NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Bortezomib for previously untreated mantle cell lymphoma

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Chemotherapy acronyms

A number of acronyms are used throughout the manufacturer's submission, ERG report and premeeting briefing and these are defined here for clarity.

Treatment	Abbreviation
Bortezomib (Velcade) + rituximab, cyclophosphamide, doxorubicin and prednisone	**VR-CAP**
Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone	**R-CHOP**
rituximab with fludarabine and cyclophosphamide	**R-FC**

Key issues for consideration

Clinical effectiveness

- The company submission focuses on the comparison of VR-CAP with R-CHOP stating that R-CHOP is established standard of care with alternative regimens (rituximab plus bendamustine, and R-FC) used only where they are unsuitable for people because of frailty as a result of advanced age and/or comorbidities. Does the Committee agree with that R-CHOP is the most relevant comparator?

- What is the normal clinical course and treatment regimen for people with untreated mantle cell lymphoma who are ineligible for haematopoietic stem cell transplant (HSCT)? Is maintenance therapy with rituximab routinely used in clinical practice?
- How generalisable does the Committee consider the LYM-3002 trial to be given:
  - no patients from the UK were included, 30% were recruited from the European Union, while more than two thirds were from the “rest of the world”, particularly Russia and China;
  - patients were younger in the trial compared with clinical practice;
  - 16.4% of patients included in the trial would have been eligible for haematopoietic stem cell transplantation (outside of the scope);
  - bortezomib was administered exclusively intravenously in the LYM-3002 trial; however the indication granted by the European Medicines Agency includes both intravenous and subcutaneous administration of bortezomib?

- The primary outcome of the trial was progression-free survival (PFS) which was statistically significantly improved for VR-CAP compared with R-CHOP (HR 0.63, 95% confidence interval 0.50 to 0.79) for the whole trial population, In the European Union subgroup analysis, median PFS improvement for VR-CAP compare with R-CHOP was not statistically significant. The ERG highlighted that endpoints other than PFS might have been underpowered, and if considering data from only Europe and North America, all outcomes including PFS were likely to be underpowered. What is the Committee’s view of the available data?

- The company assumed that benefits of overall survival were likely to be directly related to improvements in PFS although the available data from LYM-3002 were still immature. The ERG questioned this and suggested that overall survival did not necessarily depend on progression status. What is the Committee's view?

- Does the Committee consider the indirect comparison conducted by the company to be appropriate? What is the Committee's view of these results?

- Some adverse event rates were higher in the VR-CAP treatment arm compared with the R-CHOP arm. Does the Committee think the use of a subcutaneous injection rather than intravenous administration will have an impact on adverse event rates?

Cost effectiveness

- The company used data from the whole trial population of LYM-3002 for its cost effectiveness model, whereas the ERG preferred using the subgroup from Europe. Which approach does the Committee agree with?

- The company used a 5 state model that included 'treatment-free interval'. The ERG had concerns about the inclusion of 'treatment-free interval' in the model and considered that a more reliable approach would be to exclude this health state and implement second-line treatment at time of progression. Is this reasonable?

- In the company's base case analysis, the ICER for VR-CAP compared with R-CHOP was £20,362 per QALY gained, £18,509 compared with R-FC and £13,797 per QALY gained compared with R-bendamustine. The ERG's various amendments, in their base case, combined to yield an ICER of £34,039 per QALY gained for VR-CAP compared with R-CHOP, with R-FC and R-bendamustine being dominated by R-CHOP. The individual changes suggested by the ERG (detailed in table 7.1 of the ERG report) showed that the major factors affecting the ICER were:

    - using the hazard ratio for PFS from the Europe subgroup (increases ICER to £24,190 per QALY gained);

- using a utility value of 0.63 (based upon disutility from Doorduijn et al.) compared with the company's value of 0.45 for progression from second-line treatment (increases ICER to £22,144 per QALY gained);
- using per protocol dosage rather than using observed dose reduction in the trial because the ERG suggest it is unknown whether dose reductions are applicable to UK patients increases (ICER to £24,410 per QALY gained);
- using exponential distribution for the extrapolation of PFS in the VR-CAP arm and log-logistic distribution to extrapolate the R-CHOP arm (increases ICER to £33,087 per QALY gained);
- and, overall survival not differentiated between people with and without disease progression, but between treatments instead (increases ICER to £21,987 per QALY gained).

Does the Committee consider that these are the key issues driving the cost effectiveness estimates? What is the Committee's view of these issues?

- Does the Committee have a view on whether cost effectiveness would be affected if:
  - the subcutaneous injection formulation was used?
  - maintenance therapy with rituximab was added to both treatment arms?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of bortezomib within its licensed indication for treating previously untreated mantle cell lymphoma.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population	People with previously untreated mantle cell lymphoma, who are not going to have a stem cell transplant.	As per scope	-	Overall, the ERG was satisfied that the population is in line with the final scope. However, the ERG noted that the main trial included no UK patients.
Intervention	Bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (VR-CAP).	As per scope	-	The intervention in the company submission matches the intervention described in the final scope.
Comparators	• R-CHOP (rituximab, cyclophosphamide, vincristine , doxorubicin and prednisolone) • bendamustine plus rituximab (with or without cytarabine) • R-FC (rituximab, fludarabine and cyclophosphamide)	As per scope	R-CHOP is established standard of care. Bendamustin plus rituximab and rituximab, fludaribine and cyclophosphamide are only used when R-CHOP is considered unsuitable for patients due to frailty as a result of advanced age and/or comorbidities. R-CHOP is therefore considered the key comparator to VR-CAP but to align with the final appraisal scope and for	Overall, the ERG was satisfied that the comparators are in line with the final scope.

			transparency, the other comparators included in the decision problem are also addressed in this submission.	
Outcomes		As per scope	-	The ERG was satisfied that the outcomes are in line with the final scope.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	A cost-effectiveness analysis expressed in terms of incremental cost per quality-adjusted life year is presented. A lifetime time horizon of 20 years is used in the base case analysis. Costs are considered from an NHS and Personal Social Services perspective.		
Subgroups to be considered	None stated.	None. Although not specified in the scope, a number of subgroup analyses were presented in the company submission from the LYM-3002 trial. In particular, the		

		Western European and North American subgroup may be of relevance.		
Special considerations including issues related to equity or equality	None stated.	None.	-	

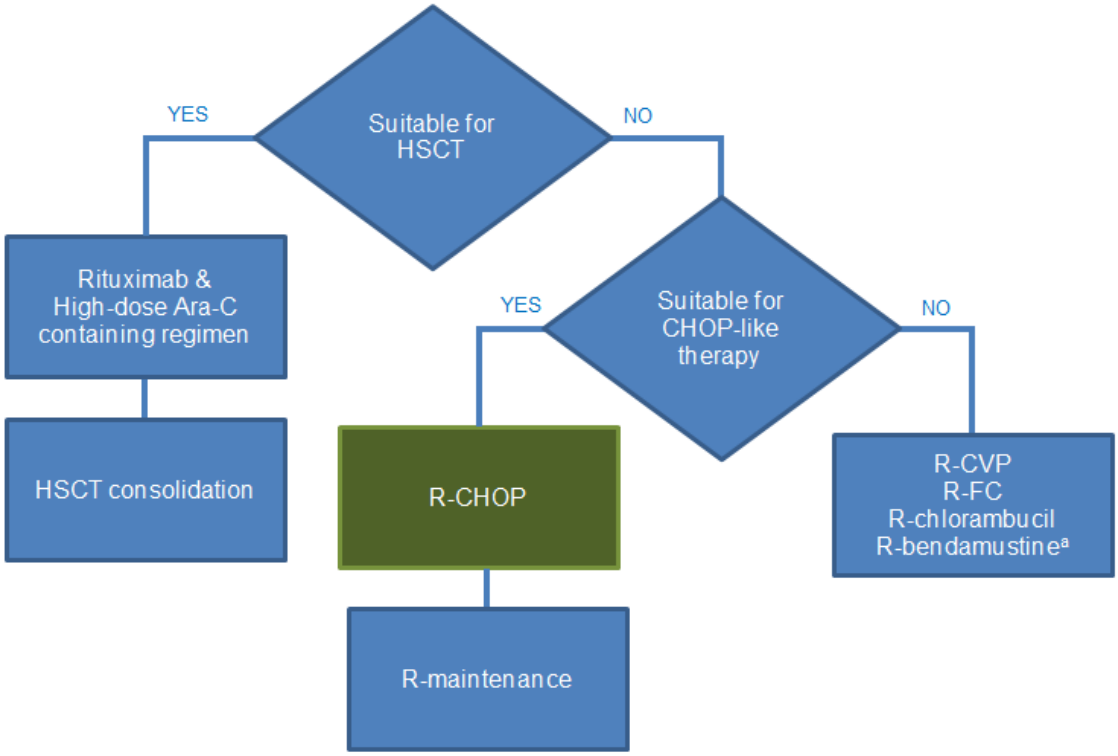
2 The technology and the treatment pathway

2.1 Bortezomib has a marketing authorisation for treating adults with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation (HSCT).

2.2 Bortezomib is a highly selective proteasome inhibitor specifically designed to inhibit the chymotrypsin-like activity of the 26S proteasome in mammalian cells. This proteasome is a large protein complex that degrades unneeded or damaged proteins tagged with ubiquitin. The ubiquitin-proteasome pathway plays an essential role in many cellular processes, including the cell cycle.

2.3 For people who are not eligible for high-intensity induction therapy, that is those for whom HSCT is unsuitable, there are no licensed induction therapy regimens. The company highlighted that in the UK, R-CHOP is the most commonly used induction therapy option for patients with previously untreated MCL for whom HSCT is unsuitable, with more than two thirds of such patients estimated to receive R-CHOP in the front-line setting. The company stated that only patients not deemed fit enough to receive cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)-like induction therapy would receive alternative rituximab-chemotherapy regimens first line. The company presented a treatment pathway for first-line treatment of mantle cell lymphoma for England and Wales (figure 1). The company stated that bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is considered a ‘CHOP-like’ induction therapy and this is where it is expected to be used.

Figure 1. Treatment pathway for first-line treatment of mantle cell lymphoma in England and Wales (figure 1, Company submission, page 27)



Key: Ara-C, cytarabine; HSCT, haematopoietic stem cell transplantation; R-CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone

2.4 The company highlighted that mantle cell lymphoma is included in the NICE pathway: Blood and bone marrow cancers, but there is currently no published NICE guidance on the treatment of mantle cell lymphoma. A clinical guideline for NHL entitled 'non-Hodgkin's lymphoma: diagnosis and management of non-Hodgkin's lymphoma' is in preparation, with an earliest anticipated date of publication of December 2015. NICE also provides cancer service guidance in 'Improving outcomes in haemato-oncology cancer, noting that precise identification and accurate staging is crucial to optimising treatment and monitoring progress in aggressive NHL, but this guidance does not recommend specific treatments for mantle cell lymphoma.

2.5 UK and European clinical guidelines for mantle cell lymphoma have been published which suggest that rituximab in combination with chemotherapy such as CHOP or bendamustine should be used in people who are not eligible for autologous transplant.

Table 2. Technology

	Bortezomib	**Rituximab in combination with CHOP**	**Rituximab with fludarabine and cyclophosphamide**	**Rituximab with bendamustine**
Marketing authorisation	Bortezomib (Velcade®) in combination with rituximab, cyclophosphamide, doxorubicin and prednisone for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.	Not specifically licensed for mantle cell lymphoma	Not specifically licensed for mantle cell lymphoma	Not specifically licensed for mantle cell lymphoma
Administration method	Twice weekly for 2 weeks, on days 1, 4, 8, and 11, followed by a 10-day rest period on days 12-21. This 3-week period is considered a treatment cycle. Administered by intravenous or subcutaneous injection. Given with rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, and doxorubicin 50 mg/m^2 by IV on day 1, and with prednisone 100 mg/m^2 orally on day 1 through day 5 of a 21-day (3-week) cycle.	Rituximab 375 mg/m^2 IV on day 1; cyclophosphamide 750 mg/m^2 IV on day 1; doxorubicin 50 mg/m^2 on day 1; vincristine 1.4 mg/m^2 (max. total of 2 mg) IV on day 1 and prednisone 100 mg/m^2 orally on day 1 through day 5 of a 21 day (3-week) cycle.	Rituximab 375mg/m^2, fludarabine 70 mg (oral) cyclophosphamide 750 mg/m^2 IV on day 1 of a 28-day cycle,	Rituximab 375mg/m^2, and bendamustine 90 mg/m^2 on day 1 of a 28-day cycle.

Costs (See tables 48-52 of the company's submission for complete summary)	Total per cycle: £4,426 Admin costs per cycle: Cycle 1 - £1,116 Other cycles - £980	Total per cycle: £1,383 Admin costs per cycle: Cycle 1 - £381 Other cycles - £245	Total per cycle: £1,764 Admin costs per cycle: Cycle 1 - £381 Other cycles - £245	Total per cycle: £2,359 Admin costs per cycle: £490

See summary of product characteristics for details on adverse reactions and contraindications.

Component drug acquisition costs: Bortezomib 3.5mg £762.38; Rituximab 100mg £174.63, 500mg £873.15, 1400mg £1,344.65 (all from MIMS online April 2015); cyclophosphamide 50mg £0.82, 500mg £8.87, 1000mg £16.49 (eMIT); Doxorubicin 10mg £1.72, 50mg £4.41, 200mg £19.09, (eMIT), Prednisone 5mg £0.01 (eMIT); Vincristine 1mg £3.09, 2mg £6.16 (eMIT); Bendamustine 25mg £69.45 (MIMS online), 100mg £275.81 (MIMS online April 2015); Fludarabine10mg £20.17 (MIMS online April 2015).

3 Comments from consultees

3.1 Patient experts commented that mantle cell lymphoma is a quickly developing ‘high-grade’ form of NHL that if left untreated grows quickly. The most common sign of mantle cell lymphoma is a “rubbery” lump in any/some/all of the neck, armpit, groin or stomach. Other symptoms include frequent and persistent infections; fever; drenching night sweats; severe fatigue; itching; unexplained weight loss and pain in the chest, abdomen or bones. Patient experts highlighted that these symptoms can be extremely draining and hugely impact on quality of life.

3.2 Patient experts emphasized that the key aims of current treatments are to increase survival times and induce long-lasting remissions for people with mantle cell lymphoma. In addition to this patients would like to see reduced side effects and improved quality of life but that people are willing to endure increased side effects if the treatment has improved efficacy. The apparent increased side effect profile of bortezomib may mean that the group of patients who are able to tolerate the treatment is limited. However, for the patients who can tolerate bortezomib treatment, it may have improved efficacy.

3.3 Clinical experts commented that the approach to treating mantle cell lymphoma is relatively uniform across the UK. For younger patients this involves an intensive course of chemotherapy (cytarabine based) followed by an autologous transplant and for older people combination chemotherapy together with rituximab followed by rituximab maintenance. For frail and older people with mantle cell lymphoma, there is no standard of care. It is for the older fitter patients that this technology applies. Generally the chemotherapy of choice would be CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), but bendamustine and to a lesser extent FC (fludarabine and cyclophosphamide) are the regimens of choice.

3.4 The clinical expert highlighted that one of the disadvantages of the LYM-3002 trial was the lack of rituximab maintenance following the chemotherapy phase. The clinical expert stated that this has now become standard of care and the outcomes of patients treated with R-CHOP followed by R maintenance are better than those seen in this study. However it was suggested that there is no reason that this benefit would not be seen if applied following VR CAP as well. Another issue was that bortezomib was given intravenously twice a week for 2 weeks in the VR CAP arm. This would now be given sub-cut and weekly and this form of delivery significantly reduces toxicity.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company's systematic literature review identified one RCT investigating the clinical efficacy and safety of VR-CAP in adult patients with previously untreated mantle cell lymphoma. LYM-3002 trial was a randomised, open-label, multicentre, phase III study that compared bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (VR-CAP) against rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP). The study involved 128 sites worldwide, and people were randomised in a 1:1 ratio based on the International Prognostic Index (IPI) and the stage of disease at diagnosis.

4.2 In total, 487 people were randomised, 243 to the bortezomib treatment arm and 244 to the R-CHOP treatment arm. People were given 6 to 8 cycles (18 to 24 weeks) of treatment depending upon the response documented at the cycle 6 assessment. Approximately 80% of people in both groups completed treatment. The total study duration from randomisation of the first patient until the last progression-free survival event required for the final analysis was expected to be approximately 42 months (24 months for enrolment and 18 months for follow-up). Average

treatment duration was 17.6 weeks in the bortezomib treatment group and 16.1 in the R-CHOP group. Treatment discontinuations were comparable between the 2 arms (18% and 19% respectively). The median age in the LYM-3002 trial was 69 years. The majority of people received at least six cycles of treatment: 84% of people randomised to VR-CAP, and 83% of people randomised to R-CHOP.

4.3 The company commented that one protocol amendment should be highlighted in consideration of the UK marketing authorisation. As part of the original eligibility criteria of LYM-3002, patients were to be considered ineligible for HSCT as determined by their treating physician. This was later amended, and patients ineligible or not considered for HSCT were enrolled. This amendment was thought to better reflect the real-life situation where, in some study centres, HSCT was not an available treatment option or not considered as a treatment option.

ERG comments

4.4 The ERG commented that the design used in this in this study is in line with expectations for this type of trial. The ERG highlighted that the trial did not conceal treatment from patients or care providers.

4.5 The ERG highlighted that no patients from the UK were included in the LYM-3002 trial with roughly a third of the people recruited in the European Union and North America. The other two thirds were from the “rest of the world”, in particular Russia and China. Given the different prevalence depending on the geographic region and potential differences in clinical standards (e.g. concomitant care), the ERG stated that this brings into question the generalisability of the trial to clinical practice in the UK.

4.6 The ERG noted that the inclusion criteria in the LYM-3002 trial were narrower than those defined in the NICE scope. The ERG noted that patients who might be suitable according to the final scope *(“People with previously untreated mantle cell lymphoma, who are not going to have a*

stem cell transplant") might not have been eligible for inclusion in the LYM-3002 trial.

Clinical trial results

4.7 The primary outcome of the study was progression-free survival (PFS). Secondary clinical endpoints included time to progression (TTP), time to next treatment (TTNT), treatment-free interval (TFI), overall response rate (complete response + unconfirmed complete response + partial response), complete response rates (complete response and unconfirmed complete response), time to response, duration of response, rate of durable response and overall survival. In addition, the safety of VR-CAP compared with R-CHOP was evaluated, and patient-reported outcomes were evaluated as an exploratory endpoint.

4.8 In the primary analysis of progression-free survival based on independent review committee assessment of the ITT population, median progression-free survival was 751 days (24.7 months) in subjects randomised to VR-CAP compared with 437 days (14.4 months) in subjects randomised to R-CHOP (HR=0.63, p<0.001) (see table 3). The company stated that this represented a 59% improvement in progression-free survival in the VR-CAP group, confirming the study hypothesis and exceeding the hypothesized treatment effect of 40% improvement.

Table 3 Clinical trial outcomes (source: section 4.7 of the company submission tables 13-15)

	VR-CAP (n=243)	R-CHOP (n=244)
PFS, days[a] based on IRC assessment, ITT analysis set		
Number of censored (%)	110 (45.3)[b]	79 (32.4)[b]
Number of events (%)	133 (54.7)	165 (67.6)
Median (95% CI)	751.0 (604.0; 969.0)	437.0 (365.0; 513.0)
P-value[c]	<0.001	
Hazard ratio (95% CI)	0.63 (0.50; 0.79)	
PFS, days[a] based in investigator assessment		
Number of censored (%)	115 (47.3)[b]	65 (26.6)[b]
Number of events (%)	128 (52.7)	179 (73.4)
Median (95% CI)	934.0 (763.0; 1136.0)	490 (427.0; 561.0)
P-value[c]	<0.001	
Hazard ratio (95% CI)	0.51 (0.41; 0.65)	
PFS, days[a] based on IRC alternative assessment, ITT analysis set		
Number of censored (%)	117 (48.1)[b]	82 (33.6)[b]
Number of events (%)	126 (51.9)	162 (66.4)
Median (95% CI)	866.0 (665.0; 1154.0)	450.0 (366.0; 518.0)
P-value[c]	<0.001	
Hazard ratio (95% CI)	0.56 (0.44; 0.71)	

Key: CI, confidence interval; IRC, Independent Review Committee; ITT, intent-to-treat; NE, not estimable; PFS, progression-free survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.
Notes: [a], based on Kaplan–Meier product estimates; [b], censoring was predominantly due to the clinical cut-off date with follow-up ongoing for the majority of subjects; [c], based on log rank test stratified with IPI risk and stage of disease.
Source: LYM-3002 CSR[60]; Robak et al. 2015.[59]

4.9 Further sensitivity analyses for progression-free survival, including PFS analysis in the per-protocol population and PFS analysis in the population of patients with confirmed MCL, were consistent with the primary endpoint analysis, demonstrating significant prolongation of PFS in subjects treated with VR-CAP.

4.10 The company presented secondary efficacy analysis for time to disease progression, time to next anti-lymphoma treatment, treatment-free interval, and clinical response. Based on independent review committee (IRC) assessment of the ITT population, median time to progression was 929 days (30.5 months) in subjects randomised to VR-CAP compared with 490 days (16.1 months) in subjects randomised to R-CHOP (HR=0.58; p<0.001).

4.11 In the ITT population, median time to next anti-lymphoma treatment was 1,353 days (44.5 months) for people randomised to the VR-CAP group versus 756 days (24.8 months) for those randomised to the R-CHOP group (HR=0.50; p<0.001).

4.12 Median treatment-free interval in the safety analysis set was 1,236 days (40.6 months) for people randomised to VR-CAP compared with 624 days (20.5 months) for those randomised to R-CHOP (HR=0.50; p<0.001).

4.13 Based on IRC assessment, complete response rates (complete response + complete response unconfirmed) were 53.3% in the VR-CAP group compared with 41.7% in the R-CHOP group (odds ratio=1.688; p=0.007), and the median duration of complete response was 42.1 months compared with18.0 months for people treated with VR-CAP. The median time to initial response based on IRC assessment was 42 days (1.4 months) in subjects randomised to VR-CAP compared with 50 days (1.6 months) in subjects randomised to R-CHOP (HR=1.54; p<0.001). The company also highlighted that median duration of response was markedly longer in subjects responding to VR-CAP treatment compared with subjects responding to R-CHOP treatment (median duration of overall response, 1,110 days (36.5 months) versus 459 days (15.1 months); median duration of response for complete responders, 282 days (42.1 months) versus 563 days (18.5 months) and median duration of complete response, 1,282 days (42.1 months) versus 547 days (18.0 months).

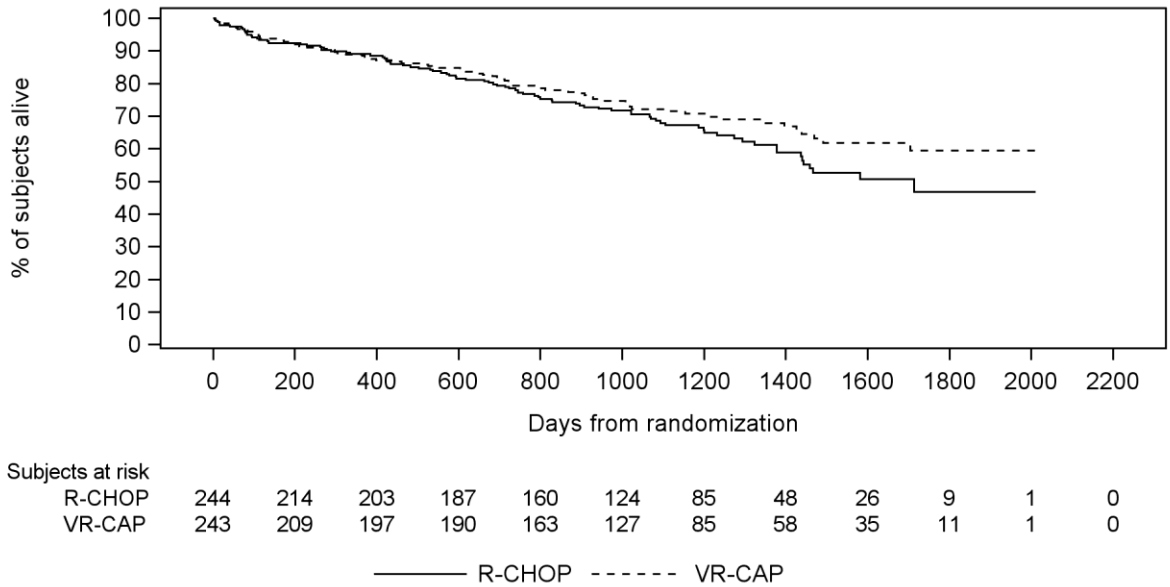
4.14 At the time of the company's submission, overall survival data were not mature in the LYM-3002 trial. However, interim analysis indicated a consistent survival trend favouring the VR-CAP group. Based on a median duration of 40 months follow-up (in which 158 deaths had been observed: 71 in the VR-CAP group [29%] and 87 in the R-CHOP group [36%]), the estimated HR (95% confidence interval [CI]) for death is 0.80 (0.59, 1.10) in favour of VR-CAP (see table 4). The company stated that the interim Kaplan–Meier plot of overall survival demonstrates a consistent trend in improved OS in subjects randomised to VR-CAP, with a separation of survival curves that appears to widen over time.

Table 4. Overall Survival, ITT analysis set

	VR-CAP (n=243)	**R-CHOP (n=244)**
OS, median days (95% CI)	NE (1704.0; NE)	1714.0 (1436.0; NE)
HR (95% CI)	0.80 (0.59; 1.10)	
p-value	0.173	
18-month survival rate % (95% CI)	84.9 (79.6; 88.9)	83.8 (78.4; 87.9)
3-year survival rate % (95% CI)	72.2 (65.6; 77.8)	67.9 (61.1; 73.8)
4-year survival rate % (95% CI)	64.4 (56.4; 71.4)	53.9 (45.2; 61.9)

Key: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; NE, not estimable; OS, overall survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.
Source: LYM-3002 CSR[60]; Robak et al. 2015.[59]

Figure 2. Kaplan–Meier plot of OS, ITT analysis set



Key: ITT, intent-to-treat; OS, overall survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.
Source: figure 6 of company submission (LYM-3002 CSR; Robak et al. 2015)

4.15 Three different patient-reported outcome tools were used to assess health related quality of life (HRQoL) in the LYM-3002 trial: the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30); the Brief Fatigue Inventory (BFI); and the EuroQol (EQ)-5D. The company reported that utility values, translated from the EuroQoL-5 Dimension Questionnaire (EQ-5D) taken at day one of every treatment cycle and at the end-of-treatment visit, were similar between treatment groups at baseline and throughout the LYM-3002 treatment period (see table 5). The company highlighted that as the study design did not include patient-reported outcome collection after the end of treatment, it was not possible to assess the dimension of clinical benefit derived by subjects from the prolonged PFS and prolonged disease control provided by VR-CAP. However, it is expected that such improvement in long-term prognosis would positively impact patient HRQoL in practice.

Table 5. Summary of health-related quality of life analysis set (EORTC QLQ-C30, BFI and EQ-5D) - from table 20 of the company submission)

	VR-CAP	R-CHOP
EORTC QLQ-C30		
GHS at baseline, mean (SE)	61.69 (1.36)	57.33 (1.36)
GHS CFB at cycle 6, mean (SD)	-3.85 (28.83)	2.92 (24.11)
GHS CFB at EOT, mean (SD)	-0.60 (26.29)	5.47 (25.65)
Mean difference in GHS through cycle 6 (SE); p-value		-0.9 (1.44); p=0.528
BFI		
WFS at baseline, mean (SD)	3.26 (2.63)	3.49 (2.64)
WFS CFB at cycle 6, mean (SD)	0.83 (3.07)	0.12 (2.75)
WFS CFB at EOT, mean (SD)	0.27 (3.10)	0.07 (2.92)
Mean difference in WFS through cycle 6 (SE); p-value		0.2 (0.18); p=0.244
FIS at baseline, mean (SD)	2.33 (2.33)	2.70 (2.41)
FIS CFB at cycle 6, mean (SD)	1.06 (2.65)	0.24 (2.29)
FIS CFB at EOT, mean (SD)	0.57 (2.71)	0.17 (2.58)
EQ-5D		
Utility at baseline, mean (SD)	0.79 (0.20)	0.76 (0.21)
Utility CFB at cycle 6, mean (SD)	-0.11 (0.29)	-0.02 (0.27)
Utility CFB at EOT, mean (SD)	-0.07 (0.28)	-0.02 (0.28)
VAS at baseline, mean (SD)	69.34 (20.63)	64.97 (19.93)
VAS CFB at cycle 6, mean (SD)	-1.99 (24.67)	3.71 (18.53)
VAS CFB at EOT, mean (SD)	1.23 (24.15)	5.65 (19.94)

Key: BFI, Brief Fatigue Inventory; CFB, change from baseline; CSR, clinical study report; EOT, end of treatment; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, EuroQol 5 Dimension Questionnaire; FIS, fatigue interference score; GHS, global health status; HRQL, health-related quality of life; PRO, patient-reported outcome; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; SD, standard deviation; SE, standard error; VAS, visual analogue scale; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone; WFS, worst fatigue score.
Source: LYM-3002 CSR.[60]

ERG comments

4.16 The ERG highlighted that no results were reported for the subgroup of participants from Europe and North America.

Subgroup analysis

4.17 Eleven subgroups were pre-planned. These were based on international prognostic index (IPI) risk, sex, race, geographic region, age, stage of disease at diagnosis, baseline Eastern Cooperative Oncology Group score, lactate dehydrogenase levels and white blood cell count were consistent with the results of the ITT population, with significant prolongation of PFS associated with VR-CAP.

4.18 In subgroup analyses based on region, the North America subgroup was combined with the European Union subgroup post-hoc as the former had very few subjects, most of whom had a PFS event (5 people with a PFS event out of 8 enrolled into the R-CHOP group, and 4 people out of 6 enrolled into the VR-CAP group) that resulted in a very large CI (0.44, 41.96) for the estimated HR (which was >1).

4.19 In the pre-specified North American and Western European subgroup, clinical benefit similar to that observed in the ITT population was also observed in favour of the VR-CAP group: median PFS 19.4 months versus 14.4 months (HR [95% CI]: 0.77 [0.43, 1.38]). Post-hoc analysis was also conducted to investigate the impact of bortezomib dose intensity on overall survival by splitting between lower or higher (<4.6 vs ≥4.6 mg/m^2/cycle) dose intensity groups. Overall survival was found to be significantly longer in the higher (n=93) versus lower (n=88) bortezomib dose intensity group in univariate analysis (HR [95% CI]: 0.43 [0.23, 0.80]; p=0.0059) with 4-year overall survival rates of 79.5% versus 57.1%, respectively.

ERG comments

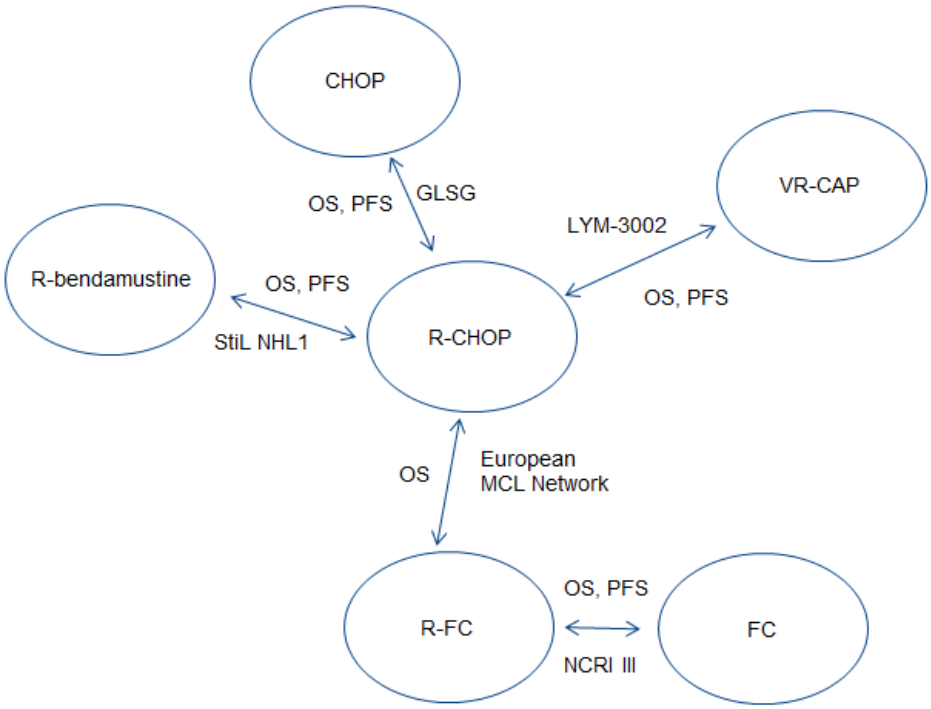
4.20 The ERG noted that only approximately a third of the participants of LYM-3002 were recruited in Northern America or Western Europe. The ERG highlighted that numbers of included patients as well as events were small. In addition endpoints other than progression-free survival might have been underpowered. When considering only participants from Europe and North America, all outcomes are likely to be underpowered. Therefore, results for this subgroup should be interpreted with caution.

Meta-analyses/indirect comparison

4.21 The company highlighted that the induction therapy regimens listed in the final appraisal scope (R-FC and R-bendamustine) are not considered to be relevant comparators for VR-CAP as these are generally reserved for patients who cannot tolerate R-CHOP and, therefore, VR-CAP. However, the company did indirect comparison analyses to alternative rituximab-chemotherapy induction regimens where possible.

4.22 The company identified four RCTs in addition to the LYM-3002 trial which reported PFS and/or overall survival data that could be used in indirect comparison analyses of relevance to the subsequent economic modelling. This potential network of evidence is presented in figure 3 below. Of these RCTs, the European MCL Elderly trial and the StiL NHL1 trial provided evidence of comparators that were included in the decision problem which could be linked to LYM-3002 for progression-free survival or overall survival analysis through the common comparator, R-CHOP. The company emphasised the limitations of the indirect comparison and considered that these analyses are not robust because of important differences between LYM-3002 and the comparator studies, and because of methodological limitations of the comparator studies. In particular the company cited between-study heterogeneity and, with respect to R-bendamustine, the small size and lack of detail on patient characteristics for the subgroup of MCL patients within the StiL NHL1 trial. The company presented the results of two indirect comparisons using the Bucher method for progression-free and overall survival (table 6).

Figure 3. Potential network of evidence for indirect comparison analyses of survival outcomes



Key: CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; FC, fludarabine and cyclophosphamide; GLSG, Grade Lymphoma Study Group; MCL, mantle cell lymphoma; NCRI, National Cancer Research Institute; NHL, non-Hodgkin's lymphoma; OS, overall survival; PFS, progression-free survival; R-bendamustine, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; R-FC, rituximab with fludarabine and cyclophosphamide; StiL, Study Group of indolent Lymphomas; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

Table 6. Bucher indirect comparison analyses of progression-free survival and overall survival

	HR	Lower 95% CI	Upper 95% CI
Overall survival			
VR-CAP vs R-FC	0.53	0.35	0.81
VR-CAP vs R-bendamustine	0.63	0.31	1.25
Progression-free survival			
VR-CAP[a] vs R-bendamustine	1.04	0.59	1.84

Key: CI, confidence interval; HR, hazard ratio; IRC, independent review committee; NHL, non-Hodgkin's lymphoma; OS, overall survival; PFS, progression-free survival; R-bendamustine, rituximab with bendamustine; R-FC, rituximab with fludarabine and cyclophosphamide; StiL, Study Group of indolent Lymphomas; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.
Notes: [a], PFS investigator data used in indirect comparison as StiL NHL1 did not use IRC assessment.

ERG comments

4.23 The ERG commented that with only a single randomised controlled study assessing VR-CAP, the LYM-3002 trial, being identified, the company was justified in not undertaking a meta-analysis.

4.24 The ERG agreed with the company that the indirect analysis should be treated with caution because of the lack of similarity between the 3 included trials. The wide confidence intervals reported above could partly be explained by this heterogeneity. The ERG noted that the three trials included in the indirect analyses are linked to high risk of bias.

Adverse effects of treatment

4.25 The company reported that both VR-CAP and R-CHOP induction regimens were generally well tolerated, with discontinuation rates of 8.8% and 7.0% respectively because of an adverse event. Fatality rates because of an adverse event were 7.0% in both treatment groups. Almost all subjects in both treatment groups experienced a treatment-emergent adverse event (AE), although VR-CAP was associated with a slightly higher rate of Grade 3 or higher AEs and serious AEs. In both treatment groups, the most commonly reported AEs and Grade 3 or higher AEs were haematological (blood and lymphatic system) disorders.

Table 7 LYM-3002 – safety and tolerability, safety analysis set (source: table 27 of the company submission)

	VR-CAP (n=240)	R-CHOP (n=242)
Any treatment-emergent AE, n (%)	238 (99.2)	238 (98.3)
At least one related[a]	231 (96.3)	226 (93.4)
None related	7 (2.9)	12 (5.0)
Any serious AE, n (%)	90 (37.5)	72 (29.8)
At least one related[a]	78 (32.5)	50 (20.7)
None related	12 (5.0)	22 (9.1)
Maximum severity of any AE, n (%)	238 (99.2)	238 (98.3)
Grade 1	2 (0.8)	6 (2.5)
Grade 2	13 (5.4)	26 (10.7)
Grade 3	31 (12.9)	53 (21.9)
Grade 4	176 (73.3)	136 (56.2)
Grade 5	16 (6.7)	17 (7.0)
Treatment discontinuation due to AEs, n (%)	21 (8.8)	17 (7.0)
Related to study drug[a]	19 (7.9)	14 (5.8)
Fatality due to AEs, n (%)	16 (7.0)	17 (7.0)
Related to study drug[a]	5 (2.0)	7 (3.0)

Key: AE, adverse event; CSR, clinical study report; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.
Notes: [a], related to any study drug
Source: LYM-3002 CSR[23], Robak et al. 2015.[11]

ERG comments

4.26 The ERG agreed with the company's view that both chemotherapy induction regimens were generally well tolerated, with low rates of discontinuation due to an AE and low fatality on treatment in both groups. However, the ERG highlighted that more serious AEs were observed for VR-CAP (37.5%) compared to R-CHOP (29.8%) and the serious AEs are usually of higher severity in VR-CAP (see table 7 above). While more treatment discontinuations related to the study drug were reported for VR-CAP (7.9%) compared to R-CHOP (5.8%), more fatalities related to R-CHOP (3.0%) compared to VR-CAP (2.0%) were reported. The ERG highlighted that this was similar to the outcomes for the Western Europe subgroup. More comprehensive results will be available with the final analysis in 2017.

5 Cost-effectiveness evidence

Model structure

5.1 A de novo cost-effectiveness model was developed by the company to assess the cost effectiveness of VR-CAP in England and Wales. The model included 5 health states: progression-free survival from first-line treatment, progressed from first-line treatment, progression-free survival from second-line treatment, progressed from second-line treatment and death.

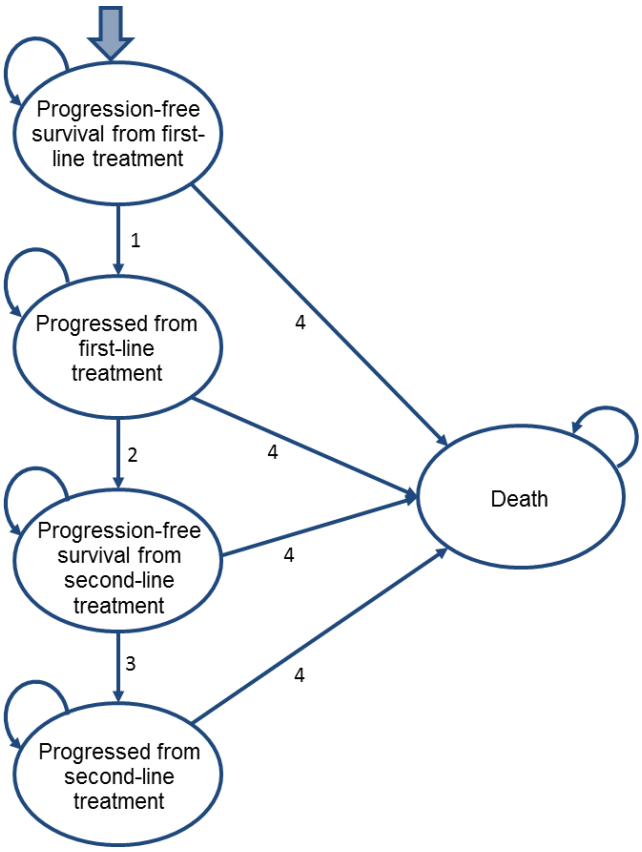


Figure 4. Company's model structure.

Key: OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; PrePS, pre-progression survival;

Notes: 1. Modelled using curve fit to progression-free survival Kaplan–Meier data; 2. Modelled using curve fit to treatment-free interval; 3. Modelled using average progression-free survival from second-line treatment; 4. Modelled using curve fit to

overall survival Kaplan–Meier curve (post-progression survival and pre-progression survival plus general population background mortality data).

5.2 The company's base case model time horizon was 20 years. The company considered this to be essentially a lifetime time horizon for patients given that the mean age assumed in the model was 69. Both costs and health outcomes were discounted at an annual rate of 3.5%. The company stated that costs were based on 2013/14 as these were the most recent cost data available at the time the model was developed.

5.3 The key clinical data used within the economic model were taken from the LYM-3002 trial. The ITT population of the LYM-3002 trial was used to assess the effectiveness and safety of VR-CAP versus R-CHOP in the *de novo* cost-effectiveness model. Based on advice from UK haematologists, the company considered that people included in the LYM-3002 trial were similar to those expected to be seen in UK clinical practice. However, baseline demographics from only the Western European and North American subgroup were used in the model because people in the LYM-3002 trial were considered by the company to be more similar to those expected to be seen in UK clinical practice in terms of age and weight.

5.4 Economic comparison was conducted primarily with R-CHOP because the company were of the opinion that R-CHOP induction therapy is the established standard of care for patients with previously untreated MCL (for whom HSCT is unsuitable). The company stated that no maintenance treatment with rituximab was assumed in the model base case because it was not identified as a comparator in the decision problem. However, the company highlighted that as R-maintenance is used in clinical practice in people with a response to induction, the potential impact of induction therapy with VR-CAP vs R-CHOP followed by R-maintenance was investigated in exploratory analyses (see section 5.8 of the company submission).

ERG comments

5.5 The ERG commented that the company's model followed a logical structure with respect to the nature of the disease. The ERG agreed that the discount rate and perspective are in line with the NICE reference case. The ERG noted that considering the average age of 69 years in the LYM-3002 trial and that the median survival is less than five years a time horizon of 20 years is considered adequate and similar to a lifetime perspective. However, a longer time horizon is feasible as not all patients died within 20 years and so the choice of a 20 year horizon can be considered conservative. The ERG identified two possible concerns: the exclusion of the half-cycle correction and the exclusion of any additional treatment lines after second-line treatment. The company highlighted that it had implemented the half cycle correction however the ERG disagreed with how it was done. Therefore the ERG has made its own correction for the new ERG base case (see sections 5.36). The ERG commented that the exclusion of any additional treatment lines seemed reasonable considering the lack of evidence of treatment efficacy and the minority of patients receiving a third treatment line.

5.6 As noted in the clinical effectiveness section, no patients from the UK were included in the LY-3002 clinical trial. Roughly a third of the participants were recruited in the European Union and North America while the other two thirds were from the "rest of the world", in particular Russia and China. Therefore the ERG considers, in terms of population included in the model, there is uncertainty regarding the generalisability of the trial population to clinical practice in the UK given the different prevalence depending on the geographic region and potential differences in clinical standards.

Model details

5.7 In the LYM-3002 trial, the primary outcome of the trial of progression-free survival was assessed by an independent review committee (IRC); however, advice to the company from clinicians suggested that in clinical

practice, progression is always confirmed by sequential assessments instead of a single CT scan. In the alternative method, an IRC reviewer performed a global review for a subgroup of patients assessed with progressed disease based solely on transient fluid collections or transient lesions. The scans of all available time points were reviewed, and the response assessment for a given time point could be revised depending on whether a lesion was assessed as resolved or persisting at subsequent time points. The company highlighted that the alternative method was more reflective of clinical practice and therefore, chose to use the alternative IRC assessment in the base case of the model because this reflected clinical practice while retaining the blinded assessment.

5.8 The company fitted the following parametric models to estimate progression-free survival in the 2 treatment arms: exponential; Weibull; lognormal; log-logistic; gamma; and Gompertz. The company used the log-logistic model in the base case based on the goodness of fit of the PFS curves (i.e. using the Akaike information criterion and the Bayesian information criterion (table 7), and visual fit and long-term fit).

5.9 Survival was subtracted from progression-free survival in the model calculations to find the actual number of people progressing, and removing those that died before progression. Figure 6 shows the base case progression-free survival used in the model.

Table 7 Goodness of fit of PFS curves (source: table 35 of the company submission).

		Exponential	Weibull	Log-logistic	Log-Normal	Gamma	Gompertz
VR-CAP	**AIC**	**603.623**	605.604	608.385	616.888	607.603	1194.398
	BIC	**607.116**	612.590	615.371	623.874	618.082	1201.384
R-CHOP	**AIC**	634.079	634.075	**622.425**	636.948	630.674	1349.269
	BIC	637.576	641.070	**629.419**	643.942	641.166	1356.263
Total	**AIC**	**1237.702**	1239.679	**1230.810**	1253.836	1238.277	2543.667
	BIC	1244.692	1253.660	1244.790	1267.817	1259.248	2557.647

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

Figure 5. Long-term fit of parametric models to PFS based on alternative IRC assessment

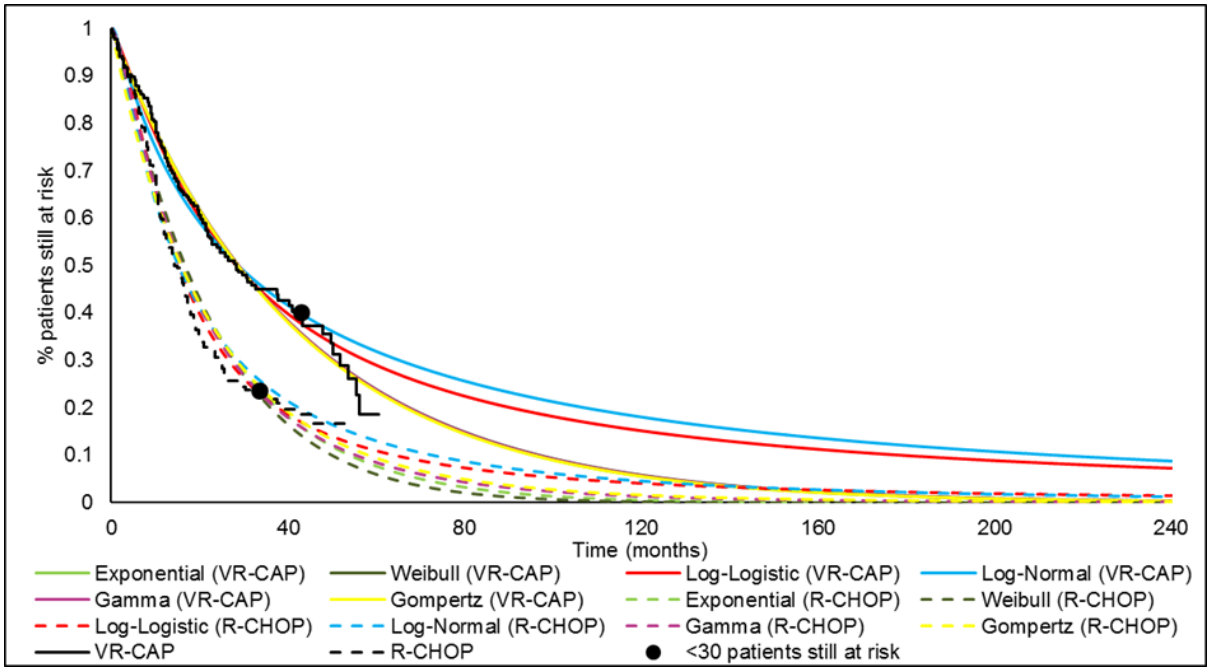
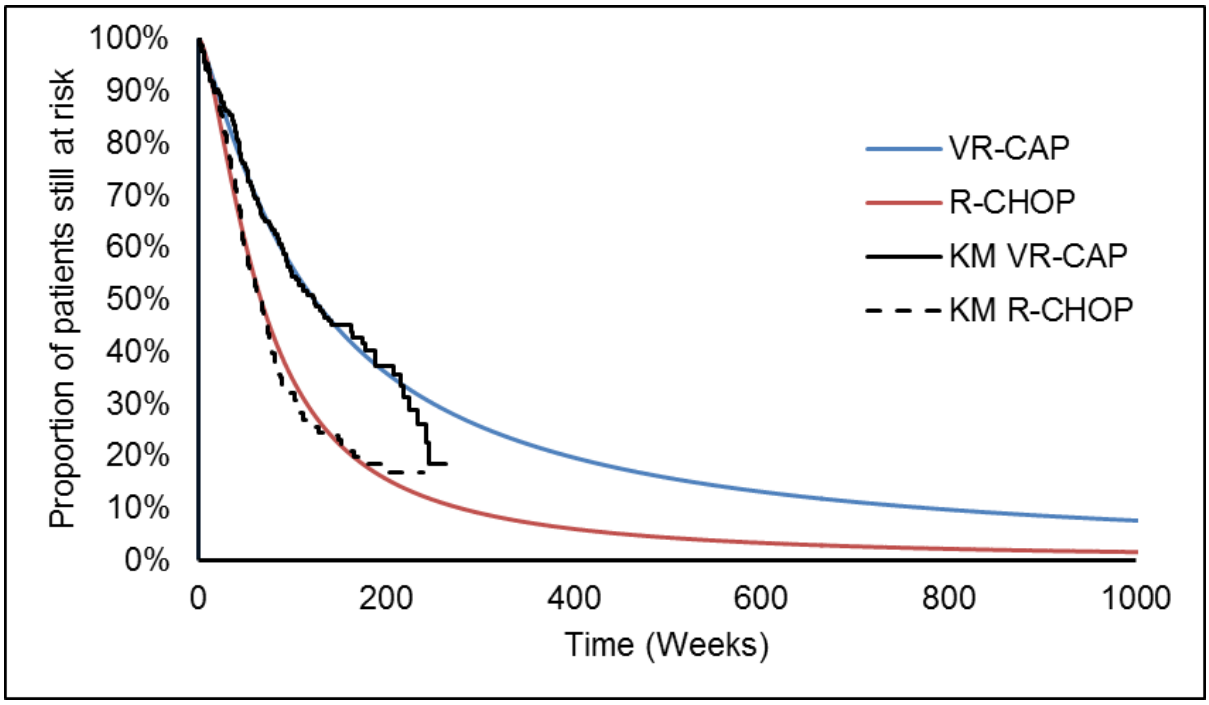


Figure 6. Base case log-logistic PFS curves



5.10 Overall survival was estimated for three different groups in the base-case analysis:

- people without progression (PrePS) treated with R-CHOP
- people without progression (PrePS) treated with VR-CAP
- people with progression (PPS) (irrespective of initial treatment)

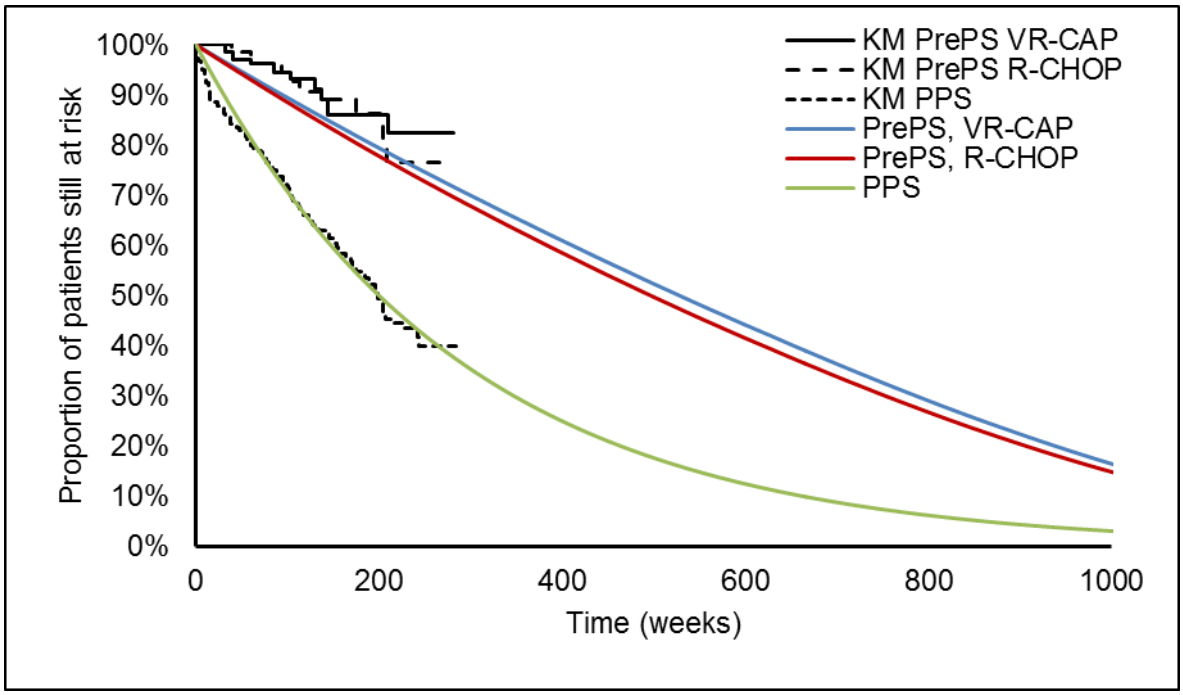
5.11 Survival was modelled with parametric models fitted using the LYM-3002 patient level data for VR-CAP and R-CHOP patients. However, overall survival data from the LYM-3002 trial are still immature; median overall survival for VR-CAP has not been reached. Because of the a wide range of potential outcomes when attempting to fit survival curves directly to the overall survival data, the company modelled survival using progression as a surrogate marker for overall survival.

5.12 For the base case, parametric curves were fitted for three categories of patients: all patients who progressed from VR-CAP or R-CHOP during the trial, all patients who did not progress from VR-CAP, and all patients who did not progress from R-CHOP. This method assumed that patients who

progressed had the same survival regardless of what treatment they received in first line (i.e. post-progression survival was the same, regardless of the first-line therapy that had been received).

5.13 The company noted advisory board comments that the long-term estimates of pre-progression survival based on curve fitting were quite high. This was likely caused by using relatively immature data, meaning that the increase in background mortality with increasing age was not fully taken into account. Therefore, the company added non-disease-specific mortality, based on age and gender, to the model to better capture long-term survival (using UK life tables). It was assumed that all deaths in the pre-progression survival curves (prior to adjustment for background mortality) in the trial were deaths from mantle cell lymphoma.

Figure 7 Base case exponential overall survival curves with general population mortality added to non-progressed curves **(see figure 18 of the company submission)**



5.14 The mean duration of second-line treatment and PFS from second-line treatment were derived from the LYM-3002 trial. In the company base case, model treatment duration (90 days) and progression-free survival

(231 days) were assumed to be the same for both arms, using data from both LYM-3002 trial arms combined.

5.15 The company highlighted that there were limited data available for the other comparators included in the scope. The company stated that the indirect comparison to R-bendamustine was too unreliable given the heterogeneity described previously, particularly for PFS, to be used to assess comparative efficacy within the cost-effectiveness model. Instead, the company assumed equal efficacy (PFS and OS) to R-CHOP which was based on clinician feedback. Similarly, the limitations of the R-FC indirect comparison meant that an assumption of equal efficacy with R-CHOP was also made for R-FC.

5.16 The company used EQ-5D data from the LYM-3002 trial for health-related quality of life estimates during and on progression from first-line treatment. Utility decrements for adverse events were included in addition to the health state utilities whilst patients were on treatment, based upon LYM-3002 trial data No long-term utility values were available from the LYM-3002 trial so instead, the company assumed equal utility while progression free during first- and second-line treatments (based upon UK clinician feedback and previous non-Hodgkin's lymphoma modelling), Utility associated with post-progression from second-line treatment was taken from the most relevant source related to aggressive non-Hodgkin's lymphoma, which the company stated was the most similar condition to mantle cell lymphoma in terms of expected impact on health status. A summary of the values used in the company's model is presented in table 8.

Table 8: Summary of utility values for cost-effectiveness analysis (source, table 47 of the company submission).

State	Utility value	95% CI	Reference in submission	Justification
Health state utility values				
PFS from first-line treatment	0.764	0.746; 0.781	Section **Error! Reference source not found.**~~5.4~~ **Error! Reference source not found.**~~Table 42~~	LYM-3002 EQ-5D data. PFS from second-line treatment assumed equal to PFS from first-line treatment[6, 117]
Progressed from first-line treatment	0.693	0.639; 0.745		
Progression free from second-line treatment	0.764	0.746; 0.781		
Progressed from second-line treatment	0.45*	0.206; 0.708	Section **Error! Reference source not found.**~~5.4~~ **Error! Reference source not found.**~~Table 44~~	Most robust literature estimate[86]
Adverse event decrements				
Neutropenia	-0.032	-0.016; -0.052	Section **Error! Reference source not found.**~~5.4~~ **Error! Reference source not found.**	LYM-3002 EQ-5D data.
Thrombocytopenia	-0.038	-0.014; -0.074		
Anaemia	-0.007	-0.000; -0.069		
Leukopenia	-0.042	-0.021; -0.070		
Lymphopenia	-0.065	-0.031; -0.110		
Febrile neutropenia	-0.014	-0.000; -0.084		
Pneumonia	-0.058	-0.002; -0.196		
Fatigue	-0.038	-0.000; -0.158		
Diarrhoea	-0.102	-0.049; -0.173		

State	Utility value	95% CI	Reference in submission	Justification
Peripheral sensory neuropathy	-0.087	-0.038; -0.154		
Sepsis	-0.175	-0.086; -0.288		
Alopecia	-0.137	-0.068; -0.227		
Key: CI, confidence interval; EQ-5D, EuroQoL-5 Dimension Questionnaire; PFS, progression-free survival. **Notes:** Derived as follows: { [aaPI 0-1 Baseline (0.74) + progression (-0.24)] + [aaPI 2-3 Baseline (0.44) + progression (-0.04)] } / 2 = 0.45.				

Costs

5.17 The company's model assumed that patients received only whole vials and that there was no vial sharing (average number of vials required per administration is presented in table 50 of the company submission). With regard to dosing regimens, cycle lengths for both VR-CAP and R-CHOP were 21 days with a maximum number of 6 cycles or 8 if first response in cycle 6 (see table 51 of the company submission). Table 52 of the company submission summarises the drug acquisition and administration costs associated with VR-CAP, R-CHOP, other comparators and second-line treatments.

5.18 In the model, the number of patients receiving treatment per cycle was informed by the LYM-3002 trial and reduced with each cycle going from 100% in cycle 1 down to 13.3% for VR-CAP and 17.4% for R-CHOP by cycle 8 (see table 53 of the company submission).

5.19 In addition to the cost of hospital visits to treat AEs, drug acquisition costs associated with concomitant medications were also included in the model (those used in the trial but unavailable in the UK were excluded). Costs for red blood cell and platelet transfusions were included in the company's model (see tables 58 to 60 of the company submission for further details).

5.20 Adverse event costs were based on NHS Reference Costs 2013-14. Weekly costs attributable to adverse events produced cycle costs of £26.41 for VR-CAP and £28.81 for R-CHOP (see tables 61 and 62 of the company submission).

Company's base-case results and sensitivity analysis

5.21 Base case results of the economic comparison between VR-CAP and R-CHOP are presented in table 9. In the company's deterministic analysis, VR-CAP was estimated to generate 0.75 incremental life years, 0.80 incremental QALYs and an incremental cost of £16,213 versus R-CHOP, leading to an ICER of £20,362 per QALY gained. In the probabilistic analyses (see ERG report table 6.25) the ICERs for VR-CAP ranged between £13,725 (versus R-bendamustine) and £20,264 (versus R-CHOP) per QALY gained.

Table 9. Company's deterministic base case results

Treatment	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
VR-CAP	£45,838	6.44	4.15				
R-CHOP	£29,625	5.69	3.35	£16,213	0.75	0.80	£20,362
R-FC	£31,370	5.69	3.36	£14,467	0.75	0.78	£18,509
R-bendamustine	£35,011	5.69	3.36	£10,826	0.75	0.78	£13,797

Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

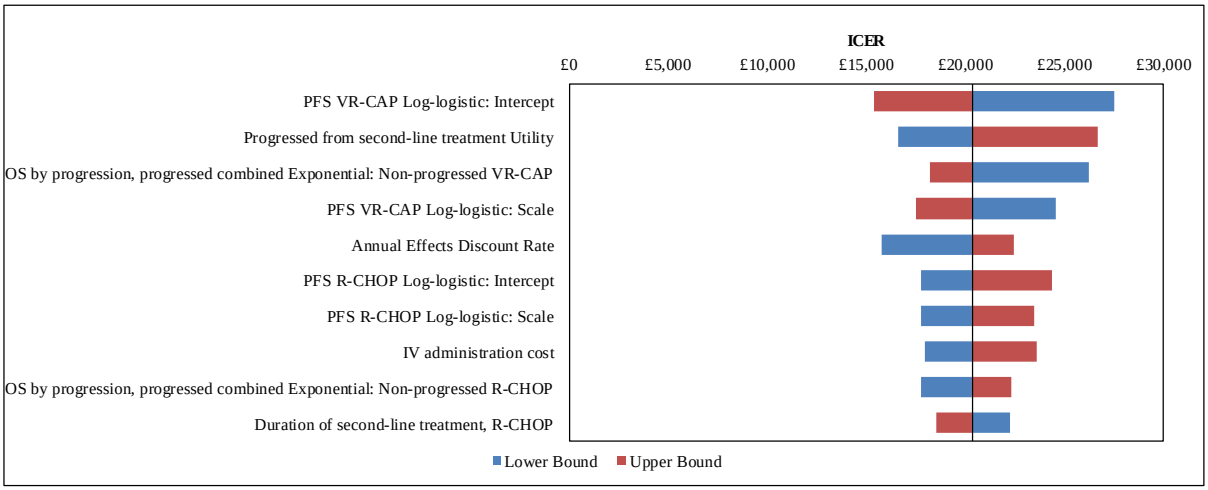
Table 10. Company's full incremental analysis for VR-CAP and all 3 comparators

	QALYs	Costs	ICER
R-CHOP	3.35	£29,625	
R-bendamustine	3.36	£35,011	Dominated
R-FC	3.36	£31,370	Extendedly Dominated
VR-CAP	4.15	£45,838	£20,362

Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; R-bendamustine, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; R-FC, rituximab with fludarabine and cyclophosphamide; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

5.22 Cost-effectiveness acceptability curves (retrieved by the ERG from the company model) showed that R-CHOP has the highest probability of being cost-effective (51.3%) followed by VR-CAP (48.7%). The probabilities of being cost-effective for R-FC and R-bendamustine were 0.0%. VR-CAP has the highest probability (86.5%) of being cost-effective at a WTP threshold of £30,000, followed by R-CHOP (13.5%), R-FC (0.0%) and R-bendamustine (0.0%).

Figure 8. Tornado diagram displaying the ICER sensitivity of the 10 most influential model inputs (VR-CAP versus R-CHOP)



5.23 The company presented parameters that were included stochastically in the economic model and the annual discount rates. The ICERs were most sensitive to the survival functions used to model progression-free survival and overall survival, the utility value for patients progressed from second-line treatment, IV administration costs and the duration of second-line treatment. Results were presented compared with each relevant comparator, but only the tornado diagram for the comparison between VR-CAP and R-CHOP is presented here (figure 8).

ERG comments

5.24 Although a large number of deterministic sensitivity analyses were performed by the company the ERG commented that the sensitivity analyses for the parameters presented in tables 53 (percentage of patients receiving first-line treatment) and 56 (percentage of patients receiving concomitant medication) of the company submission were missing. The company performed these analyses in response to clarification question (question C19) for VR-CAP versus R-CHOP only. This did not change the tornado diagram with the 10 most influential model inputs (see figure 6.8 of the ERG report for reference). No updated tornado diagrams were provided for VR-CAP versus R-FC and VR-CAP versus R-bendamustine. The ERG noted that because the company did not consider R-FC and R-bendamustine in the scenario analyses, the impact of the scenario analyses on the comparisons with R-FC and R-bendamustine is unclear.

5.25 The ERG were satisfied that appropriate validity checks were undertaken by the company and the results are satisfactory.

5.26 The ERG did not agree with the company to not apply half cycle correction and to use the ITT population of the LYM-3002 trial to assess the effectiveness of VR-CAP versus R-CHOP instead of the European Union subgroup. The ERG acknowledged that the company stated that they had applied a half cycle correction but the ERG was not convinced that the half-cycle correction was implemented correctly by the company.

5.27 The ERG had several comments on the way the PFS, OS and TFI were estimated. Firstly, it is uncertain whether the best fitted model was selected to model the PFS for the VR-CAP arm. The ERG noted that the log-logistic distribution was selected for both treatment arms based upon clinical expert opinion. However, the exponential distribution showed the best statistical fit for the VR-CAP arm (based on AIC/BIC information). Another concern regarding the estimation of PFS is the use of a stratified model whereas an unstratified model seemed to be more appropriate. Secondly, regarding the modelling of survival, the ERG questioned the use of different survival curves based on progression status and the assumption that survival for patients without progression differed between treatment arms. Thirdly, the ERG would expect that TFI is overestimated by the company and possibly this overestimation was larger in VR-CAP patients since these estimates were based on all patients irrespective of treatment response.

5.28 The ERG agreed with the company submission that immature data may bias the extrapolation of survival data however, this was not explained further by the company. The ERG suggested that if data are too immature to model overall survival for all patients, it is questionable whether sufficient data are available to separately estimate long-term survival for patients with and without progression. This distinction would reduce the total number of patients at risk, and may increase the uncertainty about the long-term survival. The company justified the use of different survival for patients with and without progression by referencing one study in mantle cell lymphoma and one study in non-Hodgkin's lymphoma in which better progression-free survival is associated with better overall survival. Another concern raised by the ERG regarding the modelling of survival was the assumption that survival for patients without progression differs between treatment arms. The ERG suggested that as a result of using immature data, it is not feasible to identify any differences in overall survival between treatment arms. A more conservative approach would be to assume no treatment effect on overall survival, but only for progression-

free survival. The ERG has performed this in its exploratory analysis (see section 5.36).

5.29 The ERG noted that because TFI was measured in all patients who received study medication regardless of response, and that second-line treatment is only administered to patients with disease progression, all patients without progression are likely to be censored in this company's analysis. As a result, censoring was non-random meaning the TFI was overestimated. This overestimation may be larger for the VR-CAP arm since PFS was better and therefore more patients were censored. The ERG also found that the proportion of patients that have progressed was underestimated in the model as it was estimated from all previous cycles from 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 meaning that probabilities to start second line treatment were larger than one.

5.30 The ERG agreed with the company's assumption that the utility for 'PFS from second-line treatment' is similar to the 'PFS from first-line treatments'. However, the ERG did not agree with the value used for 'progressed disease from second-line treatment' because it was based on a study about aggressive NHL and is associated with uncertainty given the small patient population on which this estimate is based. The ERG also noted that some utility values used for the secondary scenario analyses were not correctly entered into the model of the company.

5.31 The ERG highlighted that the company's ICER was most sensitive to variations within the fit of the parametric models for PFS and OS. The model outcomes depended heavily on the PFS and OS curves used and the shape these curves have. The utility of patients who have progressed from second-line treatment was the parameter with the second greatest ICER sensitivity, because of people spending a relatively long time in this health state.

5.32 The ERG agreed with using the mean second-line duration for drug acquisition and administration as this was seen as conservative compared to using the maximum second-line duration. In contrast, the ERG did not agree with the dose reduction applied to the drug costs for VR-CAP and R-CHOP since it is questionable whether the dose reduction observed in the LYM-3002 trial are representative for UK clinical practice. In addition, some errors in the model were found regarding concomitant medication costs and costs for pegfilgrastim for R-CHOP.

5.33 The company did not provide a subgroup analysis for the European Union or European Union/North American region subgroup. As the treatment effectiveness appears lower for the European Union subgroup, the relative treatment effect for PFS was conservatively adjusted to reflect the European Union subgroup in the ERG base case

Company scenarios

5.34 The company performed a large number of scenario analyses for the comparison between VR-CAP and R-CHOP. The most influential scenario analyses were those incorporating different parametric distributions for PFS; using Weibull, gamma and Gompertz distributions increased the ICER to £25,849, £27,697 and £30,452 respectively. Changing the utility value for patients progressed from second-line treatment to 0.693 (equal to patients progressing from first-line treatment) increased the ICER to £26,241 per QALY gained. Changing all health state utility values to correspond with those from Doorduijn et al (i.e. 0.61 for progression free in the first- and second-line and 0.45 for progressed patients in the first- and second-line) did increase the ICER to £28,746 per QALY gained. Setting the baseline age to 75 (base case value = 69 years) the ICER increased to £26,010 per QALY gained. The company stated that cost-effectiveness results were generally robust under the sensitivity and scenario analyses conducted, with no scenarios bringing the ICER of VR-CAP versus R-CHOP above £30,000.

ERG comments

5.35 The company did not consider R-FC and R-bendamustine in the scenario analyses. Therefore, the impact of the scenario analyses on the comparisons with R-FC and R-bendamustine are unclear.

ERG exploratory analyses

5.36 In light of a number of issues highlighted in the ERG report, the ERG made a number of amendments The ERG corrected a number of errors and changed a number of assumptions in the company's model as follows:

- Corrected the unit prices which were different in the reference price list
- Corrected an error in the calculation of adverse events
- Corrected calculation of costs of concomitant medication
- Inclusion of half-cycle correction
- Age, weight and unit prices were made fixed instead of being stochastic
- Proportion of patients receiving treatment during a cycle and proportion of patients receiving concomitant medication were made stochastic to reflect second order uncertainty
- Adjusted PFS according to the HR of the EU population
- Start second line treatment at time of progression
- Utility for progression from second line treatment is calculated by subtracting the disutility as found in Doorduijn et al. from the baseline utility in the LYM-3002 trial for PFS from first line treatment. Therefore the ERG used a utility of 0.624 instead of the company's 0.45 value.
- Excluded end of life costs
- Used per protocol dosage instead of observed dose reductions since it is unknown whether the dose reduction are applicable to UK patients

- The primary assessment of progression is used instead of the alternative assessment
- Indirect treatment comparison is used for the effectiveness of R-FC and R-bendamustine instead of assuming equal effectiveness as R-CHOP
- Overall survival is not differentiated between patients with and without progression, but between treatments instead
- Excluded all-cause mortality as this is already incorporated in the overall survival estimate
- The exponential distribution is used for the extrapolation of PFS in the VR-CAP arm and the log-logistic distribution is used for the extrapolation of PFS in the R-CHOP arm

5.37 The ERG stated that the ICERs compared to R-FC and R-bendamustine were minimally influenced by the ERG changes and so table 11 focuses on the comparison with R-CHOP. Table 11 shows how each individual change impacts the ICER plus the combined effect of all changes simultaneously. Including all of the ERG's amendments increased the company's base case ICER of VR-CAP versus R-CHOP by £14,000 to £34,039 compared to the CS base case, which represents a 75% increase. The large difference between the company base case and the ERG ICER was caused mainly by changing the distribution for PFS in the VR-CAP arm to the exponential distribution, whilst keeping the distribution for R-CHOP PFS a log-logistic distribution.

Table 11. ERG amendments to the company's model.

	VR-CAP		R-CHOP		Incremental		ICER
	QALYs	Costs	QALYs	Costs	QALYs	Costs	Cost per QALY gained
Company base-case	**4.14**	**£45,724**	**3.34**	**£29,491**	**0.80**	**£16,234**	**£20,264**
1. Correction unit prices	4.12	£46,210	3.33	£29,979	0.79	£16,231	**£20,460**
2. Correction error adverse events	4.12	£45,808	3.32	£29,502	0.80	£16,306	**£20,322**

	VR-CAP		R-CHOP		Incremental		ICER
	QALYs	Costs	QALYs	Costs	QALYs	Costs	Cost per QALY gained
3. Correction costs concomitant medication	4.13	£46,137	3.33	£29,714	0.80	£16,423	**£20,507**
4. Age, weight and unit prices were not included as stochastic parameters	4.13	£45,684	3.34	£29,461	0.79	£16,223	**£20,514**
5. Proportion of patients receiving treatment included as stochastic parameter	4.17	£45,489	3.37	£29,199	0.80	£16,290	**£20,459**
6. Include half-cycle correction	4.13	£43,795	3.32	£28,289	0.81	£15,507	**£19,224**
7. PFS adjusted according to HR for European Union	4.08	£45,860	3.34	£29,398	0.74	£16,462	**£22,144**
8. Start second line treatment at time of progression	4.08	£46,267	3.31	£29,799	0.77	£16,467	**£21,354**
9. Utility progression 2nd line treatment based upon disutility Doorduijn	4.54	£45,624	3.87	£29,366	0.67	£16,257	**£24,190**
10. Per-protocol dosage	4.14	£48,838	3.35	£29,483	0.79	£19,355	**£24,410**
11.Primary assessment of progression	4.12	£45,521	3.39	£29,485	0.73	£16,035	**£21,961**
12. Survival is not distinguished between patients with and without progression	3.95	£42,843	3.24	£27,228	0.71	£15,614	**£21,987**
13. Exclude all-cause mortality	4.60	£45,871	3.52	£29,801	1.08	£16,070	**£14,818**
14. Exponential distribution for PFS in the VR-CAP arm	3.90	£47,025	3.37	£29,436	0.53	£17,589	**£33,087**
15. Indirect treatment comparison for efficacy R-FC and R-bendamustine	4.13	£45,601	3.34	£29,470	0.80	£16,130	**£20,282**
16. Excluding end-of life costs	4.11	£41,166	3.32	£24,672	0.79	£16,493	**£20,794**
ERG base case	**4.57**	**£44,140**	**3.93**	**£22,186**	**0.64**	**£21,955**	**£34,039**

Table 12 Full incremental comparison including all of the ERG's amendments

Treatment	Expected outcomes		Incremental analysis			
	Costs	QALY	Comparator	ΔCosts	ΔQALY	ICER
R-CHOP	£22,186	3.93				
R-FC	£22,370	2.96	R-CHOP	£184	-0.97	Dominated by R-CHOP
R-bendamustine	£24,957	3.43	R-CHOP	£2,771	-0.5	Dominated by R-CHOP
VR-CAP	£44,140	4.57	R-CHOP	£21,955	0.64	£34,039
Key: ICER, incremental cost-effectiveness ratio; R-bendamustine, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; R-FC, rituximab with fludarabine, and cyclophosphamide; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.						

5.38 The ERG did some additional exploratory analyses that looked at the impact of removing some assumptions from its preferred cumulative ICER estimate of £34,039 per QALY gained. The ERG combined all their preferred assumptions together but removed the following:

- PFS adjustment for the EU subgroup (remove assumption number 7),
- Distinguish survival for patients with and without progression (remove assumption number 12).
- Use the same PFS distribution (log-logistic) for all treatment arms (remove assumption number 14)

As survival for patients with and without progression is distinguished in this additional analysis by the ERG, all-cause mortality to survival pre-progression was included (in other words, analysis 13 was also removed). The result of removing these 4 assumptions from the ERG base case (table 9 of the ERG additional analysis) gave an ICER for VR-CAP compared with R-CHOP of £31,576 per QALY gained.

5.39 The utility estimate for progression from second-line treatment in the company submission was 0.45. The ERG's additional analysis (table 11) used a utility value of 0.624 calculated by subtracting the disutility found in a study by Doorduijn from the utility in people with progression-free survival from first-line treatment. The ERG explored the impact of reverting back to the company's original utility value and the exclusion of assumptions 7, 12-14 as in paragraph 5.37. The result of this analysis (that is the ERG base case excluding assumptions 7, 9, 12, 13 and 14) gave an ICER of £37,960 per QALY gained for VR-CAP compared with R-CHOP.

5.40 The ERG performed probabilistic sensitivity analyses for all comparators to capture the uncertainty in the estimation of input parameters in their additional analyses. The probability that VR-CAP is cost-effective at a threshold of £20,000 and £30,000 is smaller in the ERG analyses compared to the company's base-case (11% versus 49% and 39% versus 89% for a threshold of £20,000 and £30,000, respectively). Similar to the company's base case, the probability that R-FC or R-bendamustine are cost-effective at the usual NICE thresholds are negligible

5.41 The ERG also did a number of exploratory scenario analyses which are presented in table 13. The ERG did this for all comparators but only the scenarios comparing VR-CAP and R-CHOP are presented below.

5.42 The most extreme ICER was observed when the overall survival of VR-CAP was assumed to be similar to the overall survival of R-CHOP. This gave an ICER of £328,757 per QALY gained. The next highest ICER was found if R-maintenance is included in the model, giving an ICER of £43,779 per QALY gained.

Table 13 Exploratory scenario analyses undertaken by the ERG

	VR-CAP		R-CHOP		Incremental		ICER
	QALYs	Costs	QALYs	Costs	QALYs	Costs	Cost per QALY gained
ERG-base case	**4.57**	**£44,368**	**3.94**	**£22,467**	**0.63**	**£21,900**	**£34,738**
Exclude sepsis & alopecia	4.57	£44,278	3.94	£22,451	0.63	£21,826	£34,659
Include additional costs adverse events	4.57	£45,552	3.94	£22,847	0.63	£22,706	£36,015
Include additional costs adverse events, exclude costs concomitant medication and transfusion	4.57	£43,315	3.94	£21,455	0.63	£21,860	£34,674
No transfusion and concomitant medication costs for R-FC and R-benda	4.57	£44,368	3.94	£22,467	0.63	£21,900	£34,738
Disutility Doorduijn is only based on low risk group	4.20	£44,368	3.61	£22,467	0.59	£21,900	£37,202
Quality of life in PFS from second line is similar to the quality of life in patients with progression from first line treatment	4.56	£44,368	3.92	£22,467	0.63	£21,900	£34,728
Unstratified model for PFS	4.64	£42,828	3.98	£21,485	0.66	£21,343	£32,518
Survival VR-CAP is similar to survival R-CHOP	4.29	£43,591	4.22	£23,166	0.06	£20,425	£328,757
An average treatment-free interval of 365 days for all treatments	4.62	£43,238	3.99	£21,089	0.63	£22,149	£35,103
An average treatment-free interval of 365 days for VR-CAP and 182.5 for the other treatments	4.62	£43,238	3.97	£21,760	0.66	£21,477	£32,756
Include R-maintenance (source HR from NICE TA226)	4.66	£56,623	4.05	£31,338	0.61	£25,285	£41,585
Include R-maintenance (source HR from Kluin-Nelemans)	5.18	£58,765	4.60	£33,385	0.58	£25,379	£43,779

Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; R-bendamustine, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; R-FC, rituximab with fludarabine, and cyclophosphamide; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

Innovation

5.43 Justifications for considering bortezomib to be innovative:

- Submissions from the clinical experts stated that mantle cell lymphoma is an incurable condition that has one of the worst outcomes of the lymphoma sub-types so any advance in therapy is to be welcomed.
- The company commented that there were no licensed treatment regimens prior to the granting of a marketing authorisation for bortezomib, and no regimens have been recommended by NICE for the treatment of mantle cell lymphoma in the induction setting.
- The company stated in its submission that there is a clear unmet need for a first-line, induction therapy regimen that could improve the long-term prognosis of people with mantle cell lymphoma for whom HSCT is unsuitable. The company highlighted that VR-CAP meets this unmet need with the potential to change the treatment landscape in newly diagnosed mantle cell lymphoma, offering a significantly improved long-term prognosis that represents a step-change in the management of this condition
- Clinical experts highlighted that neurotoxicity can be a major issue for patients especially with respect to quality of life with bortezomib. Vincristine, which is in R-CHOP, can cause peripheral neuropathy therefore not including vincristine in VR-CAP appeared to prevent significant problems. Clinical experts stated that it is becoming clear that giving bortezomib subcutaneously significantly reduces neurotoxicity and it is likely that there would be widespread adoption of that mode of delivery if there is access to this treatment.

6 Equality issues

6.1 No equality issues were raised during scoping, nor by the company submission. Patient expert submission stated that any people with mantle

cell lymphoma who are less fit and consequently unable to tolerate the increased side effects will have difficulty using this treatment.

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Appendix A: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000539/WC500184919.pdf