in collaboration with:

Bortezomib for previously untreated mantle cell lymphoma

ERG comments following PMB on 14 September 2015

Commercial in confidence (CiC) data are highlighted in blue throughout the report.
Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Baseline characteristics of and results for HSCT-participants

The ERG report highlighted an issue regarding the inclusion of participants outside the final scope, namely the inclusion of participants suitable for haematopoietic stem cell transplantations from a medical perspective but for which availability and/or socio-economic reasons prevented access. During the PMB teleconference, further details on the baseline characteristics of these participants were requested.

According to chapter 5.2.1 of the ERG report: The final scope[1] uses two different definitions of the population of interest in regards to the haematopoietic stem cell transplantations (HSCT): 1) "People with previously untreated mantle cell lymphoma, *who are not going to have a stem cell transplant*" and 2) "adult patients with previously untreated mantle cell lymphoma *who are unsuitable for haematopoietic stem cell transplantation*". With that in mind, it should be noted that following a protocol amendment the LYM-3002 trial enrolled "patients ineligible *or not considered* for HSCT".[2] This amendment can be considered to be in line with the first but not second definition used in the final scope.

Later, *"concerns over the heterogeneity and interpretability of the study results resulted in a further amendment, realigning to the original criteria, and only patients who were not eligible for HSCT as assessed by the treating physician, that is, patients considered medically ineligible (e.g. due to age or the presence of co-morbid conditions that may have a negative impact on the tolerability to transplantation), were subsequently enrolled"*.[2] This second amendment could be considered to be in line with both the first and second definition used in the final scope.

The trial included 80 patients (16.4%; 38/243 in VR-CAP arm, 42/244 in R-CHOP arm) *"were suitable for HSCT from a medical perspective but availability and/or socio-economic reasons prevented access"*.

The ERG sought clarification of how these patients were accounted for. The company responded that these patients were balanced across the two patient groups and that post-hoc analysis revealed consistent treatment effect regardless of eligibility for HSCT.[3] The ERG found these statements to be true for overall survival but not progression-free survival. Progression-free survival was significantly favourable for VR-CAP for those patients that were medically ineligible for HSCT but non-significantly favourable for VR-CAP for patients who were medically eligible. The difference in statistical significance is likely due to the reduced patient numbers who were medically eligible (n=80 versus n=407). Overall the ERG does not think the difference in population inclusion criteria will significantly influence the overall results.

According to the clinical study report (CSR)[4], *"the baseline demographics, stratification factors, and disease diagnosis information for the subgroup of 80 subjects who were eligible for transplant by medical monitor assessment were well balanced between treatment groups and, in general, similar to the ITT population. Compared to the overall ITT population, subjects eligible for transplant were younger (median age 54 years versus 66 years in the ITT population), more subjects were Asian (53% versus 32% for ITT), and more subjects had an ECOG score of 0 at baseline (58% versus 40% for ITT population). (Attachment TSUB04A8,*

Table 13). The majority of subjects were from the ROW region (88% versus 69% in the ITT population); specifically, People's Republic of China (36% versus 20% in the ITT population) (Attachment TSUB01A8, Table 8). More transplant-eligible subjects had low IPI scores (50% versus 16% for ITT); fewer subjects had highintermediate scores (16% versus 35% for ITT) and high scores (3% versus 19% for ITT). More eligible subjects had Stage III disease (32% versus 20% for ITT), and fewer had Stage IV disease (60% versus 74% for ITT) (Attachment TSUB05A8, Table 12). Fewer transplant-eligible subjects (56%) had bone marrow involvement at baseline compared to 69% in the ITT population; the percentage of subjects with elevated LDH at baseline was 29% versus 36%, respectively (Attachment TSUB07A8, Table 14)."

Table 1 shows the "Demographic and Baseline Characteristics for Subjects Excluding Those Who are Ineligible for Bone Marrow Transplantation due to Age (60 Years or Older) or Medical Reasons by Medical Monitor; Intent-to-treat Analysis Set (Study 26866138-LYM-3002)" (table TSUB04A8 on page 292 of the CSR[4]).

Table 2 shows the "Distribution of Stratification Factors Based on IVRS for Subjects Excluding Those Who are Ineligible for Bone Marrow Transplantation due to Age (60 Years or Older) or Medical Reasons by Medical Monitor; Intent-to-treat Analysis Set (Study 26866138-LYM-3002)" (table TSUB05A8 on page 303 of the CSR[4]).

Table 3 shows the "Survival outcomes, medically ineligible for HSCT and medically eligible for HSCT analysis sets" (table 21 of the CS[2]).

Table 4 shows the "Post-hoc comparative efficacy assessment of survival outcomes in patients medically ineligible versus medically eligible for HSCT" (table 22 of the CS[2]).

Table 1. Baseline characteristics of HSCT-participants

	R-CHOP	VcR-CAP	Total
Analysis set: intent-to-treat subjects excluding those who are ineligible for bone marrow transplantation due to age (60 years or older) or medical reasons by medical monitor	42	38	80
Age (years) [a]			
N	42	38	80
≤ 65	42 (100.0%)	38 (100.0%)	80 (100.0%)
> 65	0	0	0
Mean (SD)	52.5 (5.69)	51.1 (6.38)	51.9 (6.04)
Median	54.0	53.0	54.0
Range	(34; 59)	(38; 59)	(34; 59)
Sex			
N	42	38	80
Male	30 (71.4%)	32 (84.2%)	62 (77.5%)
Female	12 (28.6%)	6 (15.8%)	18 (22.5%)
Race			
N	42	38	80
Asian	22 (52.4%)	20 (52.6%)	42 (52.5%)
White	20 (47.6%)	18 (47.4%)	38 (47.5%)
Weight (kg)			
N	42	38	80
Mean (SD)	70.81 (12.750)	68.68 (12.599)	69.80 (12.644)
Median	71.25	68.05	69.00
Range	(50.0; 95.0)	(38.5; 100.0)	(38.5; 100.0)
Height (cm)			
N	42	38	80
Mean (SD)	168.08 (7.019)	167.63 (8.205)	167.87 (7.560)
Median	168.00	168.00	168.00
Range	(154.0; 184.0)	(147.0; 185.0)	(147.0; 185.0)
BSA (m2)			
N	42	38	80
< 1.5	0	2 (5.3%)	2 (2.5%)
1.5 - 2	36 (85.7%)	31 (81.6%)	67 (83.8%)
> 2	6 (14.3%)	5 (13.2%)	11 (13.8%)
Mean (SD)	1.81 (0.183)	1.78 (0.198)	1.80 (0.189)
Median	1.82	1.79	1.80
Range	(1.5; 2.2)	(1.3; 2.2)	(1.3; 2.2)
ECOG			
N	42	38	80
0:Asymptomatic	23 (54.8%)	23 (60.5%)	46 (57.5%)
1:Symptomatic, fully ambulatory	17 (40.5%)	13 (34.2%)	30 (37.5%)
2:Symptomatic, in bed < 50% of the day	2 (4.8%)	2 (5.3%)	4 (5.0%)

Key: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone;
VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone.
kg=kilogram; cm=centimeter; BSA=Body Surface Area; ECOG=Eastern Cooperative Oncology Group.
[a]Age at the date of randomization.

Table 2. Distribution of stratification factors in HSCT-participants

	R-CHOP	VcR-CAP	Total
Analysis set: intent-to-treat subjects excluding those who are ineligible for bone marrow transplantation due to age (60 years or older) or medical reasons by medical monitor	42	38	80
IPI risk (IPI score)			
N	42	38	80
Low (0 - 1)	18 (42.9%)	22 (57.9%)	40 (50.0%)
Low-intermediate (2)	15 (35.7%)	10 (26.3%)	25 (31.3%)
High-intermediate (3)	7 (16.7%)	6 (15.8%)	13 (16.3%)
High (4 - 5)	2 (4.8%)	0	2 (2.5%)
Stage of disease at diagnosis			
N	42	38	80
Stage II	4 (9.5%)	3 (7.9%)	7 (8.8%)
Stage III	14 (33.3%)	11 (28.9%)	25 (31.3%)
Stage IV	24 (57.1%)	24 (63.2%)	48 (60.0%)

Key: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone; IPI=International Prognostic Index; IVRS=Interactive Voice Response System.

Table 3. Survival outcomes in HSCT-participants

	Medically ineligible for HSCT		**Medically eligible for HSCT**	
	VR-CAP (n=205)	**R-CHOP** (n=202)	**VR-CAP** (n=38)	**R-CHOP** (n=42)
Median PFS (IRC), months	22.8	14.4	32.6	12.0
HR (95% CI)[a]	0.63 (0.49; 0.81)		0.59 (0.31; 1.13)	
p-value	<0.001		0.108	
Median PFS (INV), months	28.3	15.0	42.6	20.6
HR (95% CI)[a]	0.50 (0.39; 0.65)		0.54 (0.28; 1.03)	
p-value	<0.001		0.057	
Median OS, months	NE	56.3	NE	47.3
HR (95% CI)[a]	0.83 (0.59; 1.17)		0.81 (0.33; 1.96)	
p-value	0.287		0.634	

Key: CI, confidence interval; CSR, clinical study report; HSCT, haematopoietic stem cell transplantation; INV, investigator; IPI, International Prognostic Index; IRC, independent review committee; HR, hazard ratio; NE, not estimable; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.
Notes: [a] HR estimate based on a Cox's model stratified by IPI risk and stage of disease.
Source: Drach et al. 2014[5]; LYM-3002 CSR[4].

Table 4. Post-hoc comparative efficacy assessment of survival outcomes in HSCT-participants

Endpoint	Chi-squared statistic	P-value
Median PFS (IRC)	0.0562	0.8127
Median PFS (INV)	0.8128	0.3673
Median PFS (alternative IRC)	0.2089	0.6476
Median OS	0.0006	0.9812

Key: HSCT, haematopoietic stem cell transplantation; INV, investigator; IRC, independent review committee; OS, overall survival; PFS, progression-free survival.

Baseline characteristics of participants from North American and Western Europe

The ERG report presents results for total population alongside results for the subgroup of North American and Western European participants which might be more applicable to the UK context. Table 5 shows the baseline characteristics for this subgroup (based on table 42 on page 128 of the CSR[4]).

Table 5. Baseline characteristics for participants from North America and Western Europe

[redacted]

Additional analyses

During the pre-meeting briefing (PMB) the committee requested two additional analyses based on the ERG preferred base case. For convenience, the original ERG preferred base case (as reported in the ERG report) is presented in table 6 to 8. Moreover, the incorporated corrections and amendments are now numbered.

First analysis requested by committee

The committee requested the following adjustments in the first analysis:

- Remove the 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)

Please note that the ERG excluded all-cause mortality for survival pre-progression (assumption number 13) when excluding the distinction between pre- and post-progression survival (assumption number 12) to prevent double counting. However, when the distinction in survival for patients with and without progression is incorporated, the ERG agrees with the Company that it is reasonable to incorporate all-cause mortality (given the low pre-progression mortality). Hence, as survival for patients with and without progression is distinguished, the ERG also added all-cause mortality to survival pre-progression:

- Add all-cause mortality to survival pre-progression (remove analysis number 13)

The results of this analysis (table 9) indicate that VR-CAP would be cost-effective for willing-to-pay thresholds above £31,576. Below this threshold, R-CHOP would be cost-effective.

Second analysis requested by committee

For the second analysis, in addition to the adjustments described for the first analysis, the committee requested to use the original utility for progressed patients in the second-line as incorporated by the Company (0.45) instead of the value proposed by the ERG (0.62). Hence, the following adjustment was made in addition to the adjustments described above for the first analysis:

- Incorporate a utility value of 0.45 for progressed patients in the second-line (remove assumption number 9)

The results of this analysis (table 10Table) indicate that VR-CAP would be cost-effective for willing-to-pay thresholds above £37,960. Below this threshold, R-bendamustine would be cost-effective until a willing-to-pay threshold of £5,323 at which R-CHOP becomes cost-effective.

Table 6: Original ERG preferred base case: VR-CAP versus R-CHOP

	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**
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) Exclude end-of life	4.11	£41,166	3.32	£24,672	0.79	£16,493	**£20,794**

	VR-CAP		R-CHOP		Incremental		ICER
	QALYs	**Costs**	**QALYs**	**Costs**	**QALYs**	**Costs**	**Cost per QALY gained**
costs							
ERG base case	**4.57**	**£44,140**	**3.93**	**£22,186**	**0.64**	**£21,955**	**£34,039**

Table 7: Original ERG preferred base case: VR-CAP versus R-FC

	VR-CAP		R-FC		Incremental		ICER
	QALYs	Costs	QALYs	Costs	QALYs	Costs	Cost per QALY gained
Company base-case	**4.14**	**£45,724**	**3.36**	**£31,222**	**0.79**	**£14,503**	**£18,430**
1) Correction unit prices	4.12	£46,210	3.34	£31,863	0.78	£14,348	**£18,424**
2) Correction error adverse events	4.12	£45,808	3.34	£31,236	0.79	£14,572	**£18,492**
3) Correction costs concomitant medication	4.13	£46,137	3.34	£31,586	0.79	£14,551	**£18,506**
4) Age, weight and unit prices were not included as stochastic parameters	4.13	£45,684	3.35	£31,208	0.78	£14,475	**£18,643**
5) Proportion of patients receiving treatment included as stochastic parameter	4.17	£45,489	3.38	£30,911	0.78	£14,578	**£18,641**
6) Include half-cycle correction	4.13	£43,795	3.34	£29,855	0.79	£13,940	**£17,596**
7) PFS adjusted according to HR for European Union	4.08	£45,860	3.35	£31,148	0.73	£14,713	**£20,178**
8) Start second line treatment at time of progression	4.08	£46,267	3.31	£31,670	0.77	£14,567	**£18,949**
9) Utility progression 2nd line treatment based upon disutility Doorduijn	4.54	£45,624	3.88	£31,095	0.67	£14,528	**£21,798**
10) Per-protocol dosage	4.14	£48,838	3.36	£31,218	0.78	£17,620	**£22,632**
11) Primary assessment of progression	4.12	£45,521	3.40	£31,224	0.71	£14,297	**£20,025**
12) Survival is not distinguished between patients with and without progression	3.95	£42,843	3.25	£29,038	0.70	£13,804	**£19,742**
13) Exclude all-cause mortality	4.60	£45,871	3.53	£31,543	1.07	£14,329	**£13,391**

	VR-CAP		R-FC		Incremental		ICER
	QALYs	**Costs**	**QALYs**	**Costs**	**QALYs**	**Costs**	**Cost per QALY gained**
14) Exponential distribution for PFS in the VR-CAP arm	3.90	£47,025	3.38	£31,177	0.52	£15,848	**£30,622**
15) Indirect treatment comparison for efficacy R-FC and R-bendamustine	4.13	£45,601	2.58	£29,440	1.56	£16,160	**£10,361**
16) Exclude end-of life costs	4.11	£41,166	3.33	£26,408	0.78	£14,758	**£18,960**
ERG base case	**4.57**	**£44,140**	**2.96**	**£22,370**	**1.62**	**£21,770**	**£13,455**

Table 8: Original ERG preferred base case: VR-CAP versus R-Bendamustine

	VR-CAP		R-Bendamustine		Incremental		ICER
	QALYs	Costs	QALYs	Costs	QALYs	Costs	Cost per QALY gained
Company base-case	**4.14**	**£45,724**	**3.35**	**£34.883**	**0.79**	**£10,842**	**£13,725**
1) Correction unit prices	4.12	£46,210	3.34	£35,391	0.78	£10,819	**£13,838**
2) Correction error adverse events	4.12	£45,808	3.33	£34,867	0.79	£10,941	**£13,831**
3) Correction costs concomitant medication	4.13	£46,137	3.34	£35,180	0.79	£10,957	**£13,880**
4) Age, weight and unit prices were not included as stochastic parameters	4.13	£45,684	3.35	£34,847	0.78	£10,836	**£13,902**
5) Proportion of patients receiving treatment included as stochastic parameter	4.17	£45,489	3.38	£34,603	0.79	£10,886	**£13,866**
6) Include half-cycle correction	4.13	£43,795	3.33	£33,157	0.80	£10,639	**£13,377**
7) PFS adjusted according to HR for European Union	4.08	£45,860	3.35	£34,806	0.73	£11,055	**£15,099**
8) Start second line treatment at time of progression	4.08	£46,267	3.31	£35,324	0.77	£10,943	**£14,222**
9) Utility progression 2nd line treatment based upon disutility Doorduijn	4.54	£45,624	3.88	£34,747	0.67	£10,877	**£16,288**
10) Per-protocol dosage	4.14	£48,838	3.36	£34,873	0.78	£13,965	**£17,867**
11) Primary assessment of progression	4.12	£45,521	3.40	£34,853	0.72	£10,668	**£14,872**
12) Survival is not distinguished between patients with and without progression	3.95	£42,843	3.25	£32,676	0.70	£10,166	**£14,490**
13) Exclude all-cause mortality	4.60	£45,871	3.53	£35,191	1.07	£10,680	**£ 9,953**
14) Exponential distribution for PFS in the VR-CAP arm	3.90	£47,025	3.38	£34,821	0.52	£12,204	**£23,446**
15) Indirect treatment comparison for efficacy R-FC and R-bendamustine	4.13	£45,601	3.64	£30,422	0.50	£15,179	**£30,398**
16) Exclude end-of life costs	4.11	£41,166	3.33	£30,063	0.78	£11,103	**£14,208**

	VR-CAP		R-Bendamustine		Incremental		ICER
	QALYs	Costs	QALYs	Costs	QALYs	Costs	Cost per QALY gained
ERG base case	**4.57**	**£44,140**	**3.43**	**£24,957**	**1.14**	**£19,184**	**£16,762**

Table 9: First analysis requested by the committee during PMB (excluding analyses number 7, 12-14).

Treatment	Expected outcomes		Incremental analysis			
	Costs	QALY	Comparator	ΔCosts	ΔQALY	ICER
R-CHOP	£24,537	3.86				
R-FC	£25,370	2.81	R-CHOP	£832	-1.05	Dominated by R-CHOP
R-bendamustine	£25,873	3.79	R-CHOP	£1,336	-0.07	Dominated by R-CHOP
VR-CAP	£43,453	4.46	R-CHOP	£18,915	0.60	£31,576

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.

Table 10: Second analysis requested by the committee during PMB (excluding analyses number 7, 9, 12-14).

Treatment	Expected outcomes		Incremental analysis			
	Costs	QALY	Comparator	ΔCosts	ΔQALY	ICER
R-CHOP	£24,547	3.29				
R-FC	£25,346	2.52	R-CHOP	£798	-0.76	Dominated by R-CHOP
R-bendamustine	£25,855	3.53	R-CHOP	£1,308	0.25	£5,323
VR-CAP	£43,430	4.00	R-bendamustine	£17,576	0.46	£37,960

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.

References

[1] 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

[2] Janssen-Cilag International NV. Single technology appraisal. Lymphoma (mantle cell, untreated) – bortezomib [ID724] - company evidence submission to National Institute of Health and Care Excellence. Janssen-Cilag International NV. 26 June 2015: 206.

[3] Janssen-Cilag International NV. Lymphoma (mantle cell, untreated) – bortezomib [ID724]. Response to request for clarification from the ERG. Janssen-Cilag International NV. 2015: 32.

[4] Janssen Research & Development. *A randomized, open-label, multicenter Phase III study of the combination of rituximab, cyclophosphamide, doxorubicin, VELCADE, and prednisone (VcR-CAP) or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in patients with newly diagnosed mantle cell lymphoma who are not eligible for a bone marrow transplant. (Clinical Study Report; EDMS-ERI-25850170:2.0) [Data on file provided with the company's submission]*, 27 May 2014. 1416p.

[5] Drach J, Huang H, Samoilova O, Belch A, Farber CM, Bosly A, et al. Efficacy and safety of frontline bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) vs R-CHOP in a subset of newly diagnosed mantle cell lymphoma (MCL) patients (pts) medically eligible for transplantation in the randomized Phase 3 LYM-3002 study (NCT00722137). In: 56th American Society of Hematology (ASH) Annual Meeting and Exposition; San Francisco, CA, USA, 6-9 December 2014: Abstract 3064.