NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

Single Technology Appraisal (STA)

Bortezomib for previously untreated mantle cell lymphoma [ID724]

Dear [redacted],

The Evidence Review Group, Kleijnen Systematic Reviews Ltd., and the technical team at NICE have now had an opportunity to take a look at the submission received on 26th June 2015 by Janssen. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm on 4th August 2015**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

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 you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact [redacted]. Any procedural questions should be addressed to [redacted] in the first instance.

Yours sincerely

Janet Robertson
Associate Director – Appraisals
Centre for Health Technology Evaluation

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

Encl. checklist for in confidence information

Section A: Literature searching

A1. There are no search methods or strategies reported in Section 4.12: Adverse Events. **Priority request:** Please clarify whether searches were conducted to identify adverse events data for the intervention and comparator treatments (Section 4.12: Adverse events). If searches were conducted, please provide full search strategies, as well as details of the databases and date searched. If separate adverse events searches were not conducted, please explain why this work was not carried out.

A2. Please confirm whether the clinical effectiveness strategies presented in Appendix 3 (pages 57-65) are the same as those referred to in Appendix 15, Step 1 (page 207-208, 211).

A3. Search dates are reported as 1.7.14 on page 210 and 217 for the Step 1 searches (Appendix 15), however different dates in July 2014 are reported in Appendix 3 (page 57). The ERG have assumed the later dates in Appendix 3 are correct, please could you confirm this?

A4. The search methods in Appendix 14 (page 201) reported that additional terms for non-Hodgkin lymphoma (NHL) would be included in the searches, as it was expected there would be too few studies for mantle cell lymphoma (MCL) alone. However, the reported strategies did not include NHL terms. Please clarify this statement and, if available, provide correct strategies.

Section B: Clarification on effectiveness data

B1. According to section 4.7 of the company's submission[1], "the clinical cut-off date for the primary analysis presented in this submission was 2 December 2013" and "the final analysis is expected in 2017".
Priority request: Are there any additional interim results available? If so, please provide these for all outcomes of interest, especially overall survival (OS).

B2. According to table 9 of the company submission[1], no study centres in the UK were involved in LYM-3002. Figure 8 (page 62) provides further details on the regions where participants were recruited for the trial: 73/243 in the VR-CAP arm and 77/244 in R-CHOP arm were from the European Union or North America, respectively.
Priority requests:
a. Can you confirm that no UK patients were included?
b. Please provide a list of participants by country.
c. Please provide the baseline characteristics for included participants by country and/or region.
d. Please provide subgroup-analyses for all outcomes (as specified in the final scope) for European or European/ North American participants.

B3. According to the final scope[2], "the most widely used regimens [for people with newly diagnosed mantle cell lymphoma] are rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP), rituximab, fludarabine and

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

cyclophosphamide (R-FC) and rituximab and bendamustine". This is in line with guidelines for the investigation and management of mantle cell lymphoma, cited in the company submission (reference 7)[3]: (a) Addition of rituximab to combination chemotherapy regimens improves outcomes. Rituximab should therefore be included in the first line chemotherapy regime in the treatment of MCL. (Strong, Moderate); (b) Older, less fit patients should receive R-chemo e.g. R-FC, R-CVP, R-CHOP, R-bendamustine, R-chlorambucil. (Strong, Moderate). However, the Advisory Board Summary Report (reference 6 of the company submission) mentions two additional treatments, i.e. R-CVP and R-chlorambucil[4].

Priority requests:

a. Please confirm if any studies comparing R-CVP or R-chlorambucil to any other treatment have been excluded? If so, please provide a rationale.
b. In the Advisory Board Summary Report[4], it is stated that "R-CVP is the most commonly used alternative". If feasible, please provide details and results for any possible comparisons of R-CVP (R-chlorambucil) vs. VR-CAP.
c. Can you confirm that no network meta-analyses (NMA) were possible? If NMA were possible, please provide details.
d. Please provide subgroup-analyses for indirect comparisons (as detailed in B2, c.)

B4. Section 4.10 of the company submission presents results of indirect analyses of progression-free survival and overall survival.[1]

a. There are other efficacy outcomes that were analysed by the three main trials, i.e. overall response rate and complete response (remission rate). Please provide indirect analyses for these outcomes.
b. Indirect analysis was not used for safety-related outcomes. There do not appear to be any potential outcomes for the StiL NHL1 trial, but for the European MCL Elderly trial (induction phase R-FC vs VE-CAP) the following outcomes are comparable to the LYM 3002: Anaemia, neutropenia, lymphocytopenia, thrombocytopenia, nausea constipation, fatigue, infection, febrile neutropenia (table 2 in Kluin-Nelemans 2012 (reference 41 in the company submission) and company submission table 28).[1, 5] Please provide indirect analyses for these outcomes.

B5. According to table 21 of the company submission, LYM-3002 included 80 patients (38/243 in VR-CAP arm, 42/244 in R-CHOP arm) that were "medically eligible for HSCT". The final scope[2] describes bortezomib as "indicated for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation" which is line with the summary of product characteristics (table 2 of the company submission[1]) which describes the indication of bortezomib as "for the treatment of adult patients with previously untreated MCL who are unsuitable for HSCT". Please explain how these patients were taken into account given they are outside of MA?

B6. According to table 2 of the company submission (page 15), participants received four doses of bortezomib during a 21 day treatment cycle.[1] Given that up to six cycles are given ("for patients with a response first documented at cycle 6, two additional cycles may be given"), it would be expected that participants might receive 24 or even more doses. However, according to table 5 (page 21), a median of 21 doses was assumed. Please clarify this assumption and provide further details for dosage (mean, median, range etc.).

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

B7. LYM-3002 was powered for the primary endpoint 'progression-free survival'. Please confirm whether power calculations were done for any of the other endpoints, e.g. overall survival. If so, please provide details.

Section C: Clarification on cost-effectiveness data

General

C1. **Priority request:** Please provide the results of an updated economic analysis using the data presented in response to clarification questions B1 and B2, if applicable (including all comparators, also the 'exploratory comparators', described in the scope using the hazard ratios obtained from the indirect treatment comparison).

C2. The half-cycle correction was not applied.
a. Please clarify and justify why the half-cycle correction was not applied.
b. Please provide an additional analysis which includes the half-cycle correction to either the Company base case or to the updated economic analyses if applicable.

Overall survival, progression free survival and treatment-free interval

C3. **Priority request:** The choice for modelling survival separately for patients with and without progression has major implications for the incremental cost-effectiveness ratio. More information and justification is needed to assess whether the most appropriate methodology has been applied.
a. Please provide a justification for the statement in the company submission (page 102) that many of the survival curves fitted directly to OS were not plausible.[1] These extrapolated survival curves should preferably be compared with long-term survival data in patients with MCL.
b. It is stated that because of the immaturity of the data, progression is used as a surrogate for survival. Subsequently, survival is separately estimated for patients with and without progression. Please explain why these survival estimates are considered reliable while the overall survival is not.
c. Please explain why PPS is measured from start of the trial, while it is only applicable for patients with progression. Please confirm whether it should be measured from time of progression?
d. On page 104 of the company submission, it is stated that proportional hazards (PH) were assumed because of limited availability of data for PrePS to fit individual models.[1] Please provide details and justification of the PH assumption.
e. PPS is assumed to be similar for R-CHOP and VR-CAP, while it has been shown that type of second-line treatment differs after these treatments. Furthermore, some of these second-line treatment significantly impact PPS. Please provide an additional analysis in which PPS is corrected for differences in second-line treatment and the corresponding treatment effects.

C4. **Priority request:** The relative treatment effectiveness (of VR-CAP versus R-CHOP) seems to be less for patients treated in the European Union/North America versus the rest of the world (company submission Figure 8).[1] Please provide the results of an updated economic analysis while applying a hazard ratio to PFS, OS and TFI to

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

reflect the relative effectiveness (of VR-CAP versus R-CHOP) for European Union/North America.

C5. The treatment-free interval (TFI) is derived from the safety population, which includes all patients who received at least one dose of drug. As a result, TFI also includes patients without progression who did not receive any additional treatment, while in the model second-line treatment is only applicable for patients with progression. It is expected that the inclusion of patients without progression overestimates the TFI since these patients would probably not have received any second-line treatment. Please report the TFI restricted to patients with progression and include these estimates in the cost-effectiveness analysis instead of the current TFI estimates.

C6. In the base-case analysis, the TFI begins after 18 cycles (=considered the average treatment duration). Please justify why TFI begins after 18 cycles rather than with the start of the TFI at time of progression, since it can be assumed that initial treatment is stopped at time of progression.

<u>Health related quality of life</u>

C7. Please clarify which tariff was used to calculate the EQ5D utilities.

C8. **Priority request:** Different questions arise from the utility values chosen for progressed from first-line treatment, progressed from second-line treatment and for progression-free survival from second-line treatment in the base case and scenario analysis:

a. Please explain why a utility value of 0.693 is chosen for progressed from first-line treatment in the base case analysis. This value seems to be an overestimation as this utility is measured while patients were on treatment (page 124), while probably not all patients in the progressed health state in the model are on treatment. Please confirm if alternative utility values identified in the literature?
b. Please explain why a utility value of 0.45 is chosen for progressed from second-line treatment for the base case analysis. This utility value is very different from 0.693 that is used for progressed from first-line treatment. In table 47 it is stated that the value is derived from the most robust evidence available (Doornduijn et al. 2014).[1, 6] However, this evidence is only based on 13 observations, and based on a different patient population.
c. The 0.45 value (Doornduijn et al. 2014) is calculated as the average of the utilities for 0-1 and 2-3 on the age adjusted Prognostic Index (aaPI) while the distribution of aaPI within the patient population of the LYM-3002 trial is unknown.[6] What was the rationale for assuming that 50% of the patients in the LYM-trial are classified aaPI 0-1 and 50% as 2-3?
d. A utility value of 0.764 is assumed for progression-free survival from second-line treatment in the base case analysis. Please explain the rationale behind assuming a similar utility (0.764) for progression-free survival from first- and second- line treatment.
e. A utility value of 0.693 was used in the scenario analysis for progression-free survival from second-line treatment. Please provide more justification of using a utility of 0.693 for the scenario analysis. What was the rationale for assuming progression-free survival from second line treatment has similar utility as progressed from first line treatment? Please clarify if any other values were identified in the literature review?

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

C9. It is stated on page 130 that a scenario analysis were conducted using all the utility values reported by Doorduijn et al. 2005.[6] In addition, on page 131 it is stated that utility decrements for progression reported in Hayslip et al. 2008, Soini et al. 2012 and Deconinck et al. 2010 were applied to the utility for the progression-free health state from the LYM-3002 trial in scenario analyses.[8-10]

a. Please provide a table showing all utility values that were used as inputs for scenario analyses QOL1-QOL8 and clarify how these were incorporated in the economic model.
b. Please clarify why utility decrements for progression in patients with follicular lymphoma (FL; reported in these three studies) are applicable to the progression-free health state of patients with MCL (page 131)?

C10. Table 42 describes the utilities from the LYM-3002 trial. Please provide more details regarding the estimation and validation of the mixed model used to calculate the utilities scores presented in Table 42 of the company submission.[1]

C11. Table 46 describes utility decrements of adverse events without a reference to the source.

a. Please provide more details about the utility decrements presented in table 46 (including references)
b. Please explain why utility decrements can be positive (i.e. 0.010 for anaemia and 0.090 for febrile neutropenia).
c. Please clarify whether the effect of the disabilities of adverse events was already captured by the quality of life (QoL) measurement of the trial?

C12. In table 20, utility values for VR-CAP and R-CHOP are presented at baseline, change from baseline (CFB) at cycle 6 and end of treatment (EOT). Different questions arise from this table:

a. Please explain why the utility values of VR-CAP and R-CHOP are assumed to be equal.
b. Please provide utilities for the R-CHOP group and the VR-CAP group separately for the following health states of the economic model; progression-free survival from first-line treatment and progressed from first-line treatment.
   Please provide an additional analysis of the cost-effectiveness while incorporating these utility values.

Adverse events

C13. Please clarify and justify why the duration of adverse events is assumed to be treatment dependent in the base case (particularly given the small differences in duration reported in table 45).

C14. The Company stated that “no AEs for second-line treatment were included as no EQ-5D data were available from the trial to do so”.

a. Please clarify and justify if an attempt was made to identify these data from the literature.
b. Please elaborate whether this should be regarded as a conservative assumption.

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

C15. Please provide the results of an updated economic analysis using the data presented in response to clarification question B4 (including all comparators, also the 'exploratory comparators', described in the scope using the hazard ratios obtained from the indirect treatment comparison).

C16. Please clarify why the cycle probability of Sepsis grade 4/5 is set to 0.000 (worksheet 'adverse events' cell E75), while this is 0.001 per week in cell I38 (worksheet 'adverse events').

Resources and costs

C17. **Priority request:** In table 54 of the company's submission the difference between the per protocol dose and the dose received in the LYM-3002 trial is presented.[1] These dose reductions are used in the model to adjust the per protocol dose in the economic model.

a. Please clarify and justify whether the adjusted protocol dose (i.e. the average dose received in the LYM-3002 trial) is more applicable to clinical practice in the UK than the per protocol dose.
b. Please clarify and justify why the dose reductions for Rituximab, Cyclophosphamide and Prednisone are assumed to be treatment dependent (for VR-CAP and R-CHOP).
c. Please provide a scenario analysis using the unadjusted per protocol dose while including all four comparators.
d. No dose reductions were applied for the 'exploratory comparators'. Please provide a scenario analysis wherein the same dose reductions are applied for the 'exploratory comparators' as for VR-CAP.

C18. The Company stated that "no transfusions or concomitant medication use was assumed for second-line treatment due to the lack of sufficient data".

a. Please clarify and justify if an attempt was made to identify these data from the literature.
b. Please elaborate whether this should be regarded as a conservative assumption.

C19. Not all potential stochastic parameters are incorporated as stochastic parameters in the model. As a result these parameters are not considered in the deterministic sensitivity analysis (DSA) and the uncertainty is not reflected in the probabilistic sensitivity analysis (PSA).

a. Please provide additional DSAs including all potential stochastic parameters reported in tables 50, 53, 54 and 56

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

b. Please provide additional PSA results while include all potential stochastic parameters reported in tables 50, 53, 54 and 56 as stochastic parameters

Sensitivity and scenario analyses

C20. On page 179 of the company submission, the potential impact of including rituximab maintenance followed by induction therapy was tested using an hazard ratio of 0.55 for PFS (first-scenario) and hazard ratios of 0.40 for PFS and 0.39 for OS (second-scenario).

a. Please provide details with sources and justify how these model inputs were obtained.
b. On page 27 of the company submission it is stated that: "At the NICE scoping meeting, it was noted that R-maintenance would be considered after any standard induction therapy". Please clarify and justify why rituximab maintenance therapy is only included in the scenario analyses and not in the base case analysis.

Section D: Textual clarifications and additional points

D1. The text in figure 8 is difficult to read because of the poor quality. Please provide a figure of better quality.

D2. Please confirm that the missing reference in the last paragraph on page 120 is referring to table 40 on the following page.

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)845 003 7780

References

[1] Janssen-Cilag International NV. Single technology appraisal. Lymphoma (mantle cell, untreated) – bortezomib [ID724] - company evidence submission: appendices. Janssen-Cilag International NV., June 2015: 264.

[2] National Institute for Health and Care Excellence. *Proposed Health Technology Appraisal: Bortezomib for previously untreated mantle cell lymphoma (Final scope). Appendix B [Internet]*. London: NICE, 2015 [accessed 16.7.15]. 3p. Available from: https://www.nice.org.uk/guidance/GID-TAG495/documents/lymphoma-mantle-cell-untreated-bortezomib-id724-final-scope2

[3] McKay P, Leach M, Jackson R, Cook G, Rule S. Guidelines for the investigation and management of mantle cell lymphoma. *Br J Haematol* 2012;159(4):405-26.

[4] Janssen-Cilag Ltd. *Velcade MCL HTA Advisory Board Summary*, 2014

[5] Kluin-Nelemans HC, Hoster E, Hermine O, Walewski J, Trneny M, Geisler CH, et al. Treatment of older patients with mantle-cell lymphoma. *N Engl J Med* 2012;367(6):520-31.

[6] Doorduijn J, Buijt I, Holt B, Steijaert M, Uyl-de Groot C, Sonneveld P. Self-reported quality of life in elderly patients with aggressive non-Hodgkin's lymphoma treated with CHOP chemotherapy. *Eur J Haematol* 2005;75(2):116-23.

[7] Dewilde S, Woods B, Castaigne JG, Parker C, Dunlop W. Bendamustine-rituximab: a cost-utility analysis in first-line treatment of indolent non-Hodgkin's lymphoma in England and Wales. *J Med Econ* 2014;17(2):111-24.

[8] Hayslip JW, Simpson KN. Cost-effectiveness of extended adjuvant rituximab for US patients aged 65-70 years with follicular lymphoma in second remission. *Clin Lymphoma Myeloma* 2008;8(3):166-70.

[9] Soini EJ, Martikainen JA, Vihervaara V, Mustonen K, Nousiainen T. Economic evaluation of sequential treatments for follicular non-hodgkin lymphoma. *Clin Ther* 2012;34(4):915-925 e2.

[10] Deconinck E, Miadi-Fargier H, Pen CL, Brice P. Cost effectiveness of rituximab maintenance therapy in follicular lymphoma: long-term economic evaluation. *Pharmacoeconomics* 2010;28(1):35-46.