Western Europe and North America subgroup, whereas five were reported (both ORR and CR were reported).	Replace “four” with “five”		Rephrased to: *“For the Western Europe and North America only four analyses defined in the final scope were reported. All but overall survival favoured VR-CAP but were not statistically significant. The company also reported results for overall complete response which were comparable between the two treatments (odds ratio 1.02, 95% CI 0.42 to 2.48, in favour of R-CHOP).”*
Pg 17: the ERG proposes that the treatment effectiveness ‘seems lower’ for the European Union population. Notwithstanding the differences between treatment arms in the EU subgroup, we believe that the data presented in table 2 of the company response to clarifications confirms that the outcomes for this subgroup are consistent with the ITT population with the exception of OS.	We propose to delete the statement “The treatment effectiveness in the LYM-3002 trial seems lower for the European Union population and thus using this subgroup would result in more conservative estimates”		This is not a factual error and no change was made. Looking at table 2.1 of the revised ERG report (where we added footnotes on the direction of effects), the treatment effectiveness for five of the reported results (overall survival, progression-free survival, time to new anti-lymphoma treatment/ time to progression, any SAE, TD AE) seems lower in the subgroup compared to the overall population. The effect estimate for any TEAE is unchanged (with a wider CI).

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
Pg 41: the ERG states that the Western Europe and North America subgroups were combined post-hoc. In fact the preplanned subgroups of *European Union* and North America were combined post-hoc.	Replace with "the EU and North America subgroups were combined post-hoc".		Based on page 62 of the CS and chapter 5.6.1 of the CSR, text was amended and now reads: *"Due to small numbers of participants in the North American region, Europe and North America were combined post hoc while the North American and Western European subgroup was pre-specified."*
Pg 44: In reproducing the statement below from the CSR, the ERG has omitted to correctly identify the Western European subpopulation: "twenty-nine events were observed, 15 R-CHOP subjects (31%) and 14 VcR-CAP subjects (33%). Median OS was not reached in either group (...) The median OS was not reached in either group, although there was a trend favouring VcR-CAP (HR=0.83; 95% CI: 0.34, 2.02) consistent with the overall ITT population"	"twenty-nine events were observed, 15 R-CHOP subjects (31%) and 14 VcR-CAP subjects (33%). Median OS was not reached in either group (...) *In the Western European subgroup* (…)The median OS was not reached in either group, although there was a trend favouring VcR-CAP (HR=0.83; 95% CI: 0.34, 2.02) consistent with the overall ITT population"		We believe the statement below is in line with chapter 5.6.1.4.4 of the CSR and table 5.11 of the ERG report. Therefore, we did not change the statement: *"In the subgroup of Western European and North American participants, "twenty-nine events were observed, 15 R-CHOP subjects (31%) and 14 VcR-CAP subjects (33%). Median OS was not reached in either group (...) The median OS was not reached in either group, although there was a trend favouring VcR-CAP (HR=0.83; 95% CI: 0.34, 2.02) consistent with the overall ITT population" (Table 5.11)."*
Pg 47: Overall complete response data for the Western European and North American patients incorrectly reported as 47.8% in the R-CHOP group versus 45.0% in the VR-CAP group (OR=1.150; p=0.763)	Overall complete response data for the Western European and North American patients should be amended to 54.3% in the R-CHOP group versus 50.0% in the VR-CAP group (OR=1.02; p=0.965).		The comment is correct. However, as this is quoting from the CSR, we have added a "sic!" to indicate the error made by the company. However, this is unlikely to have any meaningful impact.

Issue 4 Presentation of comparators R-FC and R-bendamustine

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
With regards to the decision to describe R-FC and R-bendamustine as exploratory comparators, the ERG notes that: "The company justified this decision by explaining that R-bendamustine is only available after treatment with R-CHOP and R-FC is mostly used in frail patients" (pg 16). This is not an accurate reflection of the company submission which justifies this decision because i) R-bendamustine is only available through the Cancer Drugs Fund for patients unsuitable for standard first-line treatment, therefore is used in patients *unsuitable for* R-CHOP and ii) R-FC is rarely used in the front-line setting due to its poorer survival benefit and concerns regarding ability to deliver further treatments at relapse. Thus only patients not deemed fit enough, or contraindicated, to receive CHOP-like therapy would receive alternative R-based chemotherapy. These patients would not be expected to eligible for VR-CAP.	We propose the statement is amended to correctly reflect our justification. For example "The company justified this decision by explaining that the other comparators included in the final appraisal scope are used in UK practice but in patients for whom both R-CHOP and VR-CAP are unsuitable".	To more closely reflect the justification proposed by the company to present limited results of the cost effectiveness analyses versus the exploratory comparators	The ERG proposes to change this sentence into *"The company justified this decision by explaining that R-CHOP is established standard of care whereas R-bendamustine and R-FC are used only for patients unsuitable due to frailty as a result of advanced age and/or comorbidities."* This is consistent with other statements in the ERG report and Table 1 from the CS.

Issue 5 Status of FDA approval of bortezomib for previously untreated MCL

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 22, the ERG suggests that there is uncertainty regarding the FDA approval status of bortezomib for the treatment of previously untreated MCL. Given the availability on the FDA website of the US prescribing information including this indication, we do not believe this is a fair reflection. The US prescribing information is available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021602s040lbl.pdf (accessed 08.09.15)	We propose that the ERG comment on this point is deleted.	There is no uncertainty regarding the FDA approval status of bortezomib	Removed as suggested. NB: This information was unavailable and information on the FDA website was incomplete regarding patients with untreated MCL.

Issue 6 PFS curve fits

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In the ERG base case the log-logistic distribution has been applied for R-CHOP PFS while the exponential distribution has been applied for VR-CAP PFS. (pg 17, 18, 82, 114) On page 82, the ERG suggests that the company approach to use the same distribution for each treatment arm is suboptimal compared to its base case using different distributions to model PFS in each treatment arm. We do not feel this is a fair and	We propose that the ERG clarifies the basis of the assumptions made and how this relates to the DSU guidance and/or any clinical validation that has been conducted.	Assumptions made in the model should be made in order to attempt to best reflect UK clinical practice. The current ERG base case does not represent the best possible reflection of UK clinical practice.	This is not a factual inaccuracy and hence no amendments were made. In general, it is recommended to use the same parametric function for both treatment arms unless *"there is strong evidence to suggest an alternative is more plausible"*. The ERG considers that the better statistical fit and being conservative are sufficient grounds to use different types of parametric models for the treatment arms, particularly

accurate interpretation of the DSU guidance on survival analysis (Latimer 2011). This DSU guidance states that where parametric curves are fitted separately to individual treatment arms, it is 'most sensible' to use the same 'type' of model. This allows a two-dimensional treatment effect in that the shape and scale parameters can both differ between treatment arms, but does not allow for each treatment arm to follow drastically different distributions. If different types of model seem appropriate for each treatment arm this should be justified using clinical expert judgement, biological plausibility, and robust statistical analysis; the DSU guidance proposing that 'substantial justification' would be required Thus the ERG's assertion that the curve that has the best statistical fit is the one that should be applied to the model, despite that this curve fit is not the best representative of clinical practice, especially in the extrapolated part of the curve, is not accurate. Clinical experts indicated that PFS as observed in LYM-3002 was shorter than they expected and therefore they advised to use the curve with a higher proportion of patients still progression-free in the tail. This is the log-logistic curve fit for VR-CAP as well as for R-CHOP. Based on the ERG's description, it is not apparent that appropriate validation and justification of its choice of distribution has occurred and therefore that it is accurate to describe the company approach in the base case as suboptimal.			given the uncertainty associated with the extrapolation.

Issue 7 Description of progression free survival calculations

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 83 the ERG state that: *"Additionally, the ERG found that the proportion of patients that have progressed was underestimated in the model as it was estimated from all previous cycle since the start of the model instead of the preceding cycle only. The correction of this error was not feasible, because at some point in time the proportion of patients with progression was very small, resulting in probabilities to start second line treatment that were larger than one"* We are unclear as to the meaning of this, however, we can confirm that at no point is the probability of either progression or starting 2nd line treatment larger than one within the data supplied. Additionally we would	We propose the statement be amended or removed.	The current statement does not accurately reflect the trial data supplied.	This sentence is clarified and replaced by the following sentence: "Additionally, the ERG found that the proportion of patients that have transited from progressed first line to second line treatment was incorrect in the model as it was estimated from all previous cycles since the start of the model instead of the preceding cycle only (leading to an underestimation of the TFI). The correction of this error (by selecting the preceding cycle only) was not feasible, because at some point in time the proportion of patients with progression was very small, resulting in probabilities to start second line treatment that were larger than one" For example, in the original model submitted by the Company, the formula in cell U13 of the PF.VR-CAP sheet is: =IF($C30>=Control_TimeHorizon_Days/7;"";IF(Control_2L="no";0;IF(V30=1;0;IF(secondline_rule="Progression";1-V30;IFERROR((1-IFERROR((VLOOKUP((C30-ROUND(AL6;0));range_subsequent;3)/VLOOKUP((C29-ROUND(AL6;0));range_subsequent;3));1))/(SUM(H$12:H29)/SUM(G$12:H29));0))))) Correcting this by selecting the preceding cycle only would result into: =IF($C30>=Control_TimeHorizon_Days/7;"";IF(Control_2L="no";0;IF(V30=1;0;IF(secondline_rule="Progression";1-V13;IFERROR((1-IFERROR((VLOOKUP((C13-ROUND(AL6;0));range_subsequent;3)/VLOOKUP((C29-ROUND(AL6;0));range_subsequent;3));1))/(H29)/(G29+H29);0))))) Notice the part of the formula 'SUM(G$12:H29)' . This appears to calculate a probability as the sum of the probabilities of having been in the health state 'Progressed from 1st line treatment', which would be greater than 1 and therefore does not make any sense(G12 by itself has value 1.000) . However, this correction would result in negative numbers in the Markov trace and is hence not plausible. Hence, TFI estimated for patients progressed in the first line only would ideally be incorporated in the model. This was requested in clarification question 5 but unfortunately

maintain that the proportion of patients who have progressed is correctly calculated.			not provided by the Company. Therefore, as no correct TFI estimate could be incorporated in the model, the ERG excluded the TFI in their preferred base case.

Issue 8 Inconsistency in discussion of stratified vs non stratified PFS

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 82 the ERG state that the evidence for a stratified versus non stratified curve fit for PFS is "*disputable"* On page 17 the conclusion is instead that *"an unstratified model seemed to be more appropriate"* These two descriptions are inconsistent.	We propose the statement on page 17 be amended to reflect the ERGs more detailed conclusion on page 82. For example: *"Another concern regarding the estimation of PFS is the use of a stratified model where the use of an unstratified model may have been equally appropriate."*	The current statement does not accurately reflect the ERGs more detailed conclusions later in the document	The ERG has changed the word 'disputable' into 'debatable'.

Issue 9 Primary instead of alternative IRC assessment

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In the ERG base case progression is based upon the primary IRC assessment. No justification is given as to why this is considered to be better reflection of routine clinical practice than the alternative IRC assessment, which was indicated to be a better reflection of UK clinical practice by practicing UK clinicians. (pg 114)	We propose that the ERG include justification for the alternative assumption they have made regarding which assessment of progression should be used in the base case.	Assumptions made in the model should be made in order to attempt to best reflect UK clinical practice. The current ERG base case does not represent the best possible reflection of UK clinical practice.	This is not a factual inaccuracy and hence no amendments were made. The primary IRC assessment was used in the ERG base case to be consistent with the primary outcome of the trial. Moreover, this can be considered as a conservative assumption.

Issue 10 Concomitant medication and transfusion costs for exploratory comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG has reported that they are unclear why concomitant and transfusion costs for RFC and R-bendamustine being assumed equal to R-CHOP is likely to be conservative, as suggested by the company (pg 103). We do not believe we have made this suggestion. The assumption was made in the absence of any other available information.	We propose that the statement is deleted.	The current statement is not a fair reflection of the company submission.	The sentence: `*Additionally, it is unclear why the assumption that concomitant and transfusion costs for R-FC and R-bendamustine are equal as for R-CHOP is likely to be conservative, as suggested by the company.´* was removed.

Issue 11 Implementation of the half-cycle correction

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On pg 71, the ERG suggests that the company may have implemented a half cycle correction incorrectly in its response to request for clarification. We do not believe this to be the case, but rather, suggest that there are a number of alternative approaches to implementation of a half cycle correction. Published literature available indicates that there are at least 3 in common usage.[1, 2]	We propose that the second part of the sentence is deleted: "the ERG is not convinced that the half-cycle correction was implemented correctly" and/or replaced with comment that the ERG has proposed an alternative approach.	We do not believe there to be an error in the implementation of the half cycle correction only a difference in preferred approach.	No factual inaccuracy. The ERG could not reproduce the results presented by the Company. Furthermore, according to the ERG, the half-cycle corrections should lead to lower costs, life years and QALYS hence the ERG was not convinced that the half-cycle correction was implemented correctly by the company.

Issue 12 Stochastic unit prices

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG has reported that they prefer to include all potential stochastic parameters as stochastic in the PSA. (pg 109) The ERG base case excludes unit costs as stochastic parameters. (pg 109, 113) The amends the ERG made are therefore inconsistent with their statement that all potential stochastic parameters should be included as stochastic in the PSA. In addition, it is unclear which unit costs (drugs or resource use) the ERG has excluded as stochastic parameters. Unit costs of some drugs	We propose to include unit costs of drugs that were taken from eMIT and NHS reference costs as stochastic parameters in the ERG base case, to keep consistency with the statement that all potential stochastic parameters should be included as stochastic in the PSA.	The ERG has reported that they prefer to include all potential stochastic parameters as stochastic in the PSA. (pg 109) Therefore these unit costs should be included as stochastic parameters.	No factual inaccuracy. Unit costs are typically not considered as potential stochastic parameters (as there is no sample uncertainty).

from eMIT are average costs of drug acquisition over 12 months. A standard deviation of these costs is given in the eMIT costing tool and therefore it is arguably that these parameters should also be considered stochastic. Similarly, NHS reference costs are average costs and should therefore be included as stochastic parameters.			

Issue 13 Transcription errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
There are the following transcription errors in the report (some of which result from transcription errors in the original submission document / clarification query response document):	The following changes are proposed to correct these transcription errors:	Transcription errors should be corrected for clarity.	These comments were addressed as follows:
Vincristine missing from the R-CHOP regimen definition (pgs 13, 26)	R-CHOP regimen should be defined as rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone.		"Vincristine" was added
The footnote to table 2.1 describes changes in VAS scores which are not relevant to the EORTC-QLQ-C30 questionnaire	Remove the word VAS		Changed as suggested
Odds ratio for durable overall response presented as odds ratio for duration of response (Table 2.1, pg 48, Table 5.25)	Description should be amended to durable overall response.		Added the median duration of response for both treatments
Lower 95% CI for time to new treatment incorrectly reported as 0.30 (Table 2.1, Table 5.16, pg 50, table 5.25)	Confidence intervals for time to new treatment analysis should be amended to 0.38 to 0.65.		Added results for "time to progression" (in line with presented

			results for subgroup)
Upper 95% CI for overall response rate incorrectly reported as 5.39 (Table 2.2, Table 5.39)	Confidence intervals for overall response rate analysis should be amended to 1.09 to 5.39		Not a factual error (in line with table 4 in the response to clarification letter)
Odds ratios for individual safety outcomes of lymphophenia, neutropenia and thrombocytopenia (pg 15) are Grade 3 or 4 events.	Grade 3 or 4 should be added to the description of lymphophenia, neutropenia and thrombocytopenia.		Changed as suggested. NB: This was not clear in the CS.
Baseline patient age in the model is incorrectly reported as 64. (pg 16) Baseline age in the model is based on the US, Canada and Western Europe population and not all patients in the trial.	Baseline patient age should be amended to 69.		This has been corrected
Cycle probability of grade 3 lymphopenia and grade 3 peripheral sensory neuropathy associated with R-CHOP are incorrectly reported as 1% (actual values are 0.45% and 0.35% respectively)(Table 6.7).	Cycle probability of grade 3 lymphopenia and grade 3 peripheral sensory neuropathy associated with R-CHOP should be amended to 0%.		This has been corrected
Average duration of second-line treatment reported as the maximum duration for second-line treatment (pg 92).	Description should be amended to average duration.		`maximum´ has been removed
Percentage of patients receiving cycle 4 of R-CHOP is incorrectly reported as 91%, while with correct rounding of 90.496% it should be reported as 90% (Table 6.12).	Percentage should be amended to 90%.		This has been corrected
Number of RBC transfusions per R-CHOP patient cycle 3 is incorrectly presented as 0.241. (table 6.17).	Number should be amended to 0.187.		This has been corrected.

Name of intervention is presented as VR-CHOP (pg 117).	Name of intervention should be amended to VR-CAP.		

References

1. Naimark DM, Bott M and Krahn M. The half-cycle correction explained: two alternative pedagogical approaches. *Med Decis Makin.* 28(5):706-12.

2. Németh B and Szekér V. Comparing three different methods of half-cycle correction. 17th International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual European Congress Amsterdam, The Netherlands. 8 - 12 November 2015. Poster PRM76.