NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Lymphoma (mantle cell, untreated) – bortezomib [ID724]

Company evidence submission

June 2015

File name	Version	Contains confidential information	Date
ID724_Janssen_Lymphoma (mantle cell, untreated) bortezomib	V1.0	Yes	26 June 2015
ID724_Janssen_Lymphoma (mantle cell, untreated) bortezomib	V1.1	No	13 August 2015

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

Contents

Instructions for companies 2
Tables and figures 5
Abbreviations 8
1 Executive summary 12
1.1 Statement of decision problem 12
1.2 Description of the technology being appraised 15
1.3 Summary of the clinical effectiveness analysis 15
1.4 Summary of the cost-effectiveness analysis 16
2 The technology 19
2.1 Description of the technology 19
2.2 Marketing authorisation and health technology assessment 19
2.3 Administration and costs of the technology 20
2.4 Changes in service provision and management 21
2.5 Innovation 22
3 Health condition and position of the technology in the treatment pathway 24
3.1 Disease overview 24
3.2 Clinical pathway of care 25
3.3 Life expectancy and epidemiology 28
3.4 NICE guidance/guidelines 28
3.5 Clinical guidelines 29
3.6 Issues in current clinical practice 29
3.7 Equality 30
4 Clinical effectiveness 31
4.1 Identification and selection of relevant studies 31
4.2 List of relevant randomised controlled trials 37
4.3 Summary of methodology of the relevant randomised controlled trials 37
4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials 42
4.5 Participant flow in the relevant randomised controlled trials 43
4.6 Quality assessment of the relevant randomised controlled trials 47
4.7 Clinical effectiveness results of the relevant randomised controlled trials 48
4.8 Subgroup analysis 62
4.9 Meta-analysis 65
4.10 Indirect and mixed treatment comparisons 65
4.11 Non-randomised and non-controlled evidence 72
4.12 Adverse reactions 75
4.13 Interpretation of clinical effectiveness and safety evidence 85
4.14 Ongoing studies 90
5 Cost effectiveness 91
5.1 Published cost-effectiveness studies 92
5.2 De novo analysis 95
5.3 Clinical parameters and variables 102
5.4 Measurement and valuation of health effects 123
5.5 Cost and healthcare resource use identification, measurement and valuation 142
5.6 Summary of base case de novo analysis inputs and assumptions 161
5.7 Base case results 166
5.8 Sensitivity analyses 171
5.9 Subgroup analysis 185
5.10 Validation 186

5.11 Interpretation and conclusions of economic evidence 191
6 Assessment of factors relevant to the NHS and other parties 194
7 References 198

Tables and figures

Table 1: The decision problem ... 13
Table 2: Technology being appraised ... 15
Table 3: Pairwise incremental cost-effectiveness results ... 18
Table 4: Full incremental analysis for VR-CAP and all three comparators ... 18
Table 5: Administration and costs of the technology being appraised ... 21
Table 6: Clinical guidelines for the management of MCL ... 29
Table 7: Eligibility criteria applied to systematic search results ... 33
Table 8: List of relevant RCTs for VR-CAP ... 37
Table 9: Summary of LYM-3002 trial methodology ... 39
Table 10: Summary of statistical analyses in LYM-3002 trial ... 42
Table 11: Key baseline demographics and disease characteristics of patients, ITT analysis set ... 46
Table 12: Summary of quality assessment ... 48
Table 13: PFS based on IRC assessment, ITT analysis set ... 49
Table 14: PFS based on investigator assessment, ITT analysis set ... 51
Table 15: PFS based on IRC alternative assessment, ITT analysis set ... 52
Table 16: Duration of TFI, safety analysis set ... 54
Table 17: Best overall response, response evaluable analysis set ... 55
Table 18: TTR and DoR, response evaluable analysis set ... 56
Table 19: OS, ITT analysis set ... 57
Table 20: Summary of PRO, HRQL analysis set ... 61
Table 21: Survival outcomes, medically ineligible for HSCT and medically eligible for HSCT analysis sets ... 64
Table 22: Post-hoc comparative efficacy assessment of survival outcomes in patients medically ineligible versus medically eligible for HSCT ... 64
Table 23: List of relevant RCTs for comparators to VR-CAP included in the final appraisal scope ... 66
Table 24: Bucher indirect comparison analyses of PFS and OS ... 71
Table 25: List of relevant non-RCTs for potential comparators to VR-CAP ... 73
Table 26: Multivariate analysis on OS in patients receiving systemic therapy for MCL in the NLG observational study, adjusted for gender and MIPI ... 74
Table 27: Safety and tolerability, safety analysis set ... 76
Table 28: Common AEs, safety analysis set ... 77
Table 29: Inclusion criteria for cost-effectiveness studies ... 93
Table 30: Features of the *de novo* analysis ... 97
Table 31: Baseline characteristics of all patients versus non-HSCT eligible patients only in the LYM-3002 trial ... 99
Table 32: Definitions of PFS, PrePS and PPS ... 103
Table 33: Goodness of fit for OS curves ... 106
Table 34: Goodness of fit of OS curves based on AIC/BIC, visual fit and long-term fit ... 106
Table 35: Goodness of fit of PFS curves ... 112
Table 36: Goodness of fit of PFS curves based on AIC/BIC, visual fit and long-term fit ... 113
Table 37: Distribution of patients over regimens at subsequent treatment lines ... 116
Table 38: Categories of second-line treatment used for regression analysis ... 117
Table 39: Mean duration and PFS for second-line treatment ... 120
Table 40: Sources of data used for exploratory analysis of impact of inclusion of R-maintenance in the model ... 122
Table 41: EQ-5D compliance in the LYM-3002 trial ... 124
Table 42: Utilities from the LYM-3002 trial ... 125
Table 43: Inclusion criteria for utility studies ... 126
Table 44: Key characteristics of the eligible utility studies ... 132
Table 45: AEs, cycle probabilities and duration ... 139

Table 46: Utility decrements for AEs from the LYM-3002 trial[56] 140
Table 47: Summary of utility values for cost-effectiveness analysis..... 140
Table 48: Drug acquisition costs for first- and second-line treatments..... 143
Table 49: Administration costs 144
Table 50: Average number of vials required per administration of IV drugs dosed per m^2. 145
Table 51: Dosing regimens 146
Table 52: Drug acquisition and administration costs 149
Table 53: Percentage of patients receiving first-line treatment per cycle (CSR table 20)[56] 150
Table 54: Difference between average dose received and per protocol dose per cycle in the LYM-3002 trial (CSR table TSS02B)[56]..... 151
Table 55: Medical resource use by health state 154
Table 56: Concomitant medication; percentage of patients using and dosing 155
Table 57: Drug acquisition costs for concomitant therapies..... 157
Table 58: Average number of vials required per administration of drugs dosed per m^2 or kg 159
Table 59: Number of transfusions 159
Table 60: Weekly costs of transfusions and concomitant medications by cycle..... 159
Table 61: Unit costs for adverse events (NHS Reference Costs 2013-2014)[124]..... 160
Table 62: Weekly costs attributable to AEs 161
Table 63: Key scenario analyses 164
Table 64: Secondary scenario analyses..... 165
Table 65: Base case results, VR-CAP versus R-CHOP 167
Table 66: Summary of model results compared with clinical data (years)..... 167
Table 67: Summary of QALY gain by health state..... 170
Table 68: Summary of life years gained by health state 170
Table 69: Disaggregated costs by health state, VR-CAP vs R-CHOP 171
Table 70: Disaggregated costs by cost category, VR-CAP vs R-CHOP 171
Table 71: Results of key scenario analyses 175
Table 72: Results of secondary scenario analyses..... 176
Table 73: Base case results, VR-CAP versus exploratory comparators 181
Table 74: Full incremental analysis for VR-CAP and all three comparators..... 181
Table 75: Base case results, VR-CAP versus exploratory comparators using HRs from Bucher indirect comparison..... 182
Table 76: Threshold analysis for exploratory comparators vs R-CHOP..... 182
Table 77: Results of scenario analyses including R-maintenance 183
Table 78: Threshold analysis for R-maintenance 184
Table 79: Current market share in the population eligible for VR-CAP 195
Table 80: Budget impact of VR-CAP in NHS England..... 196
Table 81: Budget impact of VR-CAP in NHS Wales 197

Figure 1: Clinical pathway of care for the first-line treatment of MCL in England and Wales 27
Figure 2: PRISMA flow diagram of the literature search process..... 35
Figure 3: Subject disposition 44
Figure 4: Kaplan–Meier plot of PFS based on IRC assessment, ITT analysis set 50
Figure 5: Kaplan–Meier plot of PFS based on IRC alternative assessment, ITT analysis set 52
Figure 6: Kaplan–Meier plot of OS, ITT analysis set..... 58
Figure 7: EORTC QLQ-C30 global health status over time, ITT analysis set..... 59
Figure 8: PFS subgroup analysis based on IRC assessment, ITT analysis set 62
Figure 9: Potential network of evidence for indirect comparison analyses of survival outcomes 67
Figure 10: PRISMA flow diagram of the cost-effectiveness studies..... 94
Figure 11: Model diagram 96

Figure 12: Model summary diagram 101
Figure 13: Problems with fitting curves to OS data 104
Figure 14: PPS in the LYM-3002 trial 105
Figure 15: Fit of parametric curves to OS (progression based on alternative IRC) 107
Figure 16: Long-term fit of parametric curves to OS (progression based on alternative IRC) 108
Figure 17: Base case exponential disease-specific OS curves 109
Figure 18: Base case exponential OS curves with general population mortality added to non-progressed curves 110
Figure 19: Log cumulative hazard plots for PFS 111
Figure 20: Fit of parametric models to PFS based on alternative IRC assessment 113
Figure 21: Long-term fit of parametric models to PFS based on alternative IRC assessment 114
Figure 22: Base case log-logistic PFS curves 114
Figure 23: TFI as observed in the LYM-3002 trial 115
Figure 24: Regression analysis OS from start of subsequent treatment 118
Figure 25: OS from start of second-line treatment 119
Figure 26: PRISMA flow diagram of the utility studies 130
Figure 27: Markov trace for VR-CAP 168
Figure 28: Markov trace for R-CHOP 168
Figure 29: Cumulative uptake of second-line treatment 169
Figure 30: Cost-effectiveness plane from 1,000 PSA iterations 172
Figure 31: Incremental cost-effectiveness acceptability curve for VR-CAP versus R-CHOP 173
Figure 32: Tornado diagram displaying the ICER sensitivity of the 10 most influential model inputs 174
Figure 33: Model PFS projections 187
Figure 34: Model overall survival projections 188
Figure 35: Model estimates of OS by arm versus UK general population 188
Figure 36: Comparison of R-CHOP survival in the LYM-3002 trial to available observational datasets 191

Abbreviations

ABMT	autologous bone marrow transplantation
AE	adverse event
AIC	Akaike information criterion
ALT	alanine transaminase
Ara-C	cytarabine
AST	aspartate transaminase
AWMSG	All Wales Medicines Strategy Group
BFI	Brief Fatigue Inventory
BIC	Bayesian information criterion
BL	baseline
BSA	body surface area
C	cycle
CADTH	Canadian Agency for Drugs and Technologies in Health
CDF	Cancer Drugs Fund
Chemo	chemotherapy
CHMP	Committee for Medicinal Products for Human Use
CHOP	cyclophosphamide, doxorubicin, vincristine and prednisone
CFB	change from baseline
CI	confidence interval
Combo	combination
CT	computed tomography
CR	complete response
CRu	complete response unconfirmed
CVP	cyclophosphamide, vincristine and prednisone
D	day
DoR	duration of response
DLBLC	diffuse large B-cell lymphoma
ECOG	Eastern Cooperative Oncology Group
EED	NHS Economic Evaluation Database
eMIT	electronic Market Information Tool
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EOT	end of treatment
EPAR	European public assessment report

EQ-5D	EuroQoL-5 Dimension Questionnaire
ESMO	European Society for Medical Oncology
Exp	experimental
FC	fludarabine and cyclophosphamide
FIS	fatigue interference score
FL	follicular lymphoma
G-CSF	granulocyte-colony stimulating agent
GCP	good clinical practice
GHS	global health status
GI	gastrointestinal
GLSG	Grade Lymphoma Study Group
HMRN	Haematological Malignancy Research Network
HR	hazard ratio
HRG	Healthcare Research Group
HRQL	health-related quality of life
HSCT	haematopoietic stem cell transplantation
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IDMC	independent data monitoring committee
INV	investigator
IPI	International Prognostic Index
IRC	independent review committee
ISPOR	International Society For Pharmacoeconomics and Outcomes Research
ITT	intent-to-treat
IV	intravenous
IWRC	International Workshop Response Criteria
KM	Kaplan–Meier
LDH	lactate dehydrogenase
LY	life year
MCL	mantle cell lymphoma
MIMS	Monthly Index of Medical Specialities
MIPI	MCL International Prognostic Index
MM	multiple myeloma
MRU	medical resource use
N/A	not applicable

N	number of patients
NCRI	National Cancer Research Institute
NE	not estimable
NHL	non-Hodgkin's lymphoma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NLG	Nordic Lymphoma Group
Nordic MCL2	rituximab and cytarabine with cyclophosphamide, doxorubicin, vincristine and prednisone
NR	not reported
OR	odds ratio
ORR	overall response rate
OS	overall survival
PBSCT	peripheral blood stem cell transplantation
PD	progressive disease
PFS	progression-free survival
PP	per protocol
PPS	post-progression survival
PR	partial response
PrePS	pre-progression survival
PRO	patient-reported outcome
PS	performance status
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life year
QoL	quality of life
R	rituximab
R-bendamustine	rituximab with bendamustine
RBC	red blood cell
R-chlorambucil	rituximab with chlorambucil
R-CHOP	rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone
R-CVP	rituximab with cyclophosphamide, vincristine and prednisone
R-cytarabine	rituximab with cytarabine
R-FC	rituximab with fludarabine and cyclophosphamide

RCAP	rituximab, cyclophosphamide, doxorubicin and prednisone
RCT	randomised controlled trial
SAE	serious adverse event
SD	standard deviation
SE	standard error
SMC	Scottish Medicines Consortium
SmPC	summary of product characteristics
STA	single technology appraisal
StiL	Study Group of indolent Lymphomas
TFI	treatment-free interval
TTF	time to treatment failure
TTNT	time to next treatment
TTP	time to progression
TTR	time to response
ULN	upper limit of normal
VAS	visual analogue scale
VAT	value added tax
VR-CAP	bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone
vs	versus
WBC	white blood cell count
WFS	worst fatigue score
WTP	willingness to pay

1 Executive summary

Mantle cell lymphoma (MCL) is an incurable and aggressive sub-type of non-Hodgkin's lymphoma (NHL) affecting approximately 500 patients in England and Wales each year (see section 3). For previously untreated MCL patients that are unsuitable for haematopoietic stem cell transplantation (HSCT), no licensed treatment regimens or treatment regimens with proven long-term survival benefit are available for induction therapy (see section 3). Thus, these patients present a significant challenge to the treating haematologist. The general pattern of disease progression is therefore one of relapse and remission, resulting in a median overall survival (OS) of less than 5 years with current induction therapy options, including the established standard of care in National Health Service (NHS) England and Wales, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) treatment (see section 3).

There is a clear unmet need for a licensed induction therapy regimen with proven benefit for MCL patients for whom HSCT is unsuitable. Bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone (VR-CAP) meets this unmet need, offering a cost-effective treatment option with minimal budget impact and significant clinical benefit to NHS England and Wales.

1.1 Statement of decision problem

The decision problem addressed in this submission matches the final appraisal scope issued by NICE, as summarised in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with previously untreated mantle cell lymphoma, who are not going to have a stem cell transplant.	People with previously untreated mantle cell lymphoma, who are not going to have a stem cell transplant.	-
Intervention	Bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (VR-CAP).	Bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (VR-CAP).	-
Comparator (s)	• R-CHOP (rituximab, cyclophosphamide, doxorubicin and prednisolone) • bendamustine plus rituximab (with or without cytarabine) • R-FC (rituximab, fludarabine and cyclophosphamide)	• R-CHOP (rituximab, cyclophosphamide, doxorubicin and prednisolone) • bendamustine plus rituximab (with or without cytarabine) • R-FC (rituximab, fludarabine and cyclophosphamide)	R-CHOP is established standard of care with alternative regimens used only where they are 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 transparency, the other comparators included in the decision problem are also addressed in this submission.
Outcomes	• overall survival • progression-free survival • overall response rate • duration of response/remission • time to new anti-lymphoma treatment/time to progression • adverse effects of treatment • health-related quality of life	• overall survival • progression-free survival • overall response rate • duration of response/remission • time to new anti-lymphoma treatment/time to progression • adverse effects of treatment • health-related quality of life	-

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE 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.	-
Special considerations including issues related to equity or equality	None stated.	None.	-
Key: NHS, National Health Service; NICE, National Institute for Health and Care Excellence.			

1.2 Description of the technology being appraised

Details of the technology being appraised in this submission are summarised in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Bortezomib (Velcade®)
Marketing authorisation status	Marketing authorisation approved by the European Commission on 2 February 2015.
Indications and any restriction(s) as described in the SmPC	Bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone for the treatment of adult patients with previously untreated MCL who are unsuitable for HSCT.
Method of administration and dosage	Bortezomib 1.3mg/m^2 on days 1, 4, 8 and 11 of a 21-day cycle by IV or subcutaneous injection.
Key: HSCT, haematopoietic stem cell transplantation; IV, intravenous; MCL, mantle cell lymphoma; SmPC, summary of product characteristics.	

1.3 Summary of the clinical effectiveness analysis

LYM-3002 is a randomised, open-label, multicentre, Phase III study, designed to determine whether the VR-CAP or R-CHOP chemotherapy induction regimen provides greater benefit in newly diagnosed MCL patients with advanced disease who are unsuitable for HSCT.

In this pivotal regulatory trial, patients who were treated with VR-CAP displayed a deep and durable response to induction therapy that generated significant clinical benefit, as demonstrated by the significant prolongation of progression-free survival (PFS) (primary endpoint) compared with that observed in patients treated with the established standard of care (R-CHOP) (see section 4.7):

- Median PFS (by independent review committee [IRC] assessment) was 24.7 months for VR-CAP versus 14.4 months for R-CHOP (hazard ratio [HR]=0.63; p<0.001). This exceeds the hypothesised treatment effect of 40% improvement in PFS.
- Complete response rates were 53.3% in the VR-CAP group versus 41.7% in the R-CHOP group (odds ratio [OR]=1.688; p=0.007), and the median

duration of complete response (CR) was more than twice as long in patients treated with VR-CAP: 42.1 months versus 18.0 months.

- A fixed treatment duration of approximately 4 months resulted in a median treatment-free interval (TFI) (by IRC assessment) of 40.6 months in patients treated with VR-CAP, nearly double the TFI associated with R-CHOP therapy of 20.5 months (HR=0.50, p<0.001).
- Median OS is yet to be reached for VR-CAP, compared to a median of 56.3 months for R-CHOP, suggesting a survival benefit to patients beyond the current standard of care.
- A consistent trend for improved OS in the VR-CAP treatment arm was observed with a clear separation of Kaplan–Meier curves from 12 months and a 4-year survival rate estimated at 64% (vs 54% for R-CHOP).

VR-CAP thus has the potential to change the treatment landscape in newly diagnosed MCL, offering an improved long-term prognosis to patients with this rare but aggressive condition.

1.4 Summary of the cost-effectiveness analysis

To assess the cost effectiveness of VR-CAP in patients with previously untreated MCL for whom HSCT is unsuitable, a *de novo* Markov model was constructed. This analysis was primarily informed by the LYM-3002 trial, which compared induction with VR-CAP to induction with R-CHOP.

R-CHOP is the established standard of care in the UK for previously untreated MCL patients for whom HSCT is unsuitable. Therefore, the model base case was presented versus R-CHOP. For completeness, exploratory analyses were presented versus other comparators included in the final appraisal scope that are used in UK practice in patients for whom either R-CHOP or VR-CAP is unsuitable due to frailty arising from advanced age and/or comorbidities.

A five health state model was used to evaluate the cost effectiveness of VR-CAP (PFS first-line treatment, progressed from first-line treatment, PFS second-line treatment, progressed from second-line treatment, and death). Progression status was used as a surrogate marker for overall survival.

Clinical outcomes from LYM-3002 were used to estimate the cost effectiveness of VR-CAP versus R-CHOP. An assumption of equal efficacy to R-CHOP was made for other comparators, informed by clinical trial evidence, indirect comparison and clinical expert input.

VR-CAP is shown to be cost effective as first-line induction for patients with MCL versus R-CHOP, rituximab with fludarabine and cyclophosphamide (R-FC) and rituximab with bendamustine (R-bendamustine), with base case deterministic incremental cost-effectiveness ratios (ICERs) of £20,362, £18,509 and £13,797, respectively, per quality-adjusted life year (QALY) gained, as shown in Table 3. Full incremental analysis is presented in Table 4.

Probabilistic sensitivity analyses show VR-CAP to be cost effective at a willingness to pay (WTP) threshold of £30,000 per QALY gained in over 86.5% of probabilistic model iterations versus R-CHOP. Key model sensitivities were uncertainty around PFS and survival model fit parameters and the utility of patients who had progressed from second-line treatment. In all clinically plausible scenario analyses tested, the ICER remained below £30,000.

Table 3: Pairwise incremental cost-effectiveness results

	Total			Incremental			ICER (VR-CAP vs comparator)
	Costs	Life years	QALYs	Costs	Life years	QALYs	
VR-CAP	£45,838	7.67	4.15				
R-CHOP	£29,625	6.66	3.35	£16,213	1.01	0.80	£20,362
R-FC	£31,370	6.66	3.36	£14,467	1.01	0.78	£18,509
R-bendamustine	£35,011	6.66	3.36	£10,826	1.01	0.78	£13,797

Key: ICER, incremental cost-effectiveness ratio; LYs, life years; 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.

Table 4: Full incremental analysis for VR-CAP and all three 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.

2 The technology

2.1 Description of the technology

Brand name: Velcade®

UK approved name: Bortezomib

Therapeutic class: Antineoplastic agents/other antineoplastic agents

Bortezomib is a highly selective proteasome inhibitor specifically designed to inhibit the chymotrypsin-like activity of the 26S proteasome in mammalian cells.[1] 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.

Bortezomib-mediated proteasome inhibition affects cancer cells in a number of ways, including (but not limited to) altering regulatory proteins that control cell cycle progression and altering regulatory proteins that activate nuclear factor kappa B (NF-kB), a transcription factor whose activation is required for many aspects of tumourigenesis. Ultimately, bortezomib-mediated proteasome inhibition results in cell cycle arrest and the induction of cancer cell death (apoptosis), with experiments demonstrating that cancer cells are more sensitive to the pro-apoptotic effects of proteasome inhibition than normal cells.[1, 2]

Bortezomib demonstrates a synergistic and additive effect when administered alongside other clinically active agents in MCL, such as cytotoxic agents.[2]

2.2 Marketing authorisation and health technology assessment

VR-CAP received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on 18 December 2014 for the treatment of adult patients with previously untreated MCL who are unsuitable for HSCT. This was approved by the European Commission for a marketing authorisation on 2 February 2015.

In accordance with the summary of product characteristics (SmPC) for bortezomib presented in Appendix 1, there are no restrictions on use, but contraindications of

hypersensitivity to the active substance or to any listed excipients and of acute diffuse infiltrative pulmonary and pericardial disease are noted.

The European public assessment report (EPAR), presented in Appendix 2, did not reference any issues with the clinical evidence base supporting the use of VR-CAP for the treatment of adult patients with previously untreated MCL who are unsuitable for HSCT. Outside of Europe, bortezomib has marketing authorisation for the treatment of adult patients with previously untreated MCL who are unsuitable for HSCT in US, Canada, Costa Rica, Egypt, El Salvador, Iran, Lebanon, Peru and Syria.

In the UK, an application to the Scottish Medicines Consortium (SMC) was submitted on 2 April 2015, and final advice is expected in September 2015.

2.3 Administration and costs of the technology

Bortezomib treatment must be initiated and administered under the supervision of a physician qualified and experienced in the use of chemotherapeutic agents. Bortezomib is provided as a powder for solution and must be reconstituted by a healthcare professional.

Details of the treatment regimen and costs associated with bortezomib are summarised in Table 5.

Table 5: Administration and costs of the technology being appraised

	Cost/Description	Source
Pharmaceutical formulation	Powder for solution for injection.	SmPC
Acquisition cost (excluding VAT)[a]	£762.38 for a 3.5mg vial.	MIMS
Method of administration	Intravenous or subcutaneous injection.	SmPC
Doses	1.3mg/m^2	SmPC
Dosing frequency	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.	SmPC
Average length of a course of treatment	As noted above, the 3-week period comprises one cycle. Six cycles are recommended, although for patients with a response first documented at cycle 6, two additional cycles may be given.	MIMS LYM-3002
Average cost of a course of treatment	£16,009.98 Based on patients receiving a median of 21 doses of bortezomib as per trial data.	MIMS LYM-3002
Anticipated average interval between courses of treatments	Additional courses of treatment would not be given in the first-line setting. There are no data on the use of VR-CAP retreatment in MCL.	SmPC
Anticipated number of repeat courses of treatments	As above, additional courses of treatment would not be given in the first-line setting.	SmPC
Dose adjustments	Dose adjustments should be made in accordance with Table 5 of the SmPC. Treatment must be withheld at the onset of any ≥ Grade 3 bortezomib-related non-haematological toxicities (excluding neuropathy) or ≥ Grade 3 haematological toxicities.	SmPC
Anticipated care setting	Hospital or clinic setting in established haematology day-care units.	SmPC

Key: MCL, mantle cell lymphoma; MIMS, Monthly Index of Medical Specialities; SmPC, summary of product characteristics; VAT, value added tax, VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.
Notes: [a], list price.

2.4 Changes in service provision and management

Bortezomib does not require any additional tests or investigations beyond those used to confirm MCL.

Suitability for HSCT in line with the bortezomib indication in previously untreated MCL is assessed routinely as it informs the initial therapeutic decision in current practice (see section 3), and again, this does not require any additional tests or investigations beyond those routinely performed in patients diagnosed with MCL.

Bortezomib is administered in a hospital or clinic setting in established haematology day-care units. These already have the staffing and infrastructure needed for the administration of treatments for MCL, and the administration of bortezomib would utilise this existing NHS infrastructure.

Bortezomib is administered in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (RCAP) for the treatment of adult patients with previously untreated MCL for whom HSCT is unsuitable. This RCAP backbone is currently used to treat MCL as part of the R-CHOP regimen (see section 3) and is thus familiar to haematologists who would be administering VR-CAP in practice. Bortezomib is also familiar to haematologists as it is currently used to treat multiple myeloma in accordance with NICE guidance.[3-5]

Bortezomib requires administration on two additional days within the 21-day treatment cycle compared with vincristine, the agent bortezomib replaces in the R-CHOP regimen.[1] This represents the main additional resource use to the NHS, as captured in the economic model presented in section 5. Monitoring requirements are not impacted by the introduction of bortezomib as monitoring is conducted based upon the number of treatment cycles in practice, rather than the number of drug administrations.[6]

Finally, in addition to the RCAP backbone, granulocyte-colony stimulating factor (G-CSF) may be administered alongside bortezomib for the treatment of neutropenia (according to local standard practice), and platelet transfusion should be considered for the treatment of thrombocytopenia when clinically appropriate.[1]

2.5 Innovation

MCL is a rare but aggressive type of NHL (see section 3). MCL has historically been one of the most difficult types of NHL to treat, with one of the poorest outcomes of all subtypes of lymphoma (see section 3.3).

HSCT is unsuitable for the majority of newly diagnosed MCL patients due to frailty as a result of advanced age and/or comorbidities (see section 3). For these patients, there are currently no licensed treatment regimens, and no regimens have been recommended by NICE for the treatment of MCL in the induction setting. UK guidelines recommend treatment with a rituximab-based chemotherapy induction regimen[7], and although patients often respond well to such therapy initially, the duration of remission is generally short, and the median OS is less than 5 years (see section 3.3).

There is a clear unmet need for a first-line, induction therapy regimen that could improve the long-term prognosis of MCL patients for whom HSCT is unsuitable. VR-CAP meets this unmet need with the potential to change the treatment landscape in newly diagnosed MCL, offering a significantly improved long-term prognosis that represents a step-change in the management of this condition.

3 Health condition and position of the technology in the treatment pathway

3.1 Disease overview

NHL describes a diverse group of blood cancers characterised by the abnormal proliferation of malignant lymphocytes; this group accounts for approximately 3-4% of all cancer cases worldwide.[8, 9] MCL is a rare and often aggressive sub-type of B-cell lymphoma that represents approximately 6% of all NHL cases.[10-12]

MCL is genetically characterised by the chromosomal translocation t (11;14) (q13;q32), which results in overexpression of the cell cycle protein cyclin D1.[13, 14] This deregulates the cell cycle, facilitating the malignant transformation of B-cells (MCL cells) that grow uncontrollably and form tumours in the lymph nodes.[15] The most common symptom at diagnosis (found in 90% of patients) is therefore one or more painless swellings in the neck, armpit or groin. Some patients (approximately 30%) also show signs of B symptoms including fever, night sweats or unexplained weight loss.[7, 16-18]

MCL predominantly affects elderly males. The average age at diagnosis is mid-60s, and MCL is more than twice as likely to develop in males compared with females.[12, 16, 19-29]

MCL is considered to be one of the most aggressive types of lymphoma and can spread rapidly throughout the body, infiltrating lymphoid tissues, bone marrow, liver, spleen, peripheral blood and the gastrointestinal (GI) tract.[7, 15] The majority of patients diagnosed follow this aggressive course, and this rapid disease progression means that most patients diagnosed with MCL (>80%) present at an advanced stage: Stage III or IV on the modified Ann Arbor classification scale.[19, 30] A small proportion of patients (10-30%) follow a much slower, indolent disease course.[31-33] These patients do not require active treatment and enter the decision problem of interest to this submission when their disease course becomes more aggressive.

At presentation, patients with newly diagnosed MCL will undergo a thorough examination to assess the extent of their disease and associated prognosis.[7, 34] Recognised prognostic markers include the MCL International Prognostic Index

(MIPI), which predicts the prognosis of advanced MCL by assigning points for proven risk factors of age; lactate dehydrogenase (LDH); performance status; white blood cell count (WBC)[35]; and histological predictors, particularly the Ki67 proliferation index (a marker of disease aggressiveness with an established prognostic value).[36, 37] Assessment of clinical course and prognosis is important in MCL as it impacts treatment choice (see section 3.2).

The general pattern of disease progression in MCL is one of relapse and remission, with each relapse becoming more difficult to treat, and the depth and durability of any subsequent remissions achieved invariably inferior to those achieved with first-line treatment.[7, 17, 22, 34, 38] The goal of therapy is thus to achieve as deep a response as possible with initial induction therapy, which maintains or improves HRQL by controlling symptoms and extending remission.

3.2 Clinical pathway of care

In patients first presenting with aggressive disease requiring treatment, the initial treatment decision is whether patients are suitable for high-intensity induction therapy, to be followed by HSCT. There are no strict criteria against which patients are assessed; rather, haematologists will assess eligibility on a patient by patient basis, taking into account factors, such as patient age; performance status and disease prognosis (assessed within the MCL International Prognostic Index [MIPI]); disease severity; co-morbidities status; and clinical risk.[7, 20, 34, 35, 38-40] Patients who are considered fit enough are preferentially treated with a high-dose cytarabine (Ara-C)-based induction regimen, typically consolidated with HSCT.

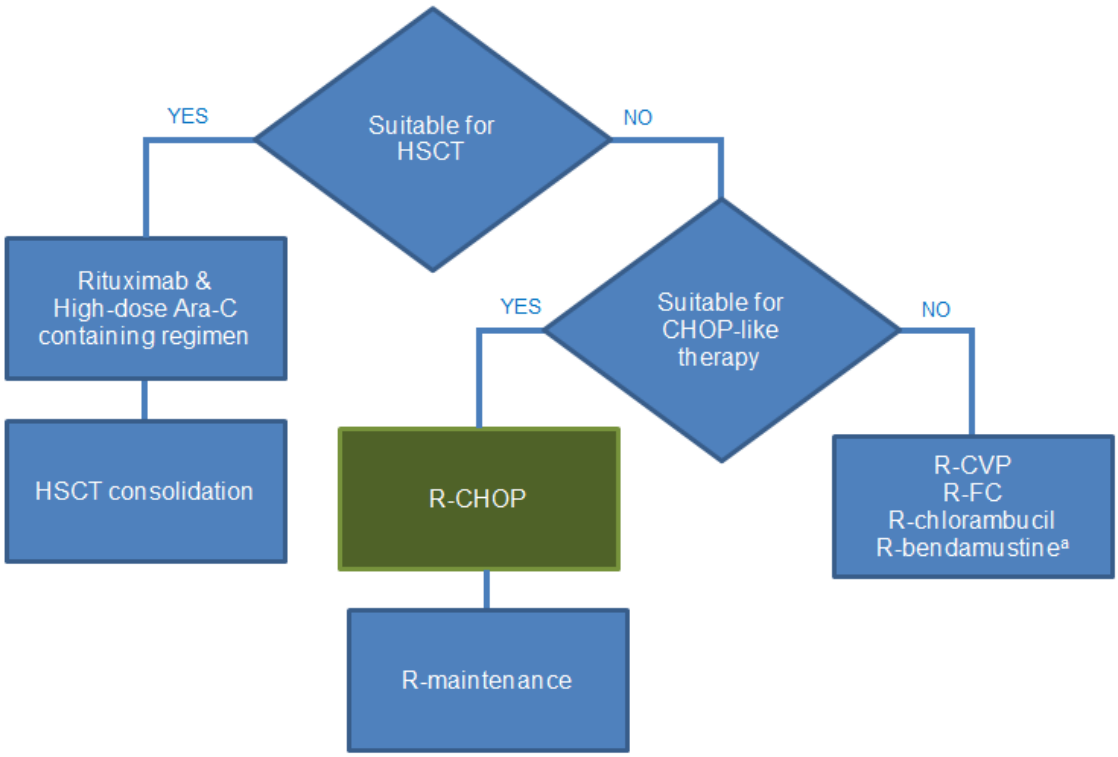
For patients who are not eligible for high-intensity induction therapy, that is those for whom HSCT is unsuitable, there are no licensed induction therapy regimens. UK guidelines recommend treatment with a rituximab-based chemotherapy induction regimen[7], and whilst there is still no unanimously accepted front-line option within these chemotherapeutic regimens, since the large scale European MCL Elderly trial demonstrated a survival benefit for R-CHOP[41], this regimen has become the preferred first-line induction therapy option in UK clinics. Alternative rituximab-based chemotherapy induction regimens are also administered in the first-line setting in some cases, but commonly only the frailest of patients considered unsuitable for R-CHOP therapy receive such regimens because, whilst they are associated with lower

toxicity, the evidence base supporting their use is considerably weaker (see sections 4.10 and 4.11).[6] More recent treatment algorithms for the first-line treatment of MCL across Europe depict this trend.[38]

Practising haematologists confirmed 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.[6] As depicted in Figure 1, 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.[6] This includes R-bendamustine, which is only available through the Cancer Drugs Fund (CDF) for patients unsuitable for standard first-line treatment.[42] Furthermore, whilst R-FC is listed in treatment guidelines as a potential treatment option for newly diagnosed MCL patients, in the UK this induction regimen is rarely used in the front-line setting due to a poorer survival benefit than R-CHOP[41] and concerns regarding the long-term impact of R-FC on myelosuppression which compromises the ability to deliver further treatments at relapse.[6]

Given its RCAP backbone, VR-CAP is considered a ‘CHOP-like’ induction therapy.Thus, patients not deemed fit enough to receive R-CHOP would not be considered for VR-CAP induction therapy.[6] VR-CAP would therefore be adopted into the first-line therapy pathway for MCL in NHS England and Wales at the location depicted by the green box in the treatment algorithm (Figure 1).

Figure 1: Clinical pathway of care for the first-line treatment of MCL in England and Wales



Key: Ara-C, cytarabine; CDF, Cancer Drugs Fund; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; HSCT, haematopoietic stem cell transplantation; MCL, mantle cell lymphoma; R, rituximab; R-chlorambucil, rituximab with chlorambucil; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP, rituximab with cyclophosphamide, vincristine and prednisone; R-FC, rituximab with fludarabine and cyclophosphamide.
Notes: [a], only available through the CDF for patients unsuitable for standard first-line treatment; green box depicts where VR-CAP would fit in this treatment algorithm.
Source: Adapted from McKay et al. 2012[7] and Campo & Rule, 2015.[38]

Within the current clinical pathway of care, rituximab maintenance (R-maintenance) can be administered in patients that respond to induction therapy (Figure 1). This practice has been adopted in recent years based on findings of the European MCL Elderly trial (see section 4.10).[41] At the NICE scoping meeting, it was noted that R-maintenance would be considered after any standard induction therapy (with the same benefit expected) and, thus, would not impact the initial treatment decision; it was not therefore considered necessary to include R-maintenance as a comparator in this appraisal.[43]

3.3 Life expectancy and epidemiology

Current rituximab-chemotherapy induction regimens in MCL are associated with a high rate of clinical response, but these responses are short, with responding patients subsequently progressing quickly.[44-46] As a result, the median PFS associated with current induction therapy in MCL is less than2 years, and median OS is less than5 years, with a median survival time post relapse of only 1 to 2 years.[19, 46-52]

As discussed in section 3.1, MCL is a rare subtype of NHL. The incidence rate of MCL in the UK is reported to be 0.9 per 100,000.[53] Based on the Office for National Statistics 2015 population estimates for England and Wales (57 million)[54], approximately 500 patients are estimated to be diagnosed with MCL in England and Wales each year (see section 6). Of these patients, approximately two thirds are likely to present with aggressive disease requiring treatment but for whom HSCT is unsuitable, and of those, a further two thirds are expected to be fit for CHOP-like therapy. [6] An estimated 215 patients in NHS England and 12 patients in NHS Wales would be eligible for VR-CAP therapy (see section 6).[6]

3.4 NICE guidance/guidelines

MCL is included in the NICE pathway: Blood and bone marrow cancers[55], but there is currently no published NICE guidance on the treatment of MCL.

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[56], 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 MCL.

Finally, a STA for bendamustine (first line, with rituximab) in MCL [ID609][57] was initiated in 2012 but was suspended in February 2013, and no further update has been published since. To date, no marketing authorisation for bendamustine has been granted for the treatment of MCL.

3.5 Clinical guidelines

UK and European clinical guidelines relating to the first-line treatment of MCL have been summarised in Table 6.

In addition, a number of expert reviews on the treatment paradigm for MCL in Europe have been published, the most recent of which discusses evolving management strategies in MCL as part of a Blood review series.[38]

Table 6: Clinical guidelines for the management of MCL

Organisation	Title	Date	Summary of recommendations
ESMO	Newly diagnosed and relapsed MCL: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	2014	Rituximab in combination with chemotherapy such as CHOP or bendamustine should be used in patients who do not qualify for dose-intensified regimens; rituximab-containing induction of CHOP and high-dose Ara-C followed by high-dose consolidation and HSCT is recommended in fit patients
ESMO	ESMO Consensus conferences: guidelines on malignant lymphoma	2013	Rituximab should be part of any chemotherapy regimen; induction with high-dose Ara-C is superior to R-CHOP in younger patients; HSCT should be carried out first line in patients fit enough to receive such therapy
UK MCL guideline group	Guidelines for the investigation and management of MCL	2012	Rituximab should be part of any chemotherapy regimen; induction with high-dose Ara-C followed by HSCT consolidation should be carried out first line in patients fit enough to receive such therapy

Key: Ara-C, cytarabine; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; ESMO, European Society for Medical Oncology; MCL, mantle cell lymphoma; HSCT, haematopoietic stem cell transplantation; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone.
Source: Dreyling et al. 2014[34]; Dreyling et al. 2013[40]; McKay et al. 2012.[7]

3.6 Issues in current clinical practice

One of the biggest issues in current clinical practice is that there are no licensed treatment regimens, no published NICE guidance and, therefore, no unanimously recognised standard of care for the induction therapy of adult patients with previously untreated MCL for whom HSCT is unsuitable. R-CHOP is the established standard of care in the UK as, until now, it had the most robust evidence base for clinical benefit, and no other induction regimen had demonstrated better efficacy. Nonetheless, rituximab-based chemotherapy induction regimens recommended in current UK guidelines, including R-CHOP, are associated with temporary clinical

response, and thus, the long-term prognosis in MCL is poor, with a median OS of <5 years.

Clearly, there remains a clinical unmet need for a licensed first-line induction therapy regimen that could improve long-term prognosis and become the unanimously recognised standard of care in NHS England and Wales for patients with MCL for whom HSCT is unsuitable.

3.7 Equality

No equality issues related to the use of bortezomib are foreseen.

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

A systematic literature review was initiated in July 2014 to identify trials of VR-CAP and alternative chemotherapy induction regimens used in the first-line treatment of MCL across Europe. This was updated in March 2015 and aligned to the first-line treatment of MCL patients for whom HSCT is unsuitable in the UK.

Information retrieval methods were based upon the research question "*What is the clinical efficacy and tolerability of VR-CAP and alternative pharmacological induction regimens for the treatment of MCL?"* This research question was intentionally broader than the decision problem to ensure high sensitivity in subsequent searches.

Searches were performed in global electronic databases:

- MEDLINE and MEDLINE In-Process
- EMBASE
- The Cochrane Library, including the following:
  - The Cochrane Database of Systematic Reviews (CDSR)
  - The Cochrane Central Register of Controlled Trials (CENTRAL)
  - The Database of Abstracts of Reviews of Effects (DARE)
  - The Health Technology Assessment (HTA) database

In addition, 2014-15 annual proceedings of the following conferences were hand searched (2015 where available prior to preparation of the submission) in order to identify any relevant, on-going research:

- The American Society of Hematology
- The British Society for Haematology
- The European Hematology Association
- The American Society of Clinical Oncology
- The European Society for Medical Oncology

The search strategies used are provided in Appendix 3.

Reference lists of previous systematic reviews/meta-analyses and clinical guidelines identified were hand-searched to highlight any further relevant studies. In addition, unpublished data on file held by Janssen were reviewed for relevance to the research question/decision problem.

The full eligibility criteria applied to the identified evidence base are presented in Table 7. Eligibility criteria applied in the original review were wider in scope than the eligibility criteria presented in Table 7 as this review was designed with a European perspective. Results of the original review were therefore reassessed against the eligibility criteria presented in Table 7 when the review was updated and aligned with the decision problem.

In summary, clinical trials of any design were included in the final evidence base of relevant studies as long as they investigated the clinical efficacy and/or safety of interventions named in the decision problem for the first-line induction therapy of adult patients with MCL and reported outcomes prior to consolidation with HSCT if this was subsequently conducted.

No restriction regarding suitability for HSCT was applied as this is assessed on a patient by patient basis in clinical practice (see section 3.2) and not a common criterion applied in clinical trial protocols. All other study population criteria were in line with the licence terms for VR-CAP and the decision problem of interest in this submission. Whilst R-CHOP is the established standard of care in the position VR-CAP would adopt in the clinical pathway of care (see section 3.2), there is no unanimously recognised standard of care for the treatment of MCL patients for whom HSCT is unsuitable, and therefore, the full suite of rituximab-chemotherapy induction regimens potentially used in the first-line setting in NHS England and Wales were included as interventions of interest to align with the final appraisal scope. Studies of these interventions were included regardless of comparator. Outcomes of interest were those considered representative of the clinical benefit and safety measures adopted in clinical practice and those named in the decision problem. Although systematic reviews of randomised controlled trials (RCTs) are the best method for revealing the effects of a therapeutic intervention, due to the paucity of RCT evidence in MCL, controlled clinical trials (non-randomised), non-controlled clinical trials (single-arm) and prospective and retrospective observational studies were also included.

Table 7: Eligibility criteria applied to systematic search results

	Inclusion criteria	Exclusion criteria
Study population	Adult patients MCL (active disease) No prior therapy for MCL	Paediatric patients Non-MCL patients Relapsed/refractory MCL patients Patients in remission
Interventions	VR-CAP R-CHOP R-FC R-bendamustine	Listed interventions with HSCT consolidation[a] Any other active therapy
Comparators	Any active therapy Placebo No treatment	None
Outcomes	DoR HRQL OS PFS Response rates Safety/tolerability TTP TTNT	None
Study design	RCTs Non-RCTs Non-controlled trials (single-arm) Prospective observational studies Retrospective observational studies	In vitro studies Case report Case studies/series Letter Commentary Editorial

Key: DoR, duration of response; HRQL, health-related quality of life; HSCT, haematopoietic stem cell transplantation; MCL, mantle cell lymphoma; OS, overall survival; PFS, progression-free survival; R-bendamustine, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; RCT, randomised controlled trial; R-FC, rituximab with fludarabine and cyclophosphamide; TTNT, time to next treatment; TTP, time to progression; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

Notes: [a], unless outcomes prior to consolidation with HSCT are reported.

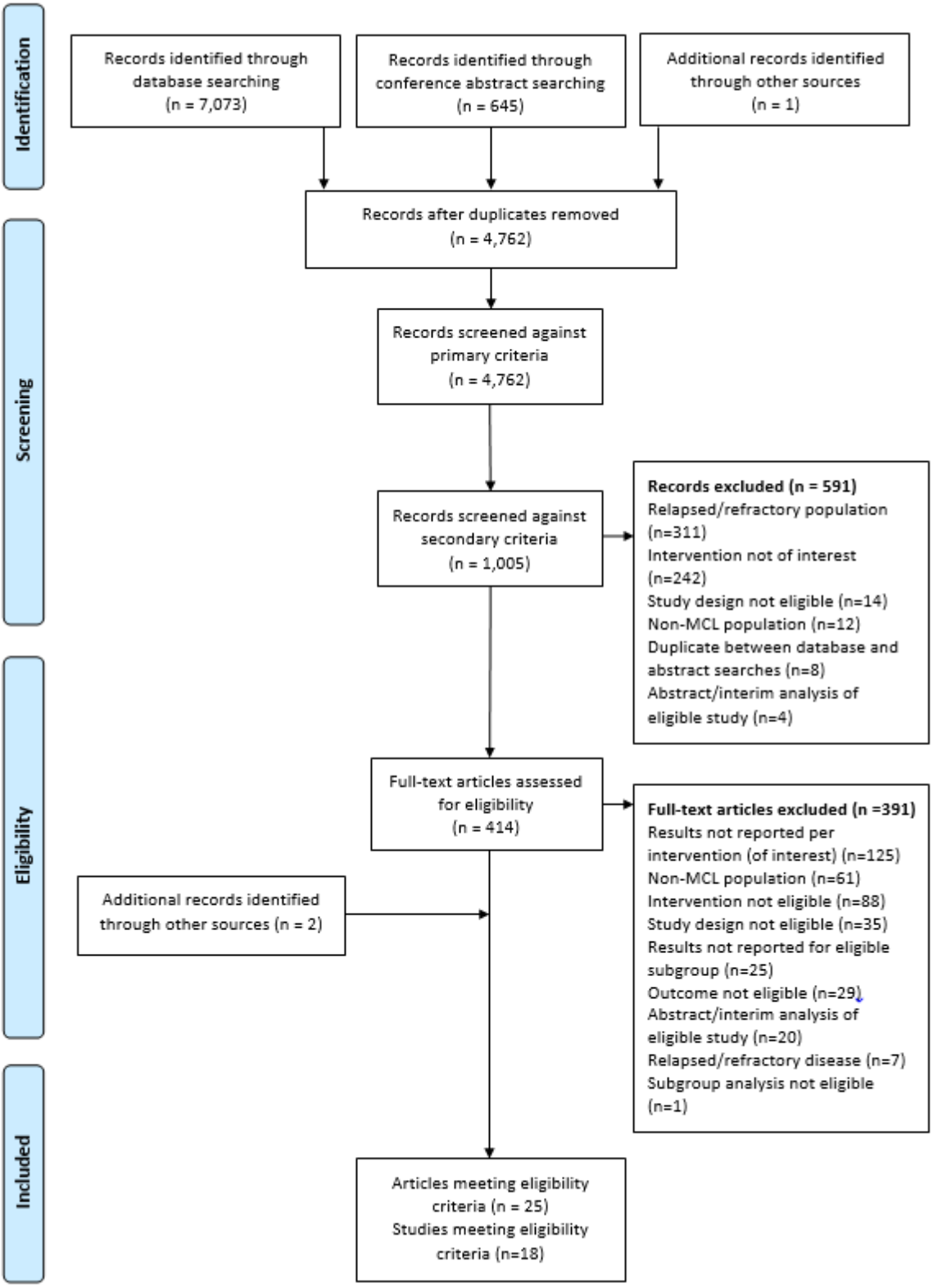
One senior reviewer inspected each reference (title and abstract) identified by the literature searches and applied basic study selection criteria based on population (MCL) and study design alone (primary screening). This single reviewer screening phase was adopted as a number of clearly irrelevant citations were identified due to the broad information retrieval methods.

Two reviewers independently inspected each reference (title and abstract) that passed the primary screening and applied study selection criteria based on detailed information regarding population (previously untreated adult patients), intervention and study design (secondary screening). Citations meeting the secondary study selection criteria (or in cases of disagreement between the two reviewers) were obtained in full and independently assessed against the full eligibility criteria for final inclusion (tertiary screening). In the event of disagreement between the two reviewers, a third reviewer would have independently assessed the paper, after which the applicability of selection criteria would have been established by consensus; however, this was not needed as no discrepancies occurred.

If study duplication within publications was suspected, author names, location and setting, specific intervention details, participant numbers, baseline data and date and duration of study were assessed. If uncertainties remained, the authors would have been contacted, but this situation did not occur. Where multiple publications were identified for the same clinical trial, those reporting additional data that met the eligibility criteria of the review were included in the final list of included articles as secondary publications (kin papers). Papers reporting post-hoc or sub-group analyses not of relevance to the decision problem were excluded, as were conference abstracts presenting results of studies identified as full publications.

A flow diagram of the systematic review process is presented as a PRISMA diagram in Figure 2.

Figure 2: PRISMA flow diagram of the literature search process



Key: MCL, mantle cell lymphoma.
Source: Moher et al. 2009.[58]

Original searches of electronic databases, conducted in July 2014, identified a total of 6,150 potentially relevant citations with some overlap between databases. After removal of duplicates, 3,713 potentially relevant citations remained. Update searches of electronic databases, conducted in March 2015, identified a total of 923 potentially relevant citations with some overlap between databases. After the removal of duplicates, 403 potentially relevant citations remained. Conference abstract searches identified a total of 645 potentially relevant citations. These were not compared with electronic database searches at this stage, but there was some overlap between the conference abstract and electronic database search results that were manually identified during secondary screening (Figure 2). An additional publication of Janssen data not yet indexed in electronic databases was also included.[59]

During primary screening, 3,757 citations were excluded as they were clearly not of relevance to the research question. During secondary screening, a further 591 citations were excluded. Common reasons for exclusion included non-MCL patient populations, relapsed/refractory patient populations, investigations of interventions not included in the decision problem, and investigations of HSCT consolidation.

A total of 414 citations were accessed in full (where applicable and necessary) for further evaluation. Of these citations, 18 were original publications of trials meeting the eligibility criteria of the review, and a further 5 were secondary publications that reported additional information meeting the eligibility criteria of the review. An additional two sources of unpublished data were also included in the final evidence base: a clinical study report held on file by Janssen[60] and subgroup analyses of a randomised Phase III study of the Study Group of indolent Lymphomas (StiL) (see section 4.10) that was provided by the primary author on request.[61]

A reference list for citations excluded at the tertiary screening stage is provided in Appendix 4.

The RCT evidence base of the technology of interest to this submission, VR-CAP, is presented in sections 4.2 to 4.8 and 4.12. The RCT evidence base of comparator therapies outlined in the decision problem is presented in section 4.10. The non-RCT evidence base identified is presented in section 4.11.

4.2 List of relevant randomised controlled trials

The systematic literature review identified one RCT investigating the clinical efficacy and safety of VR-CAP in adult patients with previously untreated MCL. This is the pivotal RCT, LYM-3002, which directly compares VR-CAP with R-CHOP induction therapy, the established standard of care in the position VR-CAP would adopt in the clinical pathway of care in NHS England and Wales (see section 3.2). Summary details of this trial are presented in Table 8.

Table 8: List of relevant RCTs for VR-CAP

Trial Number	Population	Intervention	Comparator	Primary Study Reference	Secondary Study References
LYM-3002	Adult patients with previously untreated MCL unsuitable for HSCT.	VR-CAP	R-CHOP	Robak et al. 2015[59]	Drach et al. 2014[62] Robak et al. 2014[63] LYM-3002 CSR[60]
Key: CSR, clinical study report; HSCT, haematopoietic stem cell transplantation; MCL, mantle cell lymphoma; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; RCT, randomised controlled trial; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.					

4.3 Summary of methodology of the relevant randomised controlled trials

The LYM-3002 trial is a randomised, open-label, multicentre, Phase III study designed to determine whether the VR-CAP or R-CHOP induction regimen provides greater benefit in newly diagnosed MCL patients with advanced disease who are unsuitable for HSCT.[59, 60]

The trial was initiated in May 2008 and involved 128 sites worldwide. Subjects were randomised in a 1:1 ratio based on two stratification factors: the International Prognostic Index (IPI) and the stage of disease at diagnosis.[59, 60] The IPI is a recognised prognostic marker that predicts the prognosis of patients with aggressive NHL by assigning points for known risk factors, such as age, disease stage, extranodal site involvement, LDH and performance status.[64] The IPI was chosen as

a stratification factor in LYM-3002 as the trial was initiated prior to validation of the MCL specific prognostic marker, MIPI (see section 3.1).

Subjects received 6 to 8 cycles (18 to 24 weeks) of treatment depending upon the response documented at the cycle 6 assessment. The total study duration from randomisation of the first patient until the last PFS event required for the final analysis was expected to be approximately 42 months (24 months for enrolment and 18 months for follow-up).

Clinical benefit was primarily assessed by the significance of prolongation of PFS. Secondary clinical endpoints included time to progression (TTP), time to next treatment (TTNT), TFI, overall response rate (ORR) (CR + unconfirmed complete response [CRu] + partial response [PR]), CR rates (CR+CRu), time to response (TTR), duration of response (DoR), rate of durable response and OS. In addition, the safety of VR-CAP compared with R-CHOP was evaluated, and patient-reported outcomes (PROs) were evaluated as an exploratory endpoint.

Disease assessments for the primary analysis were performed by blinded central review of radiological scans by an IRC in accordance with stringent modified International Workshop Response Criteria (IWRC)[65], and for the supportive analyses, by investigator review. Pre-specified sensitivity analysis of the primary outcome of PFS was also performed by IRC alternative assessment (see section 4.7). The study conduct, including efficacy and safety interim analyses, was overseen by an independent data monitoring committee (IDMC).

Assessment of disease response by computed tomography (CT) scans, obtained at the end of cycles 2, 4, and 6, and thereafter every 6 to 8 weeks until progression, was considered to be of adequate frequency to detect treatment effects; the CT scans were obtained symmetrically in both groups.

Key characteristics of the LYM-3002 trial are presented in Table 9.

Table 9: Summary of LYM-3002 trial methodology

Trial design	Randomised, open-label, multicentre, Phase III study to compare the efficacy and safety of VR-CAP to that of R-CHOP in patients with newly diagnosed MCL who are unsuitable for HSCT.
Location	128 sites including Austria (n=2), Belgium (n=8), Brazil (n=7), Canada (n=2), Chile (n=1), Columbia (n=2), Czech Republic (n=3), France (n=3), Germany (n=3), Hungary (n=6), India (n=3), Israel (n=3), Italy (n=5), Japan (n=10), People's Republic of China (n=10), Poland (n=3), Portugal (n=3), Republic of Korea (n=2), Romania (n=5), Russia (n=21), Singapore (n=1), Spain (n=6), Taiwan (n=1), Thailand (n=4), Tunisia (n=2), Turkey (n=2), Ukraine (n=7) and the United States (n=3).
Inclusion criteria	Male or female, 18 years or older; MCL Stage II, III or IV; at least 1 measurable site of disease; no prior therapies for MCL; ineligible for bone marrow transplantation; ECOG PS score of ≤2; absolute neutrophil count ≥1500 cells/µL; platelet count ≥100,000 cells/µL or ≥75,000 cells/µL if thrombocytopenia secondary to MCL was present; ALT and AST ≤3 times the ULN and total bilirubin ≤1.5 times the ULN; calculated creatinine clearance ≥20 mL/min; female subjects to be post-menopausal for at least 1 year, surgically sterile or using an effective method of birth control; males to use acceptable method of contraception; signed informed consent form.
Exclusion criteria	Prior treatment with bortezomib or prior treatment for MCL; major surgery within 2 weeks prior to randomisation; peripheral neuropathy or neuropathic pain of Grade 2 or higher; diagnosed or treated for a malignancy other than MCL within 1 year of randomisation; active systemic infection requiring treatment, known diagnosis of IV or active hepatitis B; history of allergic reaction attributable to compounds containing boron, mannitol or hydroxybenzoates; known anaphylaxis or immunoglobulin E-mediated hypersensitivity to murine proteins or to any component of rituximab; subjects who would not agree to using adequate contraception; serious medical condition or psychiatric illness likely to interfere with participation in the study; concurrent treatment with another investigational agent.
Intervention	Rituximab 375 mg/m^2 IV on day 1; cyclophosphamide 750 mg/m^2 IV on day 1; doxorubicin 50 mg/m^2 IV on day 1; bortezomib 1.3 mg/m^2 IV on days 1, 4, 8 and 11; and prednisone 100 mg/m^2 orally on day 1 through day 5 of a 21-day (3-week) cycle.
Comparator	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.
Subsequent therapy	After PD was established, subsequent therapy was at the investigator's discretion.

Permitted and disallowed concomitant medication	All concomitant medications for medical conditions other than MCL were permitted as clinically indicated, as were supportive therapies other than anti-cancer treatment. Any antineoplastic agent other than study drugs (with the exception of medications that may have antineoplastic activity but are taken for other reasons), any experimental agent other than that defined in the protocol and radiation therapy were prohibited at all times during the study. Short courses of steroids (maximum of 10 days and not exceeding 100 mg/day of prednisone or equivalent) were allowed to treat symptoms in subjects with advanced disease during screening and prior to randomisation.
Primary outcome	– PFS[a], defined as the interval between the date of randomisation and the date of PD or death, whichever occurred first.
Secondary outcomes	– TTP[a], defined as the duration from the date of randomisation until the date of first documented evidence of PD or relapse for subjects who experienced CR or CRu; – TTNT[a], measured from the date of initiation of study treatment as per protocol (PP) to the start date of new anti-lymphoma treatment; – Duration of TFI, measured from date of last dose plus 1 day to start date of the new treatment; – ORR[a], defined as the proportion of subjects who achieved CR, CRu, or PR relative to the response-evaluable population; – CR rate, defined as the proportion of subjects who achieved CR or CRu relative to the response-evaluable population; – TTR, measured from date of randomization to date of initial response; – Duration of radiological response[a], calculated from date of initial documentation of response to date of first documented evidence of PD or death due to PD; – Duration of CR, calculated from date of initial documentation of CR to date of first documented evidence of PD or death due to PD; – Rate of durable response, defined as the proportion of patients demonstrating a response duration ≥6 months; – OS[a], measured from the date of randomisation to the date of death. – Safety evaluations[a].
Exploratory outcomes	– PRO[a], utilising the EORTC-QLQ-C30, the EQ-5D (5 level and VAS) and the BFI, as summarised in Appendix 5:Table 20; – Medical resource utilisation; – Biomarker analyses.

Efficacy evaluations	Efficacy was assessed by blinded central review of radiology by the IRC. Radiological images were collected at baseline; cycles 2, 4, 6 (and 8, if applicable); end-of-treatment; followed by every 6 weeks for 18 weeks and thereafter every 8 weeks until confirmed PD, initiation of alternate therapy, subject withdrawal, or death. Tumour assessments were also performed locally by investigators based on radiological images and lab data (e.g. bone marrow samples and serum LDH levels). The response criteria used to assess efficacy were based on modified IWRC[65] that are summarised in Appendix 5:Table 19.
Pre-planned subgroups	IPI risk, sex, race, region, age, stage of disease at diagnosis, LDH, WBC, ECOG, renal function, liver function.

Key: ALT, alanine transaminase; AST, aspartate transaminase; BFI, Brief Fatigue Inventory; CR, complete response; CRu, complete response unconfirmed; ECOG, Eastern Cooperative Oncology Group; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, EuroQol-5 Dimension Questionnaire; HSCT, haematopoietic stem cell transplantation; IPI, International Prognostic Index; IRC, independent review committee; IV, intravenous; IWRC, International Workshop Response Criteria; LDH, lactate dehydrogenase; MCL, mantle cell lymphoma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PRO, patient reported outcome; PS, performance status; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; TFI, treatment free interval; TTNT, time to next treatment; TTP, time to progression; TTR, time to response; ULN, upper limit of normal; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone; WBC, white blood cell count.

Notes: [a], listed in the final appraisal scope and included in the decision problem.

Source: LYM-3002 CSR[60]; Robak et al. 2015.[59]

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 for socio-economic reasons. 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.

In line with this eligibility criterion, the CHMP felt the LYM-3002 trial outcomes supported an indication expansion for bortezomib to the treatment of adult patients

with previously untreated MCL who are unsuitable for HSCT, where they considered the availability of new medicinal products to be of greatest clinical value.

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

The hypothesis objective and a summary of statistical analyses used in the LYM-3002 trial are presented in Table 10.

The primary efficacy analysis set was the all randomised population (the intention-to-treat [ITT] population), with standard censoring methods used to accommodate for missing data. In the majority, censoring in the data presented in this submission was due to the clinical cut-off date, with patients still being followed up at the time of analysis.

Table 10: Summary of statistical analyses in LYM-3002 trial

Hypothesis objective	VR-CAP provides greater benefit in newly diagnosed MCL patients with Stage II, III or IV disease compared to R-CHOP, as assessed by significant prolongation of PFS.
Statistical analysis	All statistical tests were 2-sided. The primary hypothesis was tested at the 0.05 significance level (overall). The significance level at the interim analysis was determined by the observed number of events at the time of the interim analysis per the O'Brien-Fleming spending function. The secondary hypotheses were tested sequentially at the nominal 0.05 significance level in the following order: 1) TTP; 2) TTNT; 3) CR rate; and 4) OS. A secondary hypothesis was tested only if the primary hypothesis was rejected along with all the secondary hypotheses that preceded it. However, OS was to be analysed regardless of what happened to the other endpoints in the hierarchical test. The KM method was used to estimate the distribution of overall PFS for each treatment group. The primary treatment comparison was based on a stratified log-rank test. The HR and its 95% CI were estimated based on a stratified Cox's model, with treatment as the explanatory variable. Stratification factors were IPI (0-1, 2, 3, and 4-5) and stage of disease at diagnosis (II, III, and IV). The same methodology was used for other time to event endpoints, except duration of response and duration of complete response where the KM method was used as a descriptive summary. For response-related endpoints, the stratified Cochran–Mantel–Haenszel test was used to test treatment difference. The Mantel–Haenszel estimate of the OR and its 95% CI were also calculated.
Sample size, power calculation	Assuming that treatment with VR-CAP would improve the median PFS by 40% (from 18 to 25 months), a total number of 295 events would provide 80% power (alpha=0.05, 2-sided) to detect such improvement. Assuming a 24-month accrual and an 18-month follow-up, a total of 486 subjects were needed for the study (243 subjects per treatment group).

Data management, patient withdrawals	The primary efficacy analysis set was the ITT population, which included all randomised subjects. The secondary efficacy analysis set included (1) the PP population, which included all randomised subjects who met eligibility criteria, received at least 1 dose of study drug and underwent at least 1 post-baseline disease assessment, and (2) the response-evaluable population, which included all randomised subjects who received at least 1 dose of study drug, had at least 1 measurable tumour mass at baseline and had at least 1 post-baseline assessment. The safety population was defined as all randomised subjects who received at least 1 dose of the study drug. Subjects may have been withdrawn from the study for any of the following reasons: lost to follow-up, withdrawal of consent, death. If a subject withdrew before the end of the treatment phase, end-of-treatment and follow-up assessments were obtained. In efficacy analyses, subjects who withdrew from the study were censored at the time of the last adequate (CT scan available) disease assessment.
Key: CI, confidence interval; CT, computed tomography; CR, complete response; HR, hazard ratio; IPI, International Prognostic Index; ITT, intent-to-treat; KM, Kaplan-Meier; MCL, mantle cell lymphoma; OR, odds ratio; OS, overall survival; PFS, progression-free survival; PP, per protocol; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; TTNT, time to next treatment; TTP, time to progression; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone. **Source**: LYM-3002 CSR[60], Robak et al. 2015.[59]	

4.5 Participant flow in the relevant randomised controlled trials

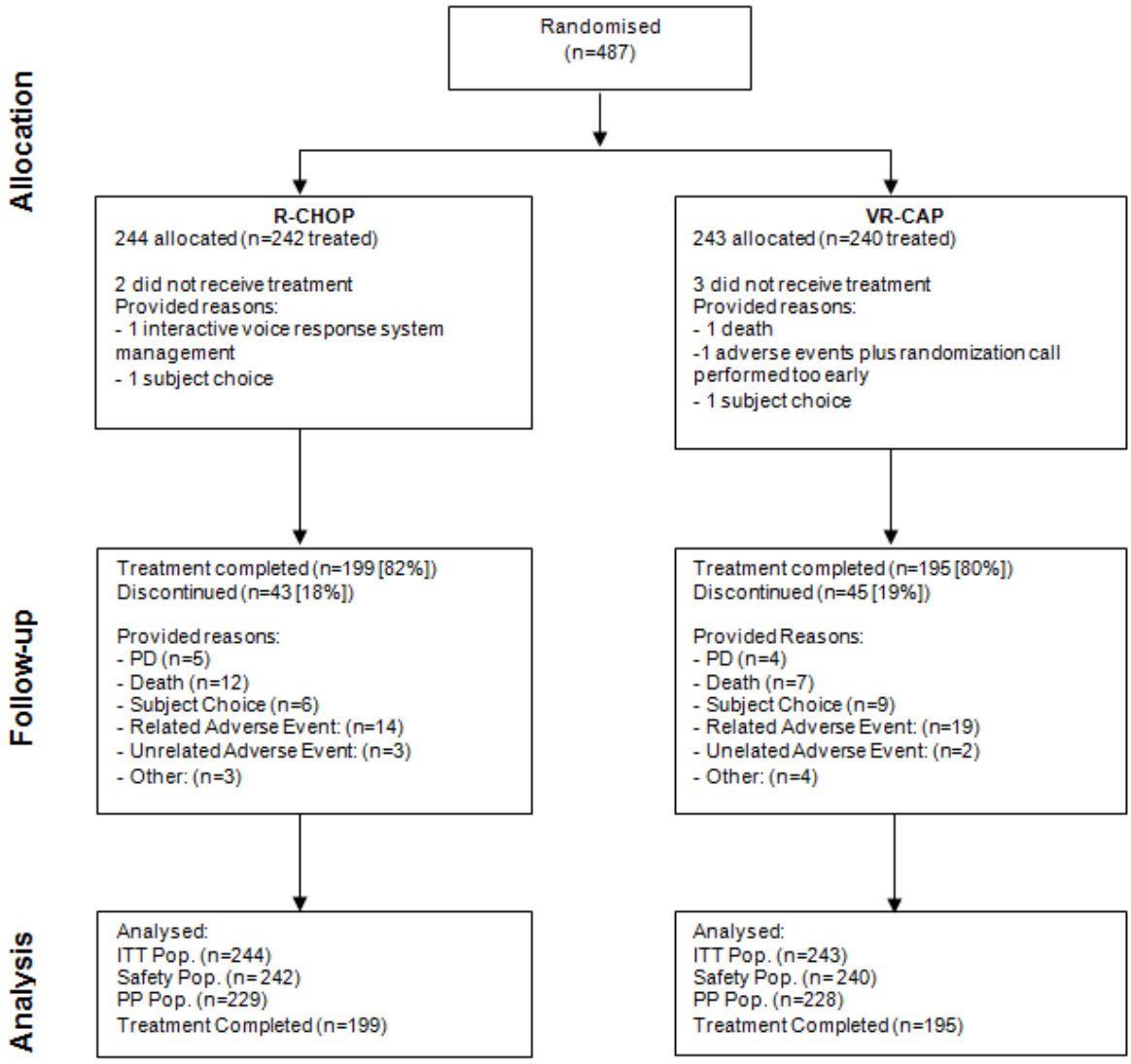
The first subject was randomised on 26 May 2008, and the last on 5 December 2011. The last dose of study medication was given on 13 May 2012.[59, 60]

In total, 487 patients were randomised into LYM-3002; 243 to the VR-CAP treatment group and 244 to the R-CHOP treatment group. Central pathology review confirmed local diagnosis of MCL in 97% of subjects. Five subjects (3 in the VR-CAP group and 2 in the R-CHOP group) did not receive any study medication.

Approximately 80% of subjects in both groups completed treatment. The median treatment duration was 17.6 weeks in the VR-CAP group and 16.1 weeks in the R-CHOP group. Eighty-eight (18%) subjects discontinued treatment (42 [18%] in the R-CHOP group and 45 [19%] in the VR-CAP group), with adverse events (AEs) being the most common reason for discontinuation.

A CONSORT flow chart for patients in the LYM-3002 trial is presented in Figure 3.

Figure 3: Subject disposition



Key: ITT, intent-to-treat; PD, progressive disease; PP, per protocol; 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]

Baseline demographics and disease characteristics of patients enrolled in the LYM-3002 trial were generally well-balanced, with no key differences between the two treatment groups, as presented in Table 11. The median age of subjects was 66 years, with 51% presenting at >65 years old, and the majority were male (74%) and Caucasian (66%), reflecting the known demographics of this disease.

The mean age of subjects was lower than expected in clinical practice for patients for whom HSCT is unsuitable. On review, many of the subjects under 65 years were enrolled at sites outside of North America and Western Europe: the mean age in the

pre-planned subgroup of patients from North America and Western Europe was closer to that expected in UK practice at 68.5 years. The only other observed difference in the baseline characteristics of subjects enrolled in the LYM-3002 trial and the typical patient presenting in UK clinical practice is average weight, which was lower in the trial population. This impacts dosing requirements, which the economic modelling accounts for (see section 5), but is not expected to impact treatment efficacy.

The majority of patients enrolled in the trial had been diagnosed in advanced stages of the disease, but many were still fully active, presenting with an Eastern Cooperative Oncology Group (ECOG) performance status of 0. There was a slight imbalance between the distributions of subjects across ECOG 0-1 between the two treatment groups. Post hoc review of the ECOG 0 subjects in both treatment arms showed that disease staging distribution, the prognostic marker for which performance status is viewed as a proxy, was similar across groups: 68 subjects (61%) in the VR-CAP arm and 57 subjects (67%) in the R-CHOP arm were Stage IV, and only 8 (7%) and 9 (11%) were Stage II, respectively.

Other disease staging and prognostic factors such as tumour histology and cellularity, IPI risk, elevated LDH levels, bone marrow involvement and extranodal disease sites were comparable between the two treatment groups and reflective of the MCL population presenting in clinical practice.

The small proportion of patients (16.4%) enrolled in the LYM-3002 trial that were not medically ineligible for HSCT (see section 4.3) was balanced across the two treatment groups. Key baseline demographics and disease characteristics of patients medically ineligible for HSCT are presented in Appendix 6 and, despite some small differences, are considered comparable to the baseline characteristics and clinical outcomes of the ITT population. Haematologists across the UK have confirmed that there is no clinical rationale not to use the ITT population analysis to represent patients who would be eligible for VR-CAP in UK clinical practice in the economic model.[6]

Table 11: Key baseline demographics and disease characteristics of patients, ITT analysis set

	VR-CAP (n=243)	R-CHOP (n=244)
Age: Median years (range) **Mean years (SD)**	65 (26-88) 64.2 (9.7)	66 (34-82) 64.4 (8.9)
Male, n (%)	178 (73.3)	182 (74.6)
White, n (%)	151 (62.1)	172 (70.5)
BSA, mean m^2 (SD)[a]	1.80 (0.22)	1.79 (0.19)
ECOG PS, n (%)[a]	0: 111 (45.7) 1: 101 (41.6) 2: 31 (12.8)	0: 85 (35.0) 1: 127 (52.3) 2: 31 (12.8)
Disease stage, n (%)	II: 12 (4.9) III: 49 (20.2) IV: 182 (74.9)	II: 16 (6.6) III: 42 (17.2) IV: 186 (76.2)
IPI risk, n (%)	Low: 38 (15.6) Low-intermediate: 75 (30.9) High-intermediate: 84 (34.6) High: 46 (18.9)	Low: 38 (15.6) Low-intermediate: 71 (29.1) High-intermediate: 88 (36.1) High: 47 (19.3)
Histology, n (%)[b]	Diffuse: 102 (42.5) Nodular: 59 (24.6) Mantle zone: 49 (20.4)	Diffuse: 103 (42.9) Nodular: 38 (15.8) Mantle zone: 70 (29.2)
Cellularity, n (%)[c]	Blastoid: 25 (10.6) Nodular: 109 (46.2)	Blastoid: 28 (11.7) Nodular: 97 (40.6)
Baseline LDH elevated, n (%)	88 (36.2)	86 (35.2)
Bone marrow involved, n (%)	165 (67.9)	171 (70.1)
Extranodal disease sites, n (%)	≥1: 139 (57.2) Spleen: 93 (38.3) GI tract: 28 (11.5) Lung: 19 (7.8) Liver: 28 (11.5)	≥1:137 (56.1) Spleen: 77 (31.6) GI tract: 39 (16.0) Lung: 32 (13.1) Liver: 19 (7.8)
Medically eligible for HSCT, n (%)	38 (15.6)	42 (17.2)

Key: BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; IPI, International Prognostic Index; HSCT, haematopoietic stem cell transplantation; LDH, lactate dehydrogenase; PS, performance status; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; SD, standard deviation; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

Notes: [a], n=243 in both treatment arms; [b], n=240 in both treatment arms; [c], n=236 in VR-CAP treatment arm, n=239 in R-CHOP treatment arm.

Source: LYM-3002 CSR[60]; Robak et al. 2015.[59]

4.6 Quality assessment of the relevant randomised controlled trials

The LYM-3002 trial was conducted in compliance with good clinical practice (GCP), with measures taken to reduce the risk of bias.[59, 60] Although the study was open-label in design, this is deemed acceptable as blinding was problematic due to the different dose schedules for bortezomib and vincristine. Primary analysis was based on blinded IRC assessment. Furthermore, the sponsor and investigational sites were blinded to all analyses reviewed by the IDMC.

The primary IRC assessment method was to read scans at sequential time points from baseline onwards only and to record response at each time point. This assessment was conducted stringently according to the pre-specified IRC charter, in which any post-baseline new or enlarging fluid collections had to be assessed as progressive disease (PD). Assessments could not be revised based on subsequent time points, even if, at a subsequent time point, there was a clear resolution or improvement of a prior fluid collection (i.e. the lesion was transient).

Fluid retention that does not reflect PD has previously been associated with bortezomib use in MCL.[66] A pre-specified sensitivity analysis was thus conducted where patients with new or enlarging fluid collections that clearly resolved or improved at a subsequent time point were reassessed by global IRC review of scans from all available time points. This sensitivity analysis allowed a more clinically relevant assessment of PD whilst retaining the benefit of a blinded IRC. Although haematologists across the UK were not familiar with the term ‘transient lesion’ when consulted on this point, when described, it was confirmed that such temporary fluid collections would not be classed as progression in clinical practice.[6]

LYM-3002 was conducted on a global scale and thus enrolled patients were not all diagnosed and treated in the European Union (although this was the region with the largest number of subjects, 28%).[60] There was, however, central pathology confirmation of MCL diagnosis; central sourcing of all study medications; central IRC assessment of primary and secondary efficacy outcomes; and investigators at individual sites were not permitted to modify treatment outside of the study protocol.

Quality assessment in accordance with the NICE-recommended checklist for RCT assessment of bias is summarised in Table 12 and presented in full in Appendix 7:Table 22.

Table 12: Summary of quality assessment

Study ID	**LYM-3002**
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Efficacy was assessed by central review of radiology that was blinded
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes
Key: ITT, intent-to-treat. **Source**: LYM-3002 CSR[60]; Robak et al. 2015.[59]	

4.7 Clinical effectiveness results of the relevant randomised controlled trials

The clinical cut-off date for the primary analysis presented in this submission was 2 December 2013.[59, 60] The final analysis is expected in 2017 (see section 4.14).

Primary efficacy analysis

The replacement of vincristine with bortezomib in the chemotherapy induction regimen resulted in significant clinical benefit, as demonstrated by significant prolongation of PFS.[59, 60]

In the primary analysis of PFS based on IRC assessment of the ITT population, median PFS 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) (Table 13; Figure 4). This represents a 59% improvement in PFS in the VR-CAP group, confirming the study hypothesis and exceeding the hypothesized treatment effect of 40% improvement.

Table 13: PFS based on IRC assessment, ITT analysis set

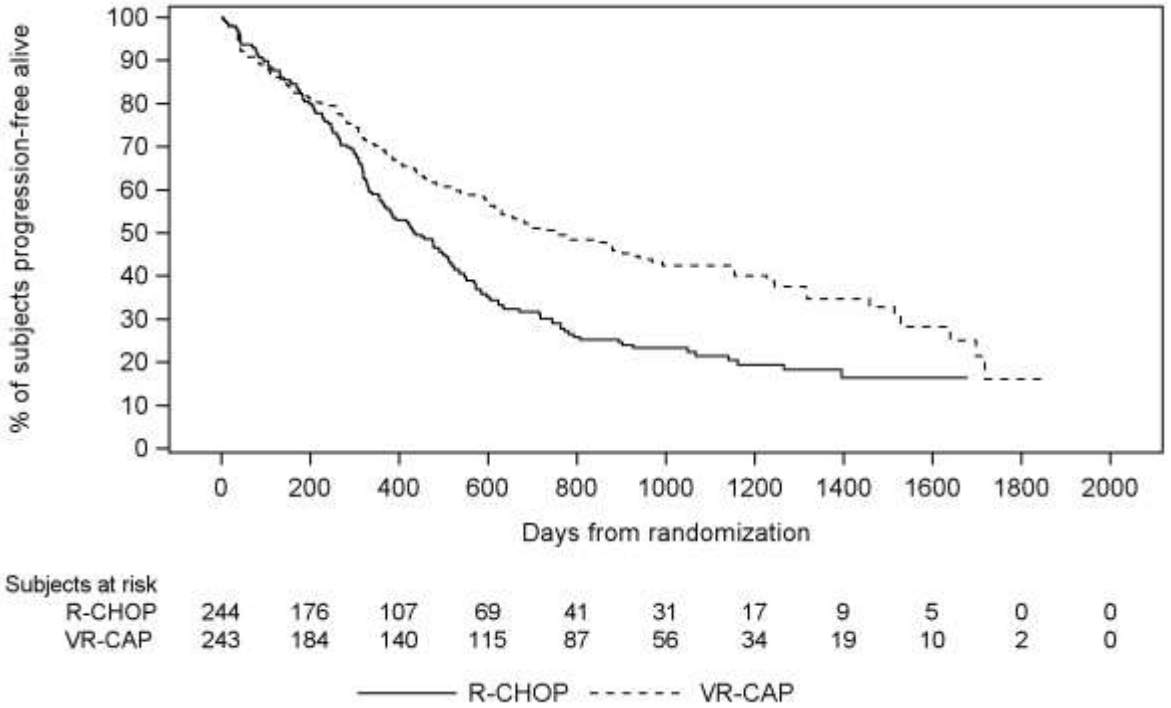
	VR-CAP (n=243)	**R-CHOP (n=244)**
PFS, days[a]		
Number of censored (%)	110 (45.3)[b]	79 (32.4)[b]
Number of events (%)	133 (54.7)	165 (67.6)
25% quartile (95% CI)	298.0 (214.0; 363.0)	248.0 (186.0; 298.0)
Median (95% CI)	751.0 (604.0; 969.0)	437.0 (365.0; 513.0)
75% quartile (95% CI)	1698.0 (1458.0; NE)	895.0 (714.0; 1266.0)
P-value[c]	<0.001	
Hazard ratio (95% CI)	0.63 (0.50; 0.79)	

Key: CI, confidence interval; IRC, independent review committee; IPI, International Prognostic Index; 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 limit estimates; [b], censoring was predominantly due to the clinical cut-off date with follow-up 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]

Figure 4: Kaplan–Meier plot of PFS based on IRC assessment, ITT analysis set



Key: IRC, independent review committee; ITT, intent-to-treat; PFS, progression-free 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]

Secondary analysis of PFS based on investigator assessment of the ITT population demonstrated a greater magnitude of improvement of PFS associated with VR-CAP compared with R-CHOP: 30.7 months versus 16.1 months (HR=0.51; p<0.001) (Table 14). This represents a 96% improvement in PFS in the VR-CAP group.

Table 14: PFS based on investigator assessment, ITT analysis set

	VR-CAP (n=243)	R-CHOP (n=244)
PFS, days[a]		
Number of censored (%)	115 (47.3)[b]	65 (26.6)[b]
Number of events (%)	128 (52.7)	179 (73.4)
25% quartile (95% CI)	383 (308.0; 481.0)	271 (246.0; 304.0)
Median (95% CI)	934.0 (763.0; 1136.0)	490 (427.0; 561.0)
75% quartile (95% CI)	NE (1538.0; NE)	793.0 (710.0; 1141.0)
P-value[c]	<0.001	
Hazard ratio (95% CI)	0.51 (0.41; 0.65)	

Key: CI, confidence interval; IPI, International Prognostic Index; 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]

Differences between the two assessments appear to be due to single versus multiple scan assessment of PD as previously described (see section 4.6).

Sensitivity analysis of IRC alternative assessment resulted in 10 fewer PFS events and demonstrated a magnitude of improvement of PFS associated with VR-CAP that was closer to that estimated by investigator assessment: 28.5 months versus 14.8 months (HR: 0.56; p<0.001) (Table 15; Figure 5).

IRC alternative assessment of PFS data is used to populate the economic model presented in section 5 (see section 4.13).

Table 15: PFS based on IRC alternative assessment, ITT analysis set

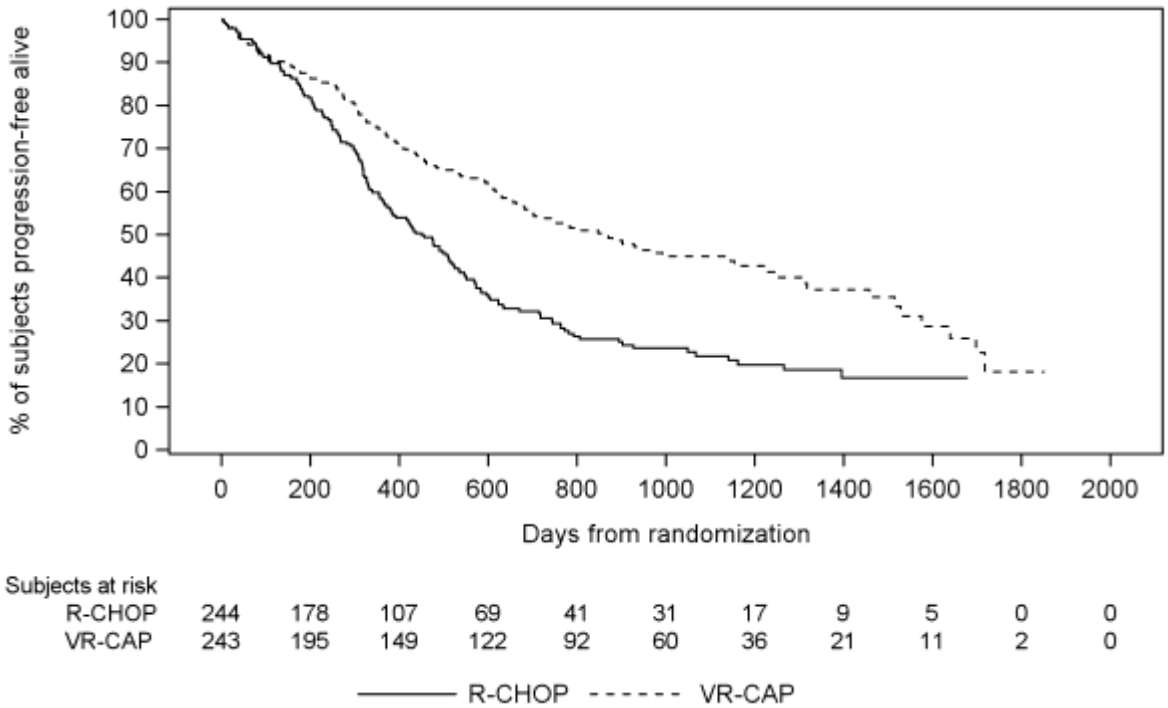
	VR-CAP (n=243)	R-CHOP (n=244)
PFS, days[a]		
Number of censored (%)	117 (48.1)[b]	82 (33.6)[b]
Number of events (%)	126 (51.9)	162 (66.4)
25% quartile (95% CI)	351.0 (298.0; 436.0)	251.0 (204.0; 302.0)
Median (95% CI)	866.0 (665.0; 1154.0)	450.0 (366.0; 518.0)
75% quartile (95% CI)	1698.0 (1515.0; NE)	902.0 (717.0; 1395.0)
P-value[c]	<0.001	
Hazard ratio (95% CI)	0.56 (0.44; 0.71)	

Key: CI, confidence interval; IPI, International Prognostic Index; 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]

Figure 5: Kaplan–Meier plot of PFS based on IRC alternative assessment, ITT analysis set



Key: IRC, independent review committee; ITT, intent-to-treat; PFS, progression-free 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]

Further sensitivity analyses for PFS, 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.

Secondary efficacy analysis

Secondary analyses of TTP, TTNT and TFI support the conclusion that replacement of vincristine with bortezomib in the chemotherapy induction regimen results in significant clinical benefit.[59, 60]

Time to disease progression

Based on IRC assessment of the ITT population, median TTP 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) (Appendix 8:Table 26, Appendix 8:Figure 1). Findings for TTP by investigator assessment were consistent with IRC assessment (Appendix 8:Figure 2). Kaplan–Meier plots of TTP and associated data are presented in Appendix 8.

Time to next anti-lymphoma treatment

In the ITT population, median TTNT was almost twice as long for subjects randomised to the VR-CAP group compared with those randomised to the R-CHOP group, at 1,353 days (44.5 months) versus 756 days (24.8 months), respectively (HR=0.50; p<0.001) (Appendix 8:Table 27, Appendix 8:Figure 3). The Kaplan–Meier plot of TTNT and associated data are presented in Appendix 8.

At the time of clinical cut-off, 132 subjects (54%) randomised to the R-CHOP group had received at least 1 subsequent anti-lymphoma treatment compared to 82 subjects (34%) in the VR-CAP group. Of the 132 subjects in the R-CHOP group who received subsequent therapy, 67 subjects (51%) received at least 2 lines of therapy, and 28 subjects (21%) received at least 3 lines of therapy. Of the 82 subjects in the VR-CAP group who received subsequent therapy, 32 subjects (39%) received at least 2 lines, and 13 subjects (16%) received at least 3 lines of subsequent therapy.

Treatment-free interval

In the safety population, the TFI was approximately twice as long for subjects treated with VR-CAP. Median TFI was 1,236 days (40.6 months) in subjects randomised to VR-CAP compared with 624 days (20.5 months) in subjects randomised to R-CHOP (HR=0.50; p<0.001) (Table 16).

Table 16: Duration of TFI, safety analysis set

	VR-CAP (n=240)	**R-CHOP (n=242)**
TFI, days[a]		
Number of censored (%)	147 (61.3)	97 (40.1)
Number of events (%)	93 (38.8)	145 (59.9)
25% quartile (95% CI)	573 (417.0; 745.0)	324 (263.0; 403.0)
Median (95% CI)	1236 (1023.0; NE)	624 (542.0; 693.0)
75% quartile (95% CI)	NE (NE; NE)	1275 (1069.0; NE)
P-value[b]		<0.001
Hazard ratio (95% CI)[c]		0.50 (0.38; 0.65)

Key: CI, confidence interval; IPI, International Prognostic Index; NE, not estimable; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; TFI, treatment-free interval; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.
Notes: [a], based on Kaplan–Meier product limit estimates; [b], based on Log rank test stratified with IPI risk and stage of disease; [c], based on Cox's model stratified by IPI risk and stage of disease.
Source: LYM-3002 CSR[60]; Robak et al. 2015.[59]

Clinical response

Both VR-CAP and R-CHOP were associated with a high rate of clinical response. However, VR-CAP demonstrated a superior depth of response with a higher rate of overall CR, shorter TTR and longer DoR.

Based on IRC assessment of the response evaluable population, 53.3% of subjects in the VR-CAP group demonstrated a complete response (CR + CRu) to treatment (confirmed by evidence of bone marrow clearance and LDH normalisation), compared with 41.7% of subjects in the R-CHOP group (OR: 1.69; p=0.007). Investigator response assessment demonstrated consistent results in favour of the VR-CAP group (41.5% vs 27.6%; OR: 1.89; p=0.002) (Table 17).

Table 17: Best overall response, response evaluable analysis set

	IRC assessment		Investigator assessment	
	VR-CAP (n=229)	**R-CHOP** (n=228)	**VR-CAP** (n=229)	**R-CHOP** (n=228)
Overall response (CR+CRu+PR), n (%)	211 (92.1)	204 (89.5)	219 (95.6)	209 (91.7)
OR (95% CI)	1.428 (0.749, 2.722)		2.022 (0.920, 4.446)	
p-value	0.275		0.073	
Overall complete response, n (%)	122 (53.3)	95 (41.7)	95 (41.5)	63 (27.6)
OR (95% CI)	1.688 (1.148, 2.481)		1.884 (1.259, 2.819)	
p-value	0.007		0.002	

Key: CI, confidence interval; CR, complete response; CRu, complete response unconfirmed; IRC, independent review committee; LDH, lactate dehydrogenase; OR, odds ratio; PR, partial response; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

Notes: [a], confirmed by evidence of bone marrow clearance and LDH normalisation.

Source: LYM-3002 CSR[60]; Robak et al. 2015.[59]

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). Investigator assessment of median time to initial response demonstrated similarly statistically significant improvement in time to initial response in favour of the VR-CAP treatment group (43 days vs 48 days; HR: 1.44; p<0.001) (Table 18).

Median DoR was markedly longer in subjects responding to VR-CAP treatment compared with subjects responding to R-CHOP treatment (Table 18). Based on IRC assessment, median duration of overall response, median DoR for complete responders and median duration of complete response were more than twice as long in the VR-CAP treatment group compared with the R-CHOP treatment group: 1,110 days (36.5 months) versus 459 days (15.1 months); 1,282 days (42.1 months) versus 563 days (18.5 months); and 1,282 days (42.1 months) versus 547 days (18.0 months), respectively (Table 18).

Based on IRC assessment, the associated rate of durable response (response with a duration ≥6 months) was also significantly higher in the VR-CAP treatment group compared with the R-CHOP treatment group, at 75.1% versus 66.2% (OR: 1.56;

p=0.035). The same applied to the rate of durable complete response: 48.9% versus 36.0% (OR: 1.80; p=0.003).

Similar results in response duration, in favour of the VR-CAP group, were observed based on investigator assessment (Table 18).

Table 18: TTR and DoR, response evaluable analysis set

	IRC assessment		Investigator assessment	
	VR-CAP (n=229)	**R-CHOP** (n=228)	**VR-CAP** (n=229)	**R-CHOP** (n=228)
Median TTR, days (95% CI)	42.0 (42.0; 43.0)	50.0 (44.0; 74.0)	43.0 (42,0; 43.0)	48.0 (43.0; 75.0)
HR (95% CI)	1.54 (1.26; 1.89)		1.44 (1.18; 1.75)	
p-value	<0.001		<0.001	
Median DoR, days (95% CI)	1110.0 (813.0; 1420.0)	459.0 (379.0; 518.0)	1060.0 (892.0; 1366.0)	491.0 (410.0; 560.0)
DoR for complete responder, days (95% CI)	1282.0 (933.0; 1602.0)	563.0 (486.0; 738.0)	NE (1255.0; NE)	684.0 (603.0; 913.0)
Duration of CR, days (95% CI)	1282.0 (933.0; 1495.0)	547.0 (425.0; 711.0)	1516.0 (1150.0; NE)	568.0 (476.0; 833.0)
Durable overall response (CR+CRu+PR) rate, n (%)	172 (75.1)	151 (66.2)	187 (81.7)	164 (71.9)
OR (95% CI)	1.563 (1.032, 2.367)		1.693 (1.090, 2.632)	
p-value	0.035		0.018	
Durable CR (CR+CRu) rate, n (%)	112 (48.9)	82 (36.0)	90 (39.3)	57 (25.0)
Odds ratio (95% CI)	1.799 (1.219, 2.656)		1.960 (1.302, 2.950)	
p-value	0.003		0.001	

Key: CI, confidence interval; CR, complete response; CRu, complete response unconfirmed; DoR, duration of response; IRC, independent review committee; NE, not estimable; OR, odds ratio; PR, partial response; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; TTR, time to response; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

Source: LYM-3002 CSR[60]; Robak et al. 2015.[59]

Overall survival

Overall survival data are not yet mature in the LYM-3002 trial. However, interim analysis indicates a consistent survival trend favouring the VR-CAP group.

Based on a median duration of 40 months follow-up (in which 158 deaths have 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 (Table 19). The interim Kaplan–Meier plot of OS 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 (Figure 6).

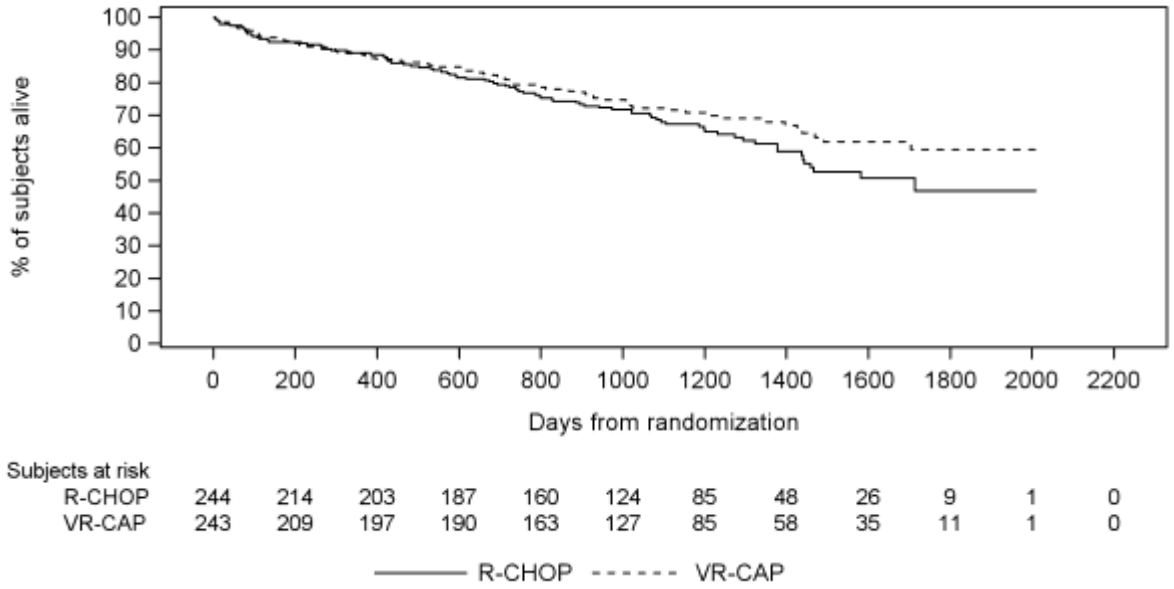
Survival rate estimates also demonstrate the clinical benefit of bortezomib replacement of vincristine in the chemotherapy regimen with a 4-year survival rate estimate of 64.4% in subjects randomised to VR-CAP compared with 53.9% in subjects randomised to R-CHOP (Table 19).

Table 19: OS, 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 6: 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: LYM-3002 CSR[60]; Robak et al. 2015.[59]

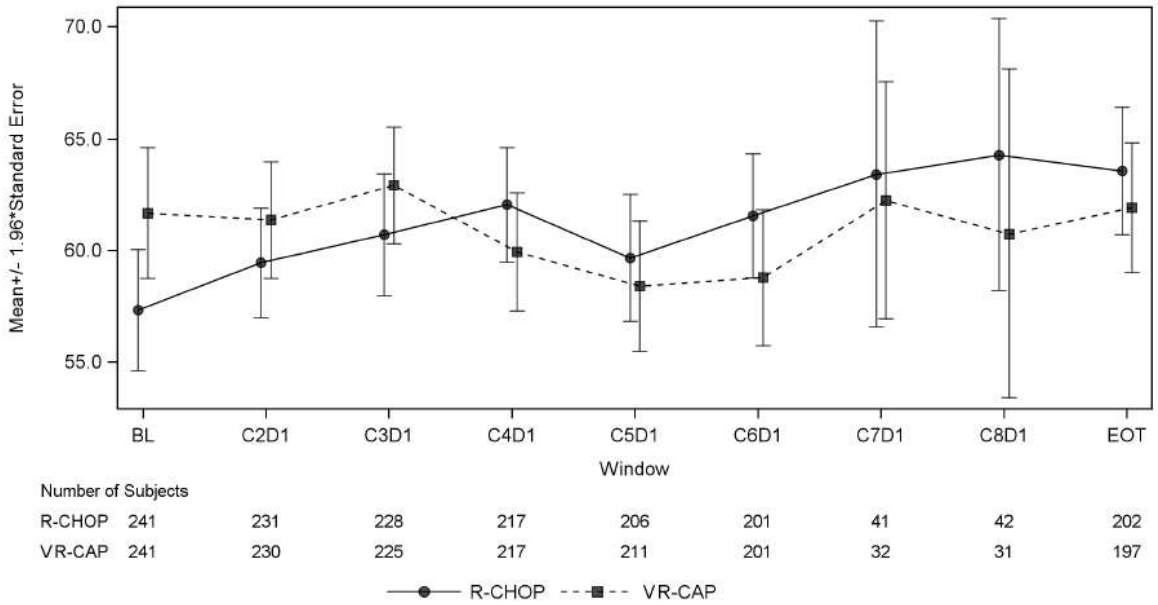
Exploratory analysis

Three different PRO tools were used to assess HRQL 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.[60] These tools are summarised in Appendix 5:Table 20. Questionnaires were completed at the screening visit, on day 1 of every treatment cycle before any other procedures were performed, and at the end-of-treatment visit. HRQL was not captured after the end-of-treatment visit.

During the treatment period, no statistically significant or clinically meaningful changes (defined as ≥10 point change[67]) in EORTC QLQ-C30 global health status were observed within either treatment group or between treatment groups from baseline to cycle 6 or end of treatment (Table 20; Figure 7). Mixed model analysis similarly showed no statistically significant differences between treatment groups for EORTC QLQ-C30 functional scales. Three of the symptom scales (nausea and vomiting, pain, and diarrhoea) showed a statistically significant difference ($p \leq 0.05$) favouring R-CHOP, but the mean differences were too small to be considered clinically meaningful (estimates for differences between groups over time were 2.0,

3.4 and 3.3 for nausea and vomiting, pain, and diarrhoea respectively). A significant difference favouring R-CHOP was also observed for the function scale of financial problems, although the relevance of this scale on the impact of treatment in a clinical study setting is unknown.

Figure 7: EORTC QLQ-C30 global health status over time, ITT analysis set



Key: BL, baseline; C, cycle; D, day; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EOT, end of treatment; ITT, intent-to-treat; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.
Source: LYM-3002 CSR.[60]

Subjects randomised to both VR-CAP and R-CHOP had slightly increased mean worst fatigue scores and mean fatigue interference scores through the end of treatment according to the BFI, with no statistically significant differences observed between groups (Table 20).

Utility values, translated from health profiling in accordance with the descriptive system of the EuroQoL-5 Dimension Questionnaire (EQ-5D), were similar between treatment groups at baseline and throughout the LYM-3002 treatment period (Table 20). A greater reduction in utility at cycle 6 was observed in the VR-CAP arm, which could be considered relevant in accordance with published minimal important difference (defined as ≥0.05-0.1[68, 69]). However, this was not considered clinically meaningful by practising haematologists in the context of the short duration of treatment for both therapies; that is, they would expect the negative impact on HRQL

to be a temporary on-treatment effect, which is anticipated with all chemotherapy regimens.[6]

Both treatment groups had slightly improved EQ-5D visual analogue scale (VAS) scores from baseline through the end of treatment, but a numerical difference favouring R-CHOP was observed at cycle 6 (Table 20). None of the observed changes in VAS scores through the end of treatment were considered clinically meaningful (defined as ≥10 point change[69]).

As the study design did not include PRO 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 HRQL in practice. Practising haematologists across the UK confirmed that they do not believe clinical trial-based HRQL assessments adequately capture differences in patient HRQL based on treatment effect. They do, however, believe that a TFI of over 3 years represents a meaningful benefit to patients with MCL for whom HSCT is unsuitable.[6, 52]

Exploratory analysis of medical resource data collected in the LYM-3002 is ongoing. Exploratory biomarker analyses are summarised in Appendix 8:Table 28; 29.

Table 20: Summary of PRO, HRQL analysis set

	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)

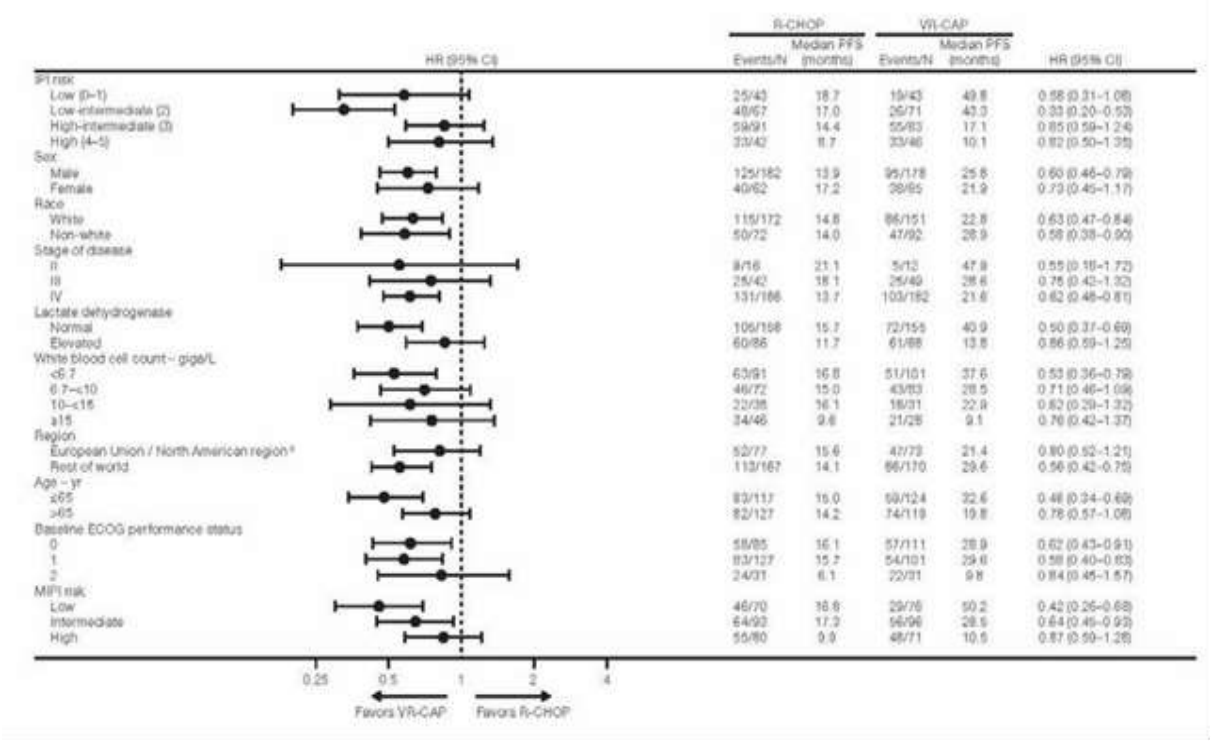
Key: BFI, Brief Fatigue Inventory; CFB, change from baseline; CSR, clinical study report; EOT, end of treatment; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, EuroQol 5 Dimension Questionnaire; FIS, fatigue interference score; GHS, global 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]

4.8 Subgroup analysis

Prospectively planned subgroup analyses of PFS based on IPI risk, sex, race, geographic region, age, stage of disease at diagnosis, baseline ECOG score, LDH and WBC were consistent with the results of the ITT population, with significant prolongation of PFS associated with VR-CAP (Figure 8).

Figure 8: PFS subgroup analysis based on IRC assessment, ITT analysis set



Key: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IPI, International Prognostic Index; IRC, independent review committee; ITT, intent-to-treat; MIPI, MCL International Prognostic Index; PFS, progression-free survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.
Source: Robak et al. 2015.[59]

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 subjects with a PFS event out of 8 enrolled into

the R-CHOP group, and 4 subjects 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).

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]). Formal comparative assessment based on region demonstrated no significant difference in survival outcomes for patients from North America and Western Europe versus the rest of the World, as presented in Appendix 8:Table 30.

Post-hoc analyses were conducted to formally investigate survival outcomes in subjects considered medically ineligible for HSCT and those who could be considered medically eligible for HSCT in UK clinical practice. Survival outcomes were consistent between these groups and with the results of the ITT population, with a positive effect attributable to VR-CAP therapy (Table 21). Formal comparative assessment confirmed that there were no significant differences in survival outcomes for patients medically ineligible for HSCT versus patients medically eligible, as presented in Table 22.

Table 21: Survival outcomes, medically ineligible for HSCT and medically eligible for HSCT analysis sets

	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[62]; LYM-3002 CSR.[60]

Table 22: Post-hoc comparative efficacy assessment of survival outcomes in patients medically ineligible versus medically eligible for HSCT

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.

Post-hoc analysis was also conducted to investigate the impact of bortezomib dose intensity on OS.[63] For this analysis, bortezomib dose intensity during cycles 1–6 was calculated, and the median value selected as a cut-off for dichotomisation of patients to be included in lower or higher (<4.6 vs ≥4.6 mg/m^2/cycle) dose intensity groups. OS was then compared between groups among patients who had received ≥6 cycles

of bortezomib (n=181) in a landmark analysis from the end of cycle 6. OS 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 OS rates of 79.5% versus 57.1%, respectively.

4.9 Meta-analysis

Meta-analysis was not conducted as a single RCT provides the evidence base supporting the use of VR-CAP for the treatment of adult patients with previously untreated MCL unsuitable for HSCT.

4.10 Indirect and mixed treatment comparisons

It is important to note that established practice for the treatment of patients with previously untreated MCL for whom HSCT is unsuitable in NHS England and Wales is the use of R-CHOP induction therapy. Other induction therapy regimens listed in the final appraisal scope 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 (Figure 1). Nevertheless, to align with the final appraisal scope, and for transparency, indirect comparison analyses to alternative rituximab-chemotherapy induction regimens have been conducted where possible. These analyses are not considered robust due to important heterogeneity between LYM-3002 and the comparator studies, and due to methodological limitations of the comparator studies.

The systematic literature review methods used to identify RCTs used in indirect comparison analyses are described in section 4.1. In addition to the LYM-3002 trial, six RCTs met the eligibility criteria presented in Table 7. These studies are listed in Table 23.

Table 23: List of relevant RCTs for comparators to VR-CAP included in the final appraisal scope

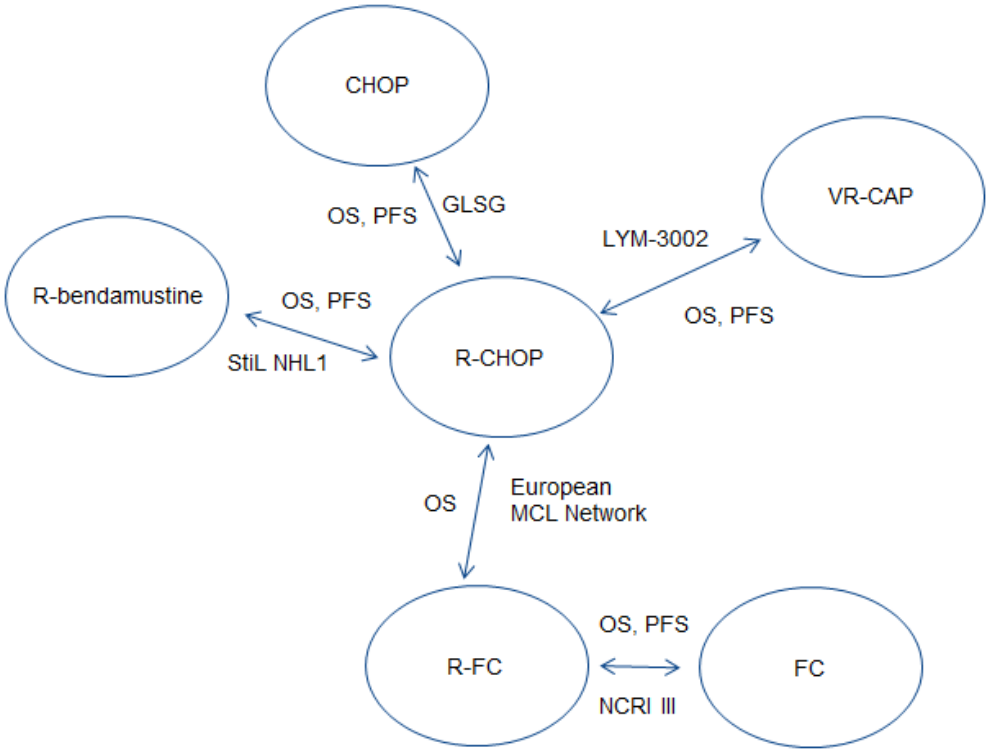
Trial Name	Population	Intervention	Comparator	Primary Study Reference	Secondary Study References
LY05	Previously untreated MCL	R-FC	FC	Eve et al. 2009[70]	Rule et al. 2005[71]
BRIGHT	Previously untreated indolent NHL or MCL	R-bendamustine	R-CHOP/ R-CVP	Flinn et al. 2014[72]	-
European MCL Elderly trial	Aged over 66 years with newly diagnosed MCL; ineligible for HSCT	R-FC	R-CHOP	Kluin-Nelemans et al. 2012[41]	-
GLSG	Previously untreated follicular lymphoma, MCL or lymphoplasma-cytic lymphoma; eligible for HSCT	R-CHOP	CHOP	Lenz et al. 2005[50]	Hoster et al. 2008[48]
NCRI III	Newly diagnosed MCL	R-FC	FC	Rule et al. 2011[73]	-
StiL NHL	Newly diagnosed indolent lymphoma or MCL	R-bendamustine	R-CHOP	Rummel et al. 2013[52]	Rummel et al. 2014[61] Rummel et al. 2014[74]

Key: FC, fludarabine and cyclophosphamide; GLSG, Grade Lymphoma Study Group; HSCT, haematopoietic stem cell transplantation; MCL, mantle cell lymphoma; NCRI, National Cancer Research Institute; NHL, non-Hodgkin's lymphoma; R-bendamustine, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP, rituximab with cyclophosphamide, vincristine and prednisone; R-FC, rituximab with fludarabine and cyclophosphamide; RCT, randomised controlled trial; StiL, Study Group of indolent Lymphomas; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

Survival outcomes were selected for indirect comparison analyses as all chemotherapy induction regimens used in the treatment of MCL are associated with a high level of clinical response, but responses tend to be temporary (see section 3.2). The benefit of VR-CAP is that it offers a greater depth of response resulting in prolonged PFS and OS. Hence, it is important to compare these clinical outcomes in order to establish the patient benefit that can be expected with VR-CAP induction therapy in clinical practice.

Only four RCTs in addition to the LYM-3002 trial reported PFS and/or OS 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 9.

Figure 9: 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.
Notes: LY-05 trial data included only 4-month survival estimates at the time of analysis; BRIGHT trial data included only response estimates at the time of analysis.

Of these RCTs, the European MCL Elderly trial[41] and the StiL NHL1 trial[52] provided evidence of comparators that were included in the decision problem which could be linked to LYM-3002 for PFS or OS analysis through the common comparator, R-CHOP (Figure 9). However, there are fundamental differences between LYM-3002 and these comparator trials, which result in marked differences between the survival times reported for common treatment arms. Key sources of heterogeneity and methodological limitations of the comparator studies are summarised here. Further

details of these trials, including key outcome data, are presented in Appendix 9; the associated quality assessment is presented in Appendix 7.

European MCL Elderly trial

Overall, baseline demographics and disease characteristics of patients enrolled in LYM-3002 and the European MCL Elderly trial are reasonably similar, with both trials only enrolling patients ineligible for HSCT. The median age of patients enrolled in the European MCL Elderly trial was slightly higher than those of patients enrolled in the LYM-3002 trial (70 vs 66 years), in line with the age eligibility criterion for this trial (Table 23). Associated disease characteristics of patients enrolled in the European MCL Elderly Trial were also slightly worse, with more patients presenting at high MIPI risk (50%) (see Appendix 9:Table 31).

There were also differences between treatment regimens, with all patients receiving 8 cycles of R-CHOP induction therapy, regardless of response at cycle 6 in the European MCL Elderly trial. This is not reflective of clinical practice.

Moreover, the European MCL Elderly trial contained a secondary randomisation phase where subjects could receive rituximab or interferon-alpha maintenance therapy post induction. Maintenance therapy is discussed further in section 4.13. Trial data used in the tentative comparative efficacy analysis presented below are survival estimates reported for induction therapy (see Appendix 9:Table 32); however, 184 patients receiving R-CHOP and 132 patients receiving R-FC induction therapy were assigned to subsequent maintenance therapy (rituximab or interferon-alpha). Survival estimates for patients who did not go on to receive maintenance therapy were markedly shorter (see Appendix 9:Table 32), although median values are associated with significant uncertainty due to small patient numbers. As the European MCL Elderly trial was not designed to assess the clinical efficacy of induction therapy ± maintenance therapy, survival estimates cannot be fully disaggregated and should be interpreted with caution.

Whilst both the European MCL Elderly trial and the LYM-3002 trial used the IWRC to assess PD, assessments were only conducted twice yearly during follow-up in the European MCL Elderly trial compared with every 6-8 weeks in LYM-3002. This 6-monthly assessment could result in overestimation of time to treatment failure (TTF) (reported for induction therapy) and duration of remission (reported for maintenance

therapy) as PD in accordance with IWRC may go undetected for a number of weeks/months. Furthermore, there was no independent (blinded) assessment of progression in the European MCL Elderly trial. This could again result in overestimation of TTF and duration of remission as it is well understood that unmasked investigator assessments are less conservative than IRC assessments, as demonstrated in the LYM-3002 trial (see section 4.7).

StiL NHL1 trial

The StiL NHL1 trial was designed to investigate clinical efficacy in the wider lymphoma population (Table 23). MCL subgroup analysis was not covered by statistical powering, as noted in the quality assessment presented in Appendix 7:Table 24.

MCL patient numbers were subsequently low in this trial (n=94), and baseline characteristic data were not available for this subgroup of patients in the majority (despite author contact) (see Appendix 9:Table 31). Comparisons outside of median age, which was slightly higher in the StiL NHL1 trial (70 years) than in LYM-3002, were therefore not possible.

In terms of comparability of treatment regimens, the StiL NHL1 trial only administered six cycles of R-CHOP induction therapy regardless of response status, that is, without the possibility to consolidate a delayed response with 2 further cycles, as was the case in LYM-3002. This is not reflective of clinical practice.

As was the case in the European MCL Elderly Trial, PD assessments were only conducted twice yearly during follow-up in the StiL NHL1 trial by unmasked investigator assessment. Concerns over the potential consequence of this in regard to overestimation of PFS are reinforced when reviewing the PFS Kaplan-Meier plot from this trial, where no MCL patients are shown to progress, relapse, or die between approximately 6-18 months. Additional uncertainty of the clinical validity of outcomes from the MCL subgroup of the StiL NHL1 trial comes from the lack of a consistent trend in clinical benefit. Reported PFS estimates favour R-bendamustine therapy, but both response analysis and recently reported OS estimates favour R-CHOP therapy (Appendix 9:Table 33).[74]

When considering the appropriateness of using data from this trial in indirect comparison analyses, a further concern of using PFS data is that the PFS Kaplan-Meier curves for R-CHOP and R-bendamustine cross-over in the first 12 months of the StiL NHL1 trial (likely due to low frequency of assessments as discussed above). Finally, the WHO criteria[75], which use a slightly different definition for PD than the IWRC, were adopted to assess response and progression in the StiL NHL1 trial. Whilst not thought to be as great a source of heterogeneity for the difference in assessment times, this is another difference between trials that further brings into question their comparability.

Indirect treatment comparison

Common limitations associated with indirect comparison analyses include the assumption of comparable patient populations and trial characteristics and the assumption of proportional hazards between treatments. In light of the differences between the RCTs identified and the non-proportional hazards observed in Kaplan-Meier survival curves (see section 4.7 and Appendix 9), these assumptions do not hold. Therefore, indirect comparison outcomes should be interpreted with caution, particularly that of VR-CAP versus R-bendamustine, where there are additional concerns over the internal validity of survival estimates reported in the StiL NHL1 trial.

Two pairwise Bucher indirect comparisons[76] were nonetheless conducted to provide indicative estimates of comparative efficacy. The results of these analyses are presented in Table 24. More sophisticated statistical methods, for example, network meta-analysis, were not deemed appropriate since the nature of confounding within the available evidence base (discussed above) cannot be quantified using these methods, that is, using purer statistical methods and presenting the surrounding uncertainty might lead to an underestimation of the level of uncertainty associated with indirect comparison estimates based on the available evidence.

Table 24: Bucher indirect comparison analyses of PFS and OS

	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.

VR-CAP induction therapy demonstrates a reduced hazard of death compared with R-FC, and a trend towards reduced hazard versus R-bendamustine, although the confidence interval crosses 1 for this comparison. This finding for R-bendamustine is inconsistent with the outcomes of PFS indirect comparison analysis, where R-bendamustine induction therapy demonstrates a reduced hazard of PD or death compared with VR-CAP albeit with a wide confidence interval. Of note, a HR for TTF, that could have been used as a proxy for PFS in indirect analysis versus R-FC, was reported for induction therapy in the European MCL Elderly trial but as no significant difference was observed between treatment arms (p=0.5), the added value of attempting to include these data in an indirect analysis was considered negligible.

Inconsistencies within the indirect comparison analyses are a result of the weak and heterogeneous evidence base on which the comparison of VR-CAP to rituximab-chemotherapy induction regimens other than R-CHOP can be made, as previously discussed in this section. In consideration of this, the indirect comparison estimates are deemed too unreliable to use in the base case cost effectiveness analysis presented in section 5. A simple and conservative assumption of comparability with R-CHOP was therefore preferred for the additional comparators named in the decision problem, an assumption that was validated by haematology experts[6] and non-RCT evidence (see section 4.11).

4.11 Non-randomised and non-controlled evidence

Due to the paucity of RCT evidence in MCL, controlled clinical trials (non-randomised), non-controlled clinical trials (single-arm) and prospective and retrospective observational studies were also included in the systematic literature review described in section 4.1.

Whilst considered less relevant to the decision problem (see section 3.2), qualitative synthesis of non-RCT evidence of rituximab-chemotherapy induction regimens beyond R-CHOP has been conducted where possible.

In total, 11 non-RCTs met the eligibility criteria presented in Table 7; references for these studies are provided in Appendix 10. Eight of the identified non-RCTs investigated R-CHOP induction therapy, and were not considered to provide additional relevant evidence further to the pivotal RCT.Three provided evidence for alternative rituximab-chemotherapy induction regimens. Two of these studies investigated R-bendamustine ± cytarabine induction therapy but enrolled too few patients (≤20 previously untreated MCL patients) to provide conclusive supportive evidence and are thus not discussed further.[77, 78] The remaining study was a large-scale observational study that provided survival data for a number of chemotherapy induction regimens ± rituximab.[79] This study is considered relevant to the decision problem as detailed in Table 25. Quality assessment for this study is presented in Appendix 7:Table 25.

Table 25: List of relevant non-RCTs for potential comparators to VR-CAP

Study ID	Objective	Population	Primary study reference	Justification for inclusion
NLG observational study	To determine the efficacy of different induction chemotherapy regimens in terms of OS to evaluate the therapy options for older patients; to study the incidence of MCL over time and the prognosis of MCL in relation to clinical prognostic factors	All patients diagnosed with MCL in Sweden between Jan 2000 and Sep 2011 and in Denmark between Jan 2001 and Dec 2010.	Abrahamsson et al. (2014)[79]	Provides survival data for chemotherapy induction regimens named in the decision problem, for which no head-to-head RCT evidence was identified.

Key: MCL, mantle cell lymphoma; NLG, Nordic Lymphoma Group; OS, overall survival; RCT, randomised controlled trial; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.
Source: Abrahamsson et al. 2014.[79]

The general trend observed was that there were no statistically significant differences between the OS associated with chemotherapy induction regimens adopted, with the exception of cyclophosphamide, vincristine and prednisone (CVP), which demonstrated a significantly shorter survival time (Table 26). However, this may simply be a reflection of the poorer health of patients that would receive such induction therapy.

Table 26: Multivariate analysis on OS in patients receiving systemic therapy for MCL in the NLG observational study, adjusted for gender and MIPI

	HR	95% CI	p-value
Chemotherapy regimen			
Nordic MCL2[a]	-	-	-
CHOP	1.080	0.73-1.59	0.698
CHOP/cytarabine	0.900	0.53-1.52	0.692
FC	1.018	0.61-1.70	0.945
Chlorambucil	1.167	0.73-1.85	0.514
Bendamustine	1.032	0.51-2.10	0.930
Other regimens	1.613	0.97-2.68	0.065
Cytarabine	1.202	0.62-2.33	0.585
CVP	2.827	1.68-4.76	<0.001
Rituximab	0.600	0.51-0.85	0.001

Key: CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CI, confidence interval; CVP, cyclophosphamide, vincristine and prednisone; FC, fludarabine and cyclophosphamide; HR, hazard ratio; MCL, mantle cell lymphoma; MIPI, MCL International Prognostic Index; NLG, Nordic Lymphoma Group; Nordic MCL2, rituximab and cytarabine with cyclophosphamide, doxorubicin, vincristine and prednisone; OS, overall survival.

Notes: [a], used as reference treatment.

Source: Abrahamsson et al. 2014.[79]

Given that VR-CAP has demonstrated a survival benefit over R-CHOP induction therapy in the LYM-3002 trial, and the comparability or inferiority to R-CHOP of other rituximab-chemotherapy induction regimens, qualitative synthesis of the complete evidence base suggests that VR-CAP would also demonstrate a survival benefit across all other rituximab-chemotherapy induction regimens potentially used in UK clinical practice.

4.12 Adverse reactions

No additional studies to the LYM-3002 trial (described in sections 4.2 to 4.6) are presented to provide evidence of the safety and tolerability of bortezomib in MCL. The LYM-3002 trial was designed to assess safety and provide information regarding the adverse effects associated with the use of bortezomib in MCL.[59, 60]

Treatment exposure

The majority of subjects received at least six cycles of treatment in the LYM-3002 trial: 84% of patients randomised to VR-CAP, and 83% of patients randomised to R-CHOP.[59, 60] Seventy-five (15%) subjects were permitted to receive up to two extra cycles of treatment, as per the protocol. This was more common in subjects randomised to the R-CHOP treatment arm, within which more patients demonstrated initial response at cycle 6 (17.2%) compared with patients randomised to VR-CAP (13.2%). The median individual treatment duration ranged from 15.4 to 16.3 weeks for the R-CHOP group, and ranged from 16.1 to 16.8 weeks for the VR-CAP group.

In the VR-CAP group, no subjects had a dose reduction of rituximab, 75 subjects (31%) had a dose reduction of cyclophosphamide, 41 subjects (17%) had a dose reduction of doxorubicin, 97 subjects (40%) had a dose reduction of bortezomib, and 22 subjects (9%) had a dose reduction of prednisone. In the R-CHOP group, 1 subject (<1%) had a dose reduction of rituximab for an infusion-related reaction, 26 subjects (11%) had a dose reduction of cyclophosphamide, 17 subjects (7%) had a dose reduction of doxorubicin, 11 subjects (5%) had a dose reduction of vincristine, and 19 subjects (8%) had a dose reduction of prednisone.

The mean relative dose intensity for the drugs common to both regimens (rituximab, cyclophosphamide, doxorubicin and prednisone) was 0.93 or higher. For subjects in the VR-CAP group, the mean relative dose intensity for bortezomib was 0.82, and for subjects in the R-CHOP group, the mean relative dose intensity for vincristine was 0.80.

Safety profile

The safety population, defined as all randomised subjects who received at least 1 dose of study medication, consisted of 240 subjects in the VR-CAP group and 242 subjects in the R-CHOP group.

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. Almost all subjects in both treatment groups experienced a treatment-emergent AE, although VR-CAP was associated with a slightly higher rate of Grade 3 or higher AEs and serious AEs (SAEs) (Table 27).

The majority of the fatal study drug-related AEs (3 subjects in each treatment group) were of infectious origin, none of which were solely attributed to the bortezomib or vincristine elements of the chemotherapeutic regimens.

Table 27: Safety and tolerability, safety analysis set

	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[60]; Robak et al. 2015.[59]

Common adverse events

In both treatment groups, the most commonly reported AEs and Grade 3 or higher AEs were haematological (blood and lymphatic system) disorders.[59, 60] There was a difference (i.e. ≥10% between treatment groups) in the incidence rates for the following AEs: neutropenia, thrombocytopenia, leukopenia, anaemia, lymphopenia, pyrexia, diarrhoea, nausea and cough, which were all more frequent in the VR-CAP group (Table 28).

Similarly, there was a difference in the incidence rates for the following Grade 3 or higher AEs: neutropenia, thrombocytopenia, leukopenia and lymphopenia, which were all more frequent in the VR-CAP group. Of the Grade 3 or higher AEs considered to be related to the study drug, the most common were neutropenia, thrombocytopenia, leukopenia, anaemia, lymphopenia and febrile neutropenia (Table 28).

All SAEs occurred at a frequency of <5% in each group, with the exception of neutropenia, pneumonia and febrile neutropenia. These were also the most commonly reported SAEs considered that were related to any study drug (Table 28).

Table 28: Common AEs, safety analysis set

	VR-CAP (n=240)	R-CHOP (n=242)
Blood and lymphatic system disorders		
Neutropenia, n (%)	211 (87.9)	178 (73.6)
Related to any study drug	209 (87.1)	172 (71.1)
Grade 3 or higher	203 (84.6)	162 (66.9)
Related to any study drug	200 (83.3)	156 (64.5)
Serious	12 (5.0)	13 (5.4)
Related to any study drug	12 (5.0)	12 (5.0)
Thrombocytopenia, n (%)	173 (72.1)	46 (19.0)
Related to any study drug	172 (71.7)	42 (17.4)
Grade 3 or higher	136 (56.7)	14 (5.8)
Related to any study drug	135 (56.3)	12 (5.0)
Serious	8 (3.3)	1 (0.4)
Related to any study drug	8 (3.3)	1 (0.4)
Leukopenia, n (%)	120 (50.0)	93 (38.4)
Related to any study drug	116 (48.3)	87 (36.0)
Grade 3 or higher	105 (43.8)	71 (29.3)

	VR-CAP (n=240)	R-CHOP (n=242)
Related to any study drug	103 (42.9)	66 (27.3)
Serious	6 (2.5)	3 (1.2)
Related to any study drug	6 (2.5)	2 (0.8)
Anaemia, n (%)	122 (50.8)	90 (37.2)
Related to any study drug	106 (44.2)	71 (29.3)
Grade 3 or higher	37 (15.4)	33 (13.6)
Related to any study drug	31 (12.9)	27 (11.2)
Serious	4 (1.7)	5 (2.1)
Related to any study drug	4 (1.7)	4 (1.7)
Lymphopenia, n (%)	74 (30.8)	32 (13.2)
Related to any study drug	68 (28.3)	28 (11.6)
Grade 3 or higher	67 (29.7)	21 (8.7)
Related to any study drug	61 (25.4)	17 (7.0)
Serious	1 (0.4)	0
Related to any study drug	0	0
Febrile neutropenia, n (%)	41 (17.1)	34 (14.0)
Related to any study drug	41 (17.1)	33 (13.6)
Grade 3 or higher	36 (15.0)	33 (13.6)
Related to any study drug	36 (15.0)	32 (13.2)
Serious	26 (10.8)	20 (8.3)
Related to any study drug	26 (10.8)	19 (7.9)
Infections and infestations		
Pneumonia, n (%)	28 (11.7)	15 (6.2)
Related to any study drug	20 (8.3)	11 (4.5)
Grade 3 or higher	17 (7.1)	11 (4.5)
Related to any study drug	13 (5.4)	8 (3.3)
Serious	19 (7.9)	7 (2.9)
Related to any study drug	14 (5.8)	5 (2.1)
General disorders and administration site conditions		
Pyrexia, n (%)	70 (29.2)	37 (15.3)
Related to any study drug	48 (20.0)	23 (9.5)
Grade 3 or higher	8 (3.3)	5 (2.1)
Related to any study drug	7 (2.9)	5 (2.1)
Serious	10 (4.2)	4 (1.7)
Related to any study drug	7 (2.9)	3 (1.2)
Fatigue, n (%)	56 (23.3)	47 (19.4)

	VR-CAP (n=240)	R-CHOP (n=242)
Related to any study drug	43 (17.9)	38 (15.7)
Grade 3 or higher	15 (6.3)	6 (2.5)
Related to any study drug	12 (5.0)	5 (2.1)
Serious	0	3 (1.2)
Related to any study drug	0	3 (1.2)
Asthenia, n (%)	38 (15.8)	26 (10.7)
Related to any study drug	29 (12.1)	18 (7.4)
Grade 3 or higher	7 (2.9)	2 (0.8)
Related to any study drug	5 (2.1)	1 (0.4)
Serious	1 (0.4)	0
Related to any study drug	1 (0.4)	0
Oedema peripheral, n (%)	37 (15.4)	25 (10.3)
Related to any study drug	16 (6.7)	13 (5.4)
Grade 3 or higher	1 (0.4)	1 (0.4)
Related to any study drug	1 (0.4)	0
Serious	0	1 (0.4)
Related to any study drug	0	1 (0.4)
Gastrointestinal disorders		
Diarrhoea, n (%)	73 (30.4)	22 (9.1)
Related to any study drug	59 (24.6)	11 (4.5)
Grade 3 or higher	12 (5.0)	5 (2.1)
Related to any study drug	11 (4.6)	4 (1.7)
Serious	4 (1.7)	3 (1.2)
Related to any study drug	4 (1.7)	2 (0.8)
Constipation, n (%)	60 (25.0)	38 (15.7)
Related to any study drug	42 (17.5)	22 (9.1)
Grade 3 or higher	1 (0.4)	2 (0.8)
Related to any study drug	1 (0.4)	1 (0.8)
Serious	0	1 (0.4)
Related to any study drug	0	1 (0.4)
Nausea, n (%)	59 (24.6)	33 (13.6)
Related to any study drug	54 (22.5)	28 (11.6)
Grade 3 or higher	1 (0.4)	0
Related to any study drug	1 (0.4)	0
Serious	0	0
Related to any study drug	0	0

	VR-CAP (n=240)	R-CHOP (n=242)
Vomiting, n (%)	30 (12.5)	13 (5.4)
Related to any study drug	24 (10.0)	8 (3.3)
Grade 3 or higher	1 (0.4)	0
Related to any study drug	1 (0.4)	0
Serious	2 (0.8)	1 (0.4)
Related to any study drug	2 (0.8)	0
Stomatitis, n (%)	26 (10.8)	21 (8.7)
Related to any study drug	20 (8.3)	19 (7.9)
Grade 3 or higher	3 (1.3)	1 (0.4)
Related to any study drug	2 (0.8)	1 (0.4)
Serious	1 (0.4)	2 (0.8)
Related to any study drug	0	2 (0.8)
Nervous system disorders		
Peripheral sensory neuropathy, n (%)	54 (22.5)	48 (19.8)
Related to any study drug	53 (22.1)	45 (18.6)
Grade 3 or higher	12 (5.0)	6 (2.5)
Related to any study drug	12 (5.0)	6 (2.5)
Serious	1 (0.4)	0
Related to any study drug	1 (0.4)	0
Neuralgia, n (%)	25 (10.4)	2 (0.8)
Related to any study drug	25 (10.4)	1 (0.4)
Grade 3 or higher	9 (3.8)	0
Related to any study drug	9 (3.8)	0
Serious	2 (0.8)	0
Related to any study drug	2 (0.8)	0
Respiratory, thoracic and mediastinal disorders, n (%)		
Cough, n (%)	49 (20.4)	20 (8.3)
Related to any study drug	11 (4.6)	6 (2.5)
Grade 3 or higher	3 (1.3)	0
Related to any study drug	2 (0.8)	0
Serious	0	0
Related to any study drug	0	0
Metabolism and nutrition disorders, n (%)		
Decreased appetite, n (%)	46 (19.2)	23 (9.5)
Related to any study drug	36 (15.0)	15 (6.2)

	VR-CAP (n=240)	R-CHOP (n=242)
Grade 3 or higher	2 (0.8)	2 (0.8)
Related to any study drug	1 (0.8)	1 (0.4)
Serious	1 (0.4)	0
Related to any study drug	1 (0.4)	0
Skin and subcutaneous tissue disorders		
Alopecia, n (%)	33 (13.8)	33 (13.6)
Related to any study drug	31 (12.9)	33 (13.6)
Grade 3 or higher	2 (0.8)	4 (1.7)
Related to any study drug	2 (0.8)	4 (1.7)
Serious	0	0
Related to any study drug	0	0
Psychiatric disorders, n (%)		
Insomnia, n (%)	27 (11.3)	18 (7.4)
Related to any study drug	16 (6.7)	8 (3.3)
Grade 3 or higher	1 (0.4)	0
Related to any study drug	1 (0.4)	0
Serious	0	0
Related to any study drug	0	0

Key: CSR, clinical study report; 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]

Despite the more frequent incidence of haematological disorders in subjects treated with VR-CAP, this induction regimen was well tolerated, with very few (if any) subjects discontinuing treatment due to the following AEs: neutropenia (n=2), thrombocytopenia (n=2), leukopenia (n=0), anaemia (n=1), lymphopenia (n=0) or febrile neutropenia (n=0).

Haematology laboratory parameter assessment demonstrated a general trend of transient, cyclical decreases of blood cell counts up to day 11, which largely recovered by day 1 of the next cycle. Higher rates of thrombocytopenia, anaemia and neutropenia, when they did occur, were managed effectively with platelet transfusions, red blood cell transfusions and prophylactic use of colony stimulating factors, respectively.

As a result, the rates of clinically meaningful consequences of haematological disorders were low and similar between groups:

- For the majority of the subjects with the worst thrombocytopenia lab values during treatment in the Grade 4 category (n=70), platelet values ranged between ≥10 giga/L and <25 giga/L.
- The incidence of bleeding events was 6% for subjects treated with VR-CAP compared with 5% for subjects treated with R-CHOP, with all but one subject (in the R-CHOP group, whose AE outcome was unknown) recovering from bleeding events without sequelae within 22 days or less; and no subjects in the LYM-3002 study died due to a bleeding AE or bleeding event related to any study drug.
- The incidence of neutropenic infection (≥Grade 3) was higher in subjects treated with VR-CAP at 17% compared with 10% in subjects treated with R-CHOP. However, this did not result in higher rates of fatality in patients with neutropenic infection: 12.2% [5/41] in the VR-CAP group versus 16.7% [4/24] in the R-CHOP group.

Some of the disparity in the incidence rates of haematological laboratory AEs between the two treatment groups may have been influenced by sampling bias, given that laboratory samples were taken twice as often for subjects in the VR-CAP group (days 1, 4, 8, and 11 every cycle) than in the R-CHOP group (days 1 and 11 every cycle), or may have been due to reporting bias since the protocol required that haematological laboratory AEs resulting in a dose modification of bortezomib or another agent had to be reported as an AE, and more dosing decisions had to be made in the VR-CAP treatment group.

Regardless of the imbalance being solely drug related or otherwise, practising haematologists across the UK confirmed that AEs of a haematological nature are expected with chemotherapeutic regimens and that the majority do not require additional follow-up or intervention.[6] There was a higher number of platelet transfusions in the VR-CAP group of the LYM-3002 trial (23% vs 3%), but given the low frequency of severe thrombocytopenia or severe thrombocytopenic bleeding events observed, this is likely the result of treating physicians prophylactically transfusing subjects with low platelet counts to avoid having to modify bortezomib

dosing. This seems aligned with common treatment paradigms for high-grade lymphoma that attempt to achieve maximum therapeutic benefit given the observed correlation between bortezomib dosing and long-term survival.[63]

Adverse events of clinical interest

Additional analyses were performed on AEs of clinical interest, which were selected based on the known safety profiles of bortezomib and R-CHOP and on AEs under surveillance in the bortezomib Risk Management Plan.[59, 60]

Of these AEs, peripheral neuropathy was the most commonly reported; its incidence was similar in subjects treated with VR-CAP and R-CHOP, at 30% and 29%, respectively. Peripheral neuropathy was completely resolved in 81% of subjects in the VR-CAP group and 75% of subjects in the R-CHOP group, with a faster median time to resolution of 91 days in the VR-CAP group versus 168 days in the R-CHOP group. Resolution/improvement was noted for 90% of subjects in the VR-CAP group within a median of 46 days versus 79% of subjects in the R-CHOP group within a median of 145 days. Furthermore, bortezomib was administered intravenously in LYM-3002, whereas routine practice in the UK is to administer the subcutaneous formulation (see section 4.13).

The incidence of all other AEs of special interest was low and similar (≤10% difference) between treatment groups (VR-CAP vs R-CHOP): cardiac rhythm abnormalities (10% vs 11%), acute hypersensitivity (9% vs 3%), herpes zoster (7% vs 1%), heart failure (3% vs 2%), acute diffuse infiltrative pulmonary disease (2% vs 3%), hepatitis B (1% vs 1%), and central nervous system disorders (<1% vs 0).

Safety overview

VR-CAP was well tolerated, with a high rate of treatment completion, a low rate of discontinuations due to an AE and low fatality. All AEs reported in the LYM-3002 trial were consistent with the known safety profile of bortezomib or the RCAP backbone common to both treatment groups and were therefore expected. AEs in patients treated with VR-CAP were manageable in the majority, with no significant effect on the number of completed cycles, median dose intensity for drugs common to both regimens, or rates of discontinuations or deaths related to AEs as compared to patients treated with R-CHOP.

Bortezomib is already available in England and Wales and used to treat multiple myeloma. No additional safety issues have emerged with its use in UK practice; in fact, subcutaneous administration has reduced bortezomib-related neurotoxicity events (see section 4.13). In addition, post-marketing surveillance of bortezomib use in MCL in the relapsed/refractory setting (for which it is authorised in the US, Japan and Switzerland) has not highlighted any additional safety concerns.

Appropriate precautions to be followed by healthcare professionals and patients in light of the potential risks associated with bortezomib use are clearly outlined in its SmPC and the bortezomib package leaflet, in accordance with the bortezomib Risk Management Plan. In addition, Janssen Cilag will ensure that healthcare professionals receive educational material explaining how to calculate the dose and how to prepare and administer bortezomib.

4.13 Interpretation of clinical effectiveness and safety evidence

Summary of clinical unmet need

MCL is a rare but aggressive sub-type of NHL. Whilst it only affects approximately 500 patients in England and Wales each year, these patients present a significant challenge to the treating haematologist, with MCL having a poorer prognosis than other, more common types of lymphoma.

There are currently no licensed induction therapy regimens for the treatment of adult patients with previously untreated MCL for whom HSCT is unsuitable, and thus no unanimously recognised standard of care, although R-CHOP is preferentially used in the first-line setting in NHS England and Wales. R-CHOP induction therapy (along with alternative rituximab-based chemotherapy induction regimens) is associated with high rates of clinical response, but these responses tend to be temporary, with high rates of relapse observed, resulting in a median PFS of less than 2 years and a median OS of less than 5 years in patients with MCL for whom HSCT is unsuitable.

Summary of key clinical outcomes from the LYM-3002 trial

- Median PFS (by IRC assessment) was 24.7 months for VR-CAP versus 14.4 months for R-CHOP (HR = 0.63; p<0.001). This exceeds the hypothesised treatment effect of 40% improvement in PFS.
- Complete response rates were 53.3% in the VR-CAP group versus 41.7% in the R-CHOP group (OR =1.688; p=0.007), and the median duration of CR was more than twice as long in patients treated with VR-CAP: 42.1 months versus 18.0 months.
- A fixed treatment duration of approximately 4 months resulted in a median TFI (by IRC assessment) of 40.6 months in patients treated with VR-CAP, nearly double the TFI associated with R-CHOP therapy of 20.5 months (HR=0.50, p<0.001).
- Median OS is yet to be reached for VR-CAP, compared to a median OS of 56.3 months for R-CHOP, suggesting a survival benefit to patients beyond the current standard of care.

- A consistent trend for improved OS in the VR-CAP treatment arm was observed, with a clear separation of Kaplan–Meier curves from 12 months and a 4-year survival rate estimated at 64% (vs 54% for R-CHOP).

Principal efficacy findings from the LYM-3002 trial

In the LYM-3002 trial, VR-CAP induction therapy demonstrated a statistically significant ($p<0.001$) and clinically meaningful improvement in PFS (primary endpoint) compared with R-CHOP. This improvement was consistently observed across sensitivity analyses, demonstrating the robustness of this outcome. The greatest magnitude of effect was observed in investigator assessed PFS analysis, which appears to be (at least partially) attributed to the fact that CT scans from multiple time points were used to assess PD alongside clinical assessment, and thus, fluid collections that were clearly resolved or improved at subsequent time points (transient lesions) were not classed as PD (see section 4.7). This better represents clinical practice, but in order to protect assessment bias minimisation in line with the LYM-3002 study design, the economic modelling is based upon the IRC alternative assessment PFS analysis.

OS data are not yet mature in the LYM-3002 trial. Nonetheless, there is a clear in-trial trend of improved long-term survival observed alongside the significant improvement in PFS. PFS has previously been reported as an acceptable surrogate marker for OS in MCL, with trial level analysis supporting the strong correlation between PFS and OS[21] as observed in the LYM-3002 trial.

Principal safety findings from the LYM-3002 trial

The VR-CAP regimen was generally well managed in the LYM-3002 trial, with high rates of treatment completion and AEs consistent with the known safety profile of bortezomib or the RCAP backbone, both of which are familiar to haematologists in NHS England and Wales.

Of the common AEs known to be associated with bortezomib, often of most concern to the patient is peripheral neuropathy as this can markedly impact independent living, even when experienced at a low level (Grade <3). Peripheral neuropathy was assessed as an AE of clinical interest in the LYM-3002 trial, and whilst incidence was reasonably high (30%), it was comparable to the incidence rate in R-CHOP treated

subjects (29%) and was completely resolved in the majority of subjects. Bortezomib-related neurotoxicity is known to be reversible[80, 81] and can be reduced in practice with subcutaneous administration of bortezomib and flexible dosing.[7, 82, 83]

AEs in patients treated with VR-CAP were manageable, with no significant effect on the number of completed cycles, median dose intensity for drugs common to both regimens, or rates of discontinuations or deaths related to AEs as compared to patients treated with R-CHOP.

Whilst bortezomib was administered exclusively intravenously in the LYM-3002 trial, the CHMP-approved indication in MCL includes both IV and subcutaneous administration of bortezomib. This was considered acceptable since no relevant pharmacokinetic or pharmacodynamic differences were observed between IV and subcutaneous administration of bortezomib in the multiple myeloma (MM) setting[84], and no significant differences on bortezomib subcutaneous bioavailability are expected between MM and MCL patients.[85] The appropriateness of subcutaneous administration of bortezomib is reflected in the SmPC and is expected to be adopted in most clinical settings. This is likely to positively impact the cost-effectiveness estimates presented in this submission through reduced AEs and administration costs. In MM patients randomly assigned to subcutaneous or IV bortezomib in a Phase III non-inferiority study, Grade 3 or worse AEs were reported in 57% (84/148) of subjects in the subcutaneous group compared with 70% (52/74) of subjects in the IV group.[84] Peripheral neuropathy of any grade (38% vs 53%; p=0·044), Grade 2 or worse (24% vs 41%; p=0·012) and Grade 3 or worse (6% vs 16%; p=0·026) was significantly less common with subcutaneous than with IV administration.[84] Clinical efficacy was not affected with non-inferiority demonstrated between treatment groups.[84]

Principal HRQL findings from the LYM-3002 trial

With regards to patient HRQL, no significant differences were consistently observed between treatment groups within the treatment phase of the LYM-3002 trial. A slight reduction in HRQL during treatment was observed with VR-CAP induction therapy, but this is expected to be a temporary on-treatment effect, anticipated with all chemotherapy induction regimens.[6]

As the study design did not include PRO collection after the end of treatment, this could not be formally investigated. Furthermore, potential improvement in HRQL during prolonged PFS and prolonged disease control was not captured. Practicing haematologists across the UK confirmed that they do not believe clinical trial-based HRQL assessments adequately capture differences in patient HRQL based on treatment effect. However, they do believe that a TFI of over 3 years from approximately 4 months on treatment represents a meaningful HRQL benefit to patients and carers.[6]

There is some added burden associated with the administration of bortezomib as it requires administration on two extra days within the 21-day treatment cycle; however, as VR-CAP is a limited duration treatment (6-8 cycles), this added burden is temporary and outweighed both by the clinical benefits observed post treatment and the extended treatment free period.

Key strengths of the clinical evidence base for VR-CAP

The LYM-3002 trial is among one of the largest RCTs investigating induction therapy in adult patients with previously untreated MCL, developed in consultation with key opinion leaders and with advice from the CHMP. It was designed for generalisability to clinical practice and conducted in compliance with GCP.[59, 60] Demographic and baseline disease characteristics of enrolled patients were largely consistent with historical observations for this patient population and generally reflective of patients presenting in clinical practice (as confirmed by practicing haematologists).[6] Furthermore, the LYM-3002 trial provides direct comparative efficacy evidence versus R-CHOP induction therapy, the established standard of care for adult patients with previously untreated MCL for whom HSCT is unsuitable in NHS England and Wales.

Improved long-term prognosis, through improved depth of clinical response and subsequent extension of survival times, as observed in the LYM-3002 trial, are the key clinical benefits expected to be achieved with the adoption of VR-CAP in clinical practice and the key clinical benefits of relevance to both patients and clinicians as reflected in the decision problem.

Specific study endpoints aimed at measuring clinical benefit, including PFS, are robust and recognised as clinically important measures of efficacy in NHL (and thus

MCL). The validity of PFS as the primary endpoint was discussed and endorsed during the EMA scientific advice procedure. The choice of TTP, TTNT and TFI as secondary endpoints is deemed valid as, at present, MCL is an incurable disease, and TFIs greatly improve the patient's HRQL.

Further to its clinical benefit, bortezomib has a clearly characterised and manageable safety profile. Tolerability and adverse effects common to chemotherapy regimens, as monitored in the LYM-3002 trial, are the key safety concerns in practice; and the key safety concerns of relevance to both clinicians and patients.

Key limitations of the clinical evidence base for VR-CAP

The primary limitation of the LYM-3002 trial results from changes in clinical practice during the trial period. At the time this trial was initiated, R-maintenance therapy was not commonly adopted; thus, a maintenance therapy period was not included in the LYM-3002 trial design. Since this time, R-maintenance therapy post R-CHOP induction has become common practice for the treatment of adult patients with previously untreated MCL for whom HSCT is unsuitable in NHS England and Wales.

Haematologists believe that R-maintenance therapy results in similar benefit post any CHOP-like induction regimen and therefore would expect to be able to give R-maintenance after VR-CAP induction with a similar extension to median survival times as observed with R-maintenance after R-CHOP induction.[6] This was also noted at the scoping meeting, with clinical experts similarly stating that R-maintenance would be considered after any standard induction therapy (with the same benefit expected) and would thus not impact the initial treatment decision.[43]

Clinical evidence supporting the use of R-maintenance post R-CHOP induction therapy is taken from the European MCL Elderly trial.[41] In this trial, an improved OS was observed in patients treated with R-CHOP induction therapy followed by R-maintenance compared with patients treated with R-CHOP induction therapy followed by interferon-alpha maintenance (see Appendix 9:Table 32). R-maintenance therapy was not associated with improved OS following R-FC induction therapy in this trial, which may appear contradictory to expert opinion of equivalent effect (see above). However, this is attributed to the well-established toxicity profile of R-FC (particularly myelotoxicity), which led to more deaths and a lower eligibility to receive rituximab in the maintenance phase, rather than a difference in effect of R-

maintenance based on the induction therapy regimen. The European MCL Elderly trial was not designed to assess the clinical efficacy of induction therapy ± maintenance therapy (see section 4.10), and therefore, outcome analysis data for R-CHOP induction therapy with consolidation of R-maintenance therapy versus R-CHOP induction therapy without consolidation are not reported. Nonetheless, in an attempt to replicate current practice, exploratory analysis investigating the potential impact of R-maintenance post VR-CAP induction therapy (based on the limited data available) is presented as a scenario in section 5.

Beyond the LYM-3002 trial, no direct comparative efficacy evidence is available for VR-CAP versus alternative rituximab-based chemotherapy regimens. Whilst VR-CAP is not expected to replace the use of therapies other than R-CHOP in NHS England and Wales, alternative regimens are named in the final appraisal scope for the treatment of adult patients with previously untreated MCL for whom HSCT is unsuitable. The available evidence base for these alternative rituximab-based chemotherapy regimens is weak and heterogeneous, giving rise to internal and external validity concerns (see section 4.10). Subsequent indirect treatment comparisons are severely limited and not considered a reliable estimate of the comparative effectiveness that would be observed in clinical practice.

4.14 Ongoing studies

The final analysis of the LYM-3002 trial, which will provide more mature survival data, is expected tobe available in 2017.

No other studies investigating VR-CAP for the treatment of adult patients with previously untreated MCL for whom HSCT is unsuitable are known to be ongoing.

5 Cost effectiveness

Key points

- An economic model was constructed to assess the cost effectiveness of VR-CAP for the treatment of patients with previously untreated MCL for whom HSCT is unsuitable
- R-CHOP is the established standard of care for previously untreated MCL patients for whom HSCT is unsuitable, although there are currently no licensed treatment regimens for this patient population. Therefore, the model base case was presented versus R-CHOP. For completeness, exploratory analyses were presented versus other comparators included in the scope that are used in UK practice in patients for whom both R-CHOP and VR-CAP are unsuitable
- A five health state model was used to evaluate the cost effectiveness of VR-CAP (PFS first-line treatment, progressed from first-line treatment, PFS second-line treatment, progressed from second-line treatment and death)
- The model was parameterised by OS, PFS and TFI data from the LYM-3002 trial
- Progression status was used as a surrogate marker for overall survival
- Patient HRQL was modelled using utilities reported by patients in the LYM-3002 trial and beyond the duration of reporting in the trial from Doorduijn et al. (2005)[86]
- Resource use data were taken from the LYM-3002 trial supplemented by clinical advice
- Cost data were taken from standard UK cost references
- The base case incremental cost-effectiveness ratio (ICER) was **£20,362** per quality-adjusted life year (QALY) gained
- The ICER was relatively insensitive to parameter uncertainty and structural assumptions:
  - Key model sensitivities were PFS and OS model fit parameters and the utility of patients who had progressed from second-line treatment
  - The use of a time horizon ranging from 10 to 30 years resulted in ICERs ranging from **£19,875** to **£27,443**
  - The use of different curve fits for PFS resulted in ICERs ranging from **£19,002** (lognormal) to **£30,452** (Gompertz) – the Gompertz curve fit was not deemed clinically plausible because of the steep drop in the tail
  - The assumption of subcutaneous (rather than IV) administration of bortezomib resulted in an ICER of **£18,775**
- In all clinically plausible scenarios, the ICER remained below **£30,000**
- ICERs versus other comparators are **£18,509** versus R-FC and **£13,797** versus R-bendamustine. For both R-FC and R-bendamustine, survival results would have to be substantially better than R-CHOP for VR-CAP to no longer be cost-effective
- The model was insensitive to the inclusion of R-maintenance after induction therapy in exploratory analysis.
- The base case ICER of £20,362 and the relative stability of the ICER when varying modelling assumptions confirms that VR-CAP is a cost-effective use of NHS resources

5.1 Published cost-effectiveness studies

To identify relevant cost-effectiveness studies, a systematic literature review was performed. The search strategy is specified in Appendix 11. The aims of the literature review were to find any previous cost-effectiveness analyses for VR-CAP and to guide the understanding of the most relevant model structure.

Methods

Literature search

The first stage in the review was to identify all relevant economic evidence for VR-CAP and other specified comparator treatments. To this end, a comprehensive literature search was commissioned by the Information Resources department of the School of Health and Related Research (ScHARR) at the University of Sheffield.

Question addressed

The question addressed in this literature search was:

- What is the cost effectiveness of VR-CAP and its comparator therapies for the treatment of MCL?

To ensure that all potentially relevant studies were identified, specific search methods were used. These included both published peer-reviewed studies and abstracts from conference proceedings. There were no limits in terms of date or language. Global electronic databases used were Medline, Medline in-Process (using Ovid platform), EconLit, Embase, the Cochrane Library, the health technology assessment (HTA) database and the NHS Economic Evaluation Database (EED), which were searched along with subject-specific conference proceedings of the American Society of Hematology (ASH), the American Society of Clinical Oncology (ASCO), the International Society For Pharmacoeconomics and Outcomes Research (ISPOR) and the European Hematology Association (EHA).

In addition to the formal electronic searches, reference lists of the included cost-effectiveness and HRQL studies identified were hand searched for additional publications of relevance to the research question.

The terms used for the literature search, are presented in Appendix 11.

Study selection

To determine studies eligible for the review, explicit pre-specified inclusion and exclusion criteria were applied to the literature search results (Table 29). In the first round of filtering, the titles and abstracts of the studies were screened to assess possible eligibility. In the second round of filtering, the full text versions of the remaining studies were identified and screened for eligibility. If two hits had the same title and authors, and were published in the same issue of the same journal, they were considered duplicates, and one of them was excluded.

Primary and secondary filtering and data extraction was performed by one reviewer, and a second reviewer carried out quality control for both filtering and extraction.

As a part of the data extraction, the included studies were assessed for quality. The methodological quality of the studies included in the cost-effectiveness category were assessed using a published checklist.[87]

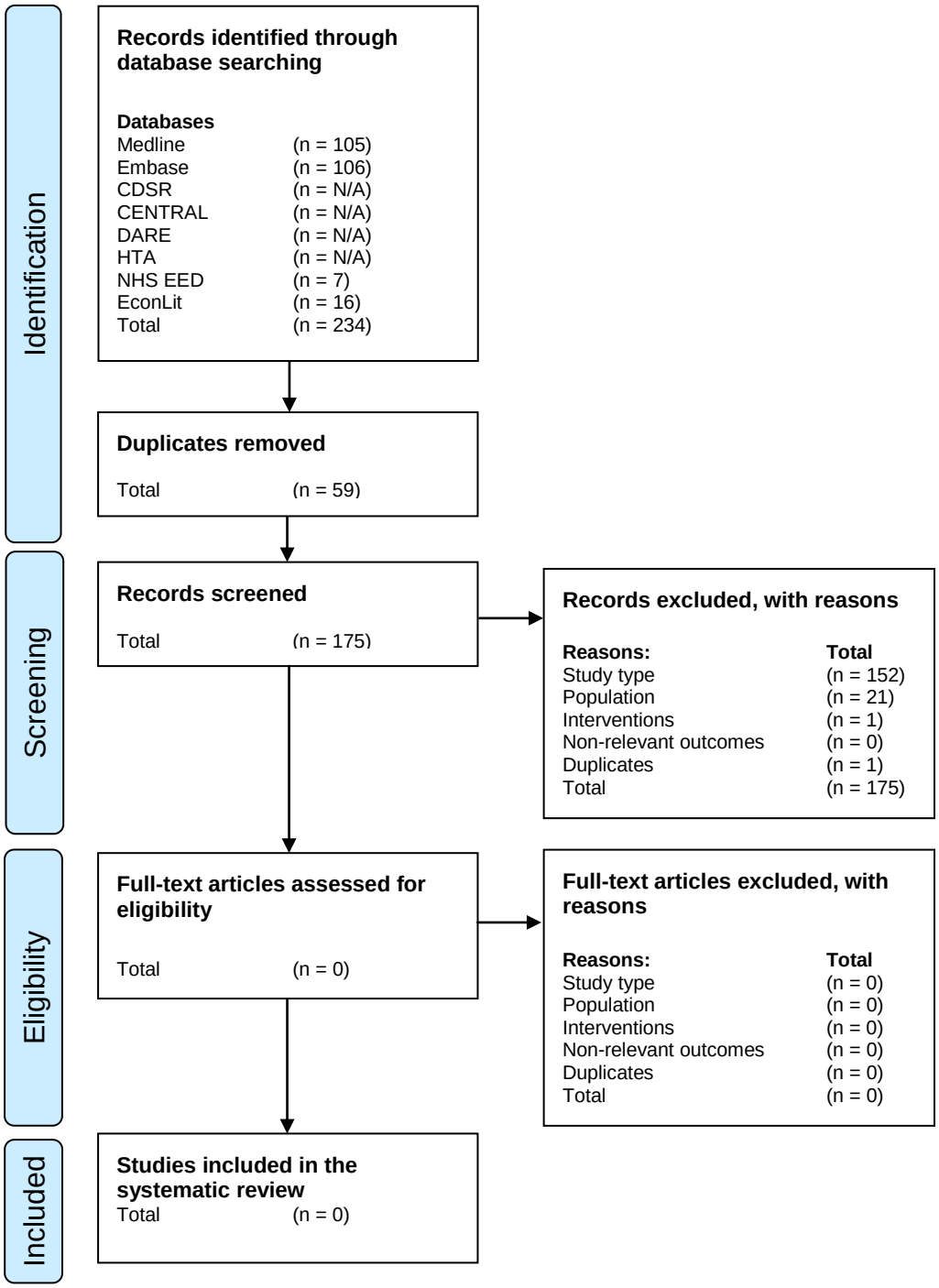
Table 29: Inclusion criteria for cost-effectiveness studies

Types of studies	Studies reporting cost-effectiveness analyses and results were not filtered by study design. All studies were included barring reviews, letters and comment articles.
Types of participants	Previously untreated adult MCL patients.
Types of intervention	First-line treatment; any intervention with active treatment could be included to allow the identification of additional potentially relevant models.
Types of outcomes	Incremental costs and QALYs or any other natural unit measure of effectiveness (e.g. life years) reported together with costs.
Key: MCL, mantle cell lymphoma; QALY, quality-adjusted life year.	

Description of identified studies

Searches were conducted between 7 and 18 July 2014, with a search update conducted between 11 and 26 March 2015. No studies were included in the review (Figure 10) and therefore no quality assessments of cost-effectiveness studies were performed (Appendix 12).

Figure 10: PRISMA flow diagram of the cost-effectiveness studies



5.2 De novo analysis

Model structure

A *de novo* cost-effectiveness model was developed to assess the cost effectiveness of VR-CAP in England and Wales. The model was developed using a standard Markov heath-state structure. This modelling approach was deemed optimal due to its common use in previous HTA oncology models for evaluating treatments for lymphoma and because Markov models lend themselves to disease areas in which patients progress through distinct and definable stages of disease; these stages can be characterised by health states between which patients can transition upon defined clinical events (such as disease progression).

In the systematic literature review described in section 5.1, no published economic models were found for previously untreated MCL.

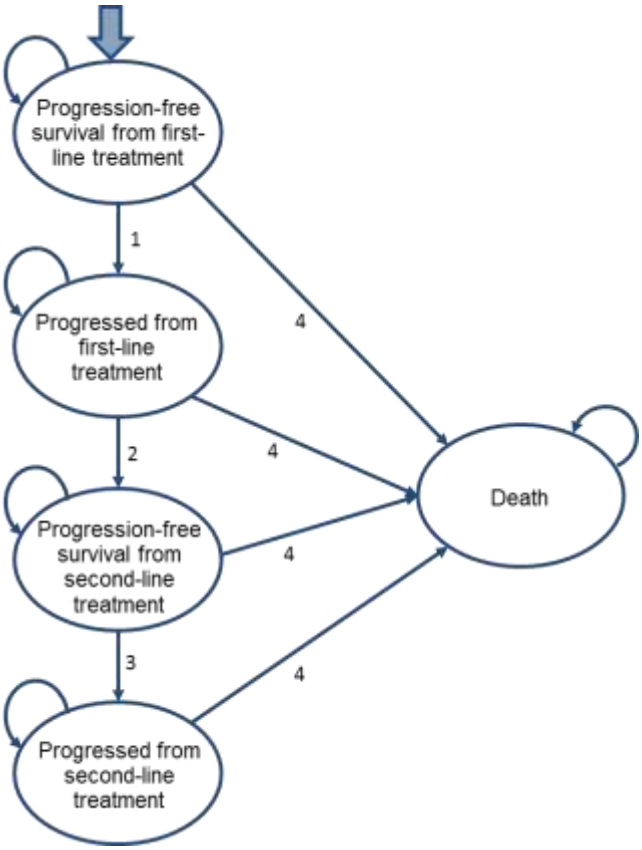
Based upon a systematic literature review for surrogate outcomes in MCL (Appendix 15), analysis of the LYM-3002 trial data and clinical advice, progression was determined to be the best surrogate for survival and the key predictor for changes in resource use. This *de novo* cost-effectiveness model therefore included five health states (Figure 11). No third or subsequent-line treatment options were included in the model as this would have added substantial additional complexity and uncertainty to the model, with minimal expected impact on the outcomes as treatment becomes palliative. Thus there was not expected to be a meaningful difference in benefit of later lines of treatment based on the choice of induction therapy. In addition, with each relapse becoming more difficult to treat and the depth and durability of any subsequent remissions achieved invariably inferior to the previous line of treatment, OS following second relapse is relatively short. Thus, the proportion of patients receiving therapy beyond second line is estimated to be small (20.3% in LYM-3002).

The definition of disease progression used within the model was based on an assessment by either the study investigator or an IRC. An alternative IRC assessment, where decisions on progression could be based on multiple assessments as detailed in section 4.7, was used within the model base case to more closely reflect routine clinical practice.

Disease progression was modelled directly from the treatment arms of the LYM-3002 trial. OS was modelled based on progression status; post-progression survival (PPS) was assumed in the base case to be equal, regardless of first-line therapy, whilst pre-progression survival (PrePS) was dependent on first-line treatment. Initiation of second-line treatment was modelled using the TFI reported in the LYM-3002 trial (Figure 11).

For PFS, OS and TFI, the exponential, Weibull, log-logistic, lognormal, gamma and Gompertz models were tested for goodness of fit statistically, visually and clinically. The base case model used log-logistic curves for PFS and exponential curves for OS and TFI.

Figure 11: Model diagram



Key: OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; PrePS, pre-progression survival;
Notes: 1. Modelled using curve fit to PFS Kaplan–Meier data; 2. Modelled using curve fit to treatment-free interval; 3. Modelled using average PFS from second-line treatment; 4. Modelled using curve fit to OS Kaplan–Meier curve (PPS and PrePS plus general population background mortality data).

The model was designed to represent the decision problem from the perspective of the NHS in England and Wales.

A cycle length of 1 week was applied in the model. This was selected as it gave sufficient granularity to capture short-term changes in progression status. The base case model time horizon was 20 years, which was assumed to be sufficiently long to be considered a lifetime time horizon for patients with a mean age of 69 (Table 31); ≥94% of patients on both arms were modelled to have died within this time horizon.

As patients progressed through the lines of treatment represented in the model structure, they incurred costs associated with drug acquisition, administration, healthcare visits and management of adverse events. Across all health states, the model estimated the total costs and QALYs that patients were expected to accumulate over the time horizon of the model. Both costs and health outcomes were discounted at an annual rate of 3.5%, as per published UK guidance.[88] Costs reflected 2013/14 as these were the most recent cost data available at the time of model development.

Key features of the economic model are described and justified in Table 30.

Table 30: Features of the *de novo* analysis

Factor	Chosen values	Justification	Reference
Time horizon	20 years	Mean age of Western patients in LYM-3002 was 69 years. Over 94% of patients in either arm of the base case model died at 20 years	Extrapolation of OS from LYM-3002
Were health effects measured in QALYs; if not, what was used?	QALYs	NICE reference case	NICE[88]
Discount of 3.5% for utilities and costs	3.5% per annum	NICE reference case	NICE[88]
Perspective (NHS/PSS)	NHS	NICE reference case	NICE[88]
Key: NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PSS, Personal Social Services; QALYs, Quality-adjusted life years.			

Patient population

VR-CAP is licensed for the treatment of adult patients with previously untreated MCL who are unsuitable for HSCT. The key clinical data used within the economic model were taken from the LYM-3002 trial, as described in detail in section 4.

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. When presented to three UK consulting haematologists, patients in the LYM-3002 trial were considered similar to those expected to be seen in UK clinical practice, although the mean age and body surface area (BSA) of participants was believed to be towards the lower end of the scale, with a mean presentation age of 65-70 in UK clinical practice. Data from patients from Western European and North American countries were closer in age and weight to what would be expected in UK clinical practice than the total trial population; therefore, the demographics from the Western European and North American subgroup were used in the model. Subgroup analysis from the LYM-3002 trial found results in this population to be consistent with the ITT population (section 4.8; Appendix 8:Table 30).

To assess the degree of bias on cost-effectiveness results, a scenario analysis was conducted using data from the population clinically ineligible for HSCT only. Full trial outcomes for the population clinically ineligible for HSCT can be found in Appendix 16.

Neither outcomes nor patient characteristics were substantially different in either the population clinically ineligible for HSCT or the Western European and North American subgroup compared to the full population (Table 31; section 4.8). No scenario analysis was conducted using trial outcomes from the Western European and North American patients only, given the small sample size of the population.

Table 31: Baseline characteristics of all patients versus non-HSCT eligible patients only in the LYM-3002 trial

Variable	All patients (n=487)	Clinically ineligible for HSCT only (n=407)	Western European and North American patients (n=91)
Age at baseline	64.29	65.82	68.5
Female	26.1%	26.8%	23.1%
European Union	27.9%	31.2%	84.6%
North America	2.9%	6.3%	15.4%
Rest of the World	69.2%	65.6%	-
Stage II	6%	6%	3%
Stage III	20%	22%	8%
Stage IV	74%	72%	89%
ECOG 0	40%	43%	43%
ECOG 1	47%	47%	48%
ECOG 2	13%	10%	9%
Mean patient weight (kg)	70.59	70.03	79.31
Body surface area (m^2)	1.80	1.79	1.91
Key: HSCT, haematopoietic stem cell transplantation; ECOG, Eastern Cooperative Oncology Group.			

Intervention technology and comparators

As discussed in section 3.2, practicing haematologists confirmed that, in NHS England and Wales, R-CHOP induction therapy is the established standard of care for patients with previously untreated MCL (for whom HSCT is unsuitable). Not taking into account the patients that receive no treatment (about 10%), more than two thirds of HSCT unsuitable patients were estimated to receive R-CHOP in the front-line setting.[6] Only patients not deemed fit enough, or contraindicated, to receive CHOP-like therapy would receive alternative rituximab-chemotherapy regimens first line in the UK.[42] Given its common RCAP backbone, VR-CAP would also be considered a CHOP-like therapy, and thus, patients not deemed fit enough to receive R-CHOP would not be considered for VR-CAP therapy.

Economic comparison was therefore conducted primarily with R-CHOP. To fulfil the requirements of the final appraisal scope and for transparency, additional exploratory comparisons were conducted with R-FC (not routinely used first line in current UK

practice) and R-bendamustine (only available via the CDF where standard treatment [e.g. R-CHOP] cannot be given) (see section 3.2).[42]

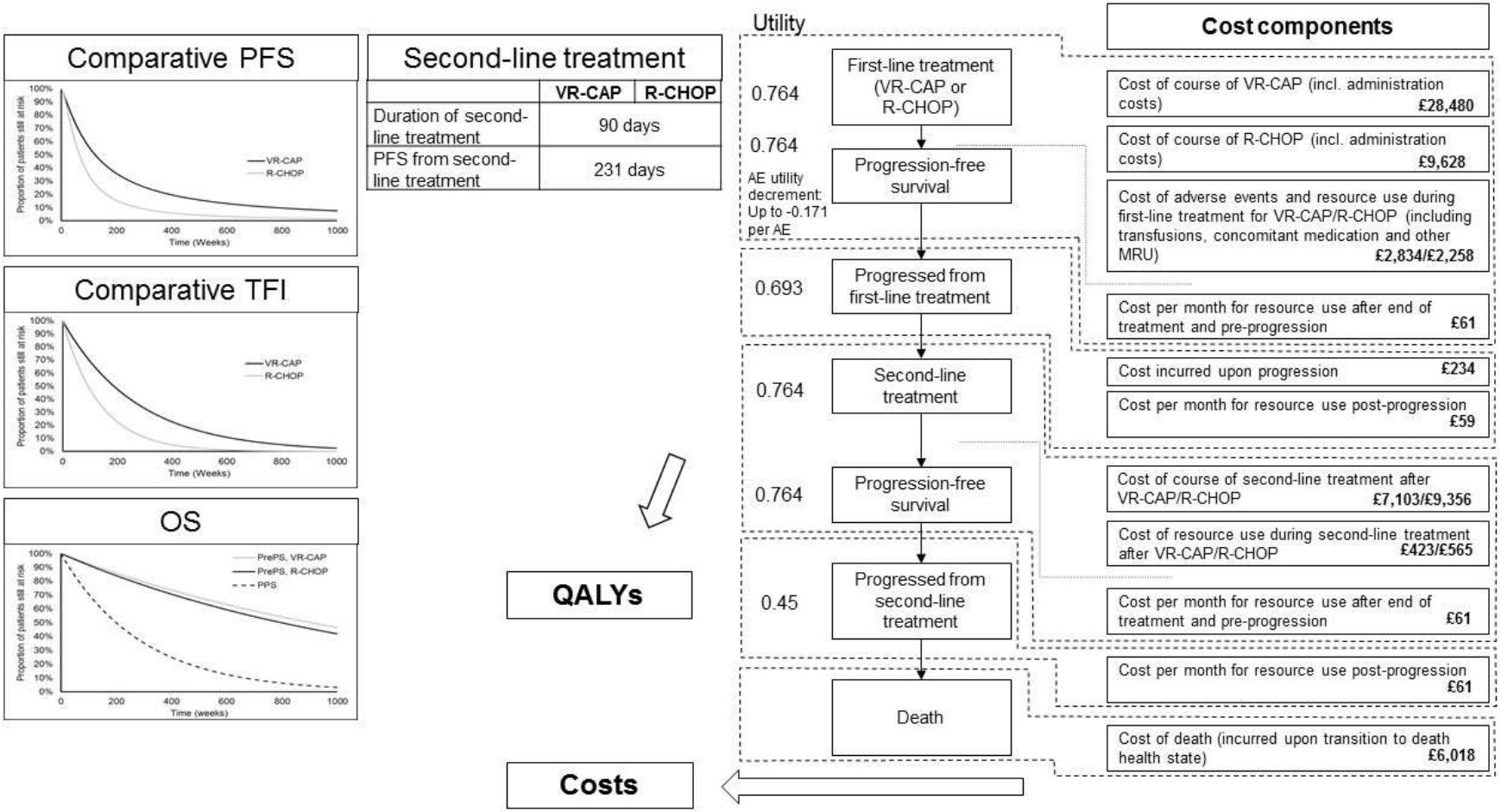
These comparisons should be viewed as exploratory because, in addition to the treatments not being used in the same placement as VR-CAP, no robust comparison can be made with the available evidence, as discussed in section 4.10.

No maintenance treatment with rituximab was assumed in the model base case as this was not identified as a comparator in the decision problem. However, as R-maintenance is used in clinical practice in patients 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. Given the limited data available for R-maintenance in MCL (see section 4.13), several different scenario and threshold analyses were performed to assess the potential impact of R-maintenance on the cost effectiveness of VR-CAP induction therapy. These are presented in section 5.8.

Model summary

The model comprised several different elements used to evaluate patient treatment experience and outcomes: patient survival, disease progression, time on each line of treatment and quality of life. These elements were combined to produce the desired output (costs and QALYs) as shown in Figure 12.

Figure 12: Model summary diagram



Key: AE, adverse event; MRU, medical resource use; OS, overall survival; PFS, progression-free survival; PrePS, pre-progression survival; PPS, post-progression survival; QALYs, quality-adjusted life year; R-bendamustine, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; R-FC, rituximab with fludarabine and cyclophosphamide; TFI, treatment-free interval; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

Note: Exploratory comparators: R-FC shows significant difference in OS favouring VR-CAP in Bucher Indirect Comparison, but no comparison of PFS possible. R-bendamustine shows nosignificant difference in the Bucher Indirect Comparison. In the base case equal efficacy to R-CHOP is assumed based upon clinician advice that this is a conservative assumption. AEs for exploratory comparators are taken from literature.

5.3 Clinical parameters and variables

Clinical evidence from the LYM-3002 trial

The pivotal study to inform the cost-effectiveness analysis is LYM-3002, described in detail in section 4.

The primary outcome of the trial was PFS by IRC assessment; however, in the primary IRC assessment, patients were classified as progressed when, on one CT scan, the disease seemed to have worsened based on the IWRC criteria. Assessments could not be revised based on subsequent time points. During the advisory board with UK clinicians, it was noted that, in clinical practice, progression would not be confirmed based on a single CT scan but would be based on sequential assessments. In the alternative IRC assessment, which was a pre-specified sensitivity analysis, an IRC reviewer performed a global review for a subgroup of patients assessed with PD 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. This is more reflective of clinical practice than the primary IRC method. It was noted that investigator-assessed outcomes are always expected to be more favourable than IRC assessed outcomes. Thus, the alternative IRC assessment was chosen to be used in the base case of the model as this reflected clinical practice whilst retaining the blinded assessment. Scenario analyses were also conducted using the primary IRC assessment and the investigator assessment for PFS.

Extrapolated PFS, PrePS, PPS and TFI data informed the proportion of patients in each model health state in each cycle. Definitions of PFS, PrePS and PPS are given in Table 32.

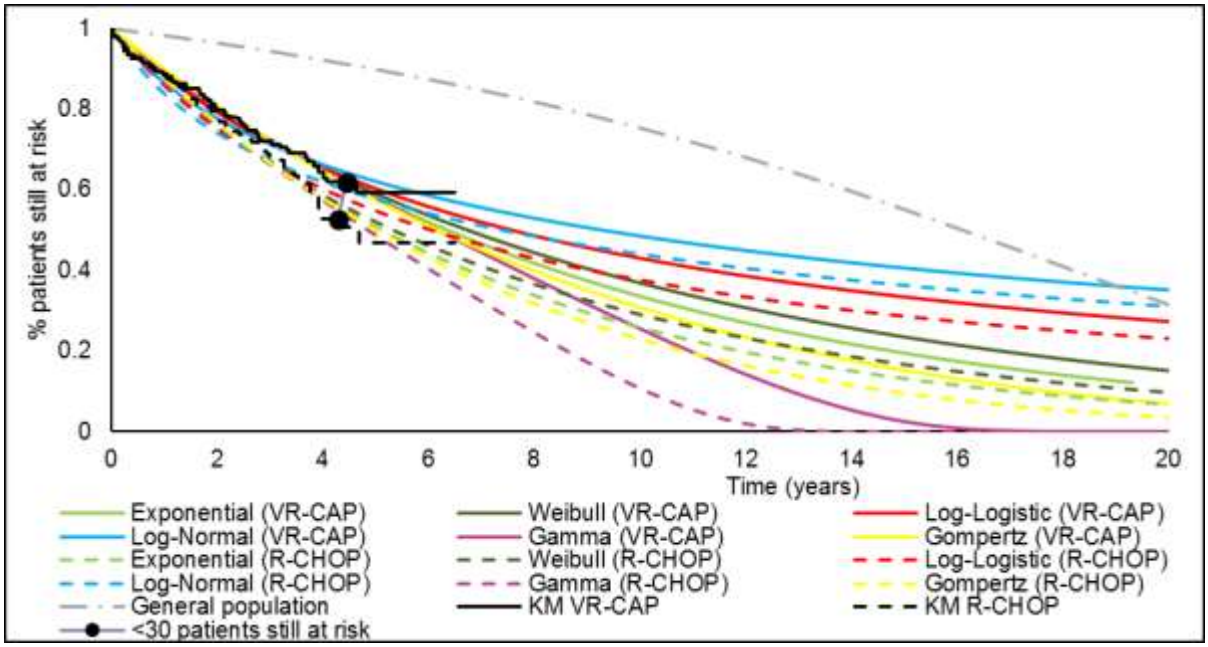
Table 32: Definitions of PFS, PrePS and PPS

Outcome	Definition	Application
Progression-free survival (PFS)	Time to progression or death for patients who have not yet progressed	PFS minus PrePS is used to model progression from the 'PFS from first-line treatment' to the 'Progressed from first-line treatment' health state
Pre-progression survival (PrePS)	Time from start of trial to death for patients who did not progress during the trial	To model the disease specific mortality for patients in the 'PFS from first-line treatment' health state
Post-progression survival (PPS)	Time from start of trial to death for patients who progressed during the trial	To model mortality of patients in all health states except 'PFS from first-line treatment'

Survival

Survival was modelled with parametric models fitted using the LYM-3002 patient level data for VR-CAP and R-CHOP patients. However, OS data from the LYM-3002 trial are still immature; median OS for VR-CAP has not been reached. Attempting to fit survival curves directly to the OS data from the clinical trial led to a wide range in potential outcomes, many of which were not plausible (Figure 13). Therefore, it was necessary to consider progression as a surrogate marker for OS. A review was performed to investigate the relationship between OS in MCL and other outcomes (Appendix 15). Based on the two studies identified through the literature search and feedback from UK clinicians, there was a strong case for the use of PFS as a surrogate for OS in MCL.[21, 89] Therefore, survival was modelled as dependent on the progression status of the patient.

Figure 13: Problems with fitting curves to OS data



Key: KM, Kaplan–Meier; OS, overall survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

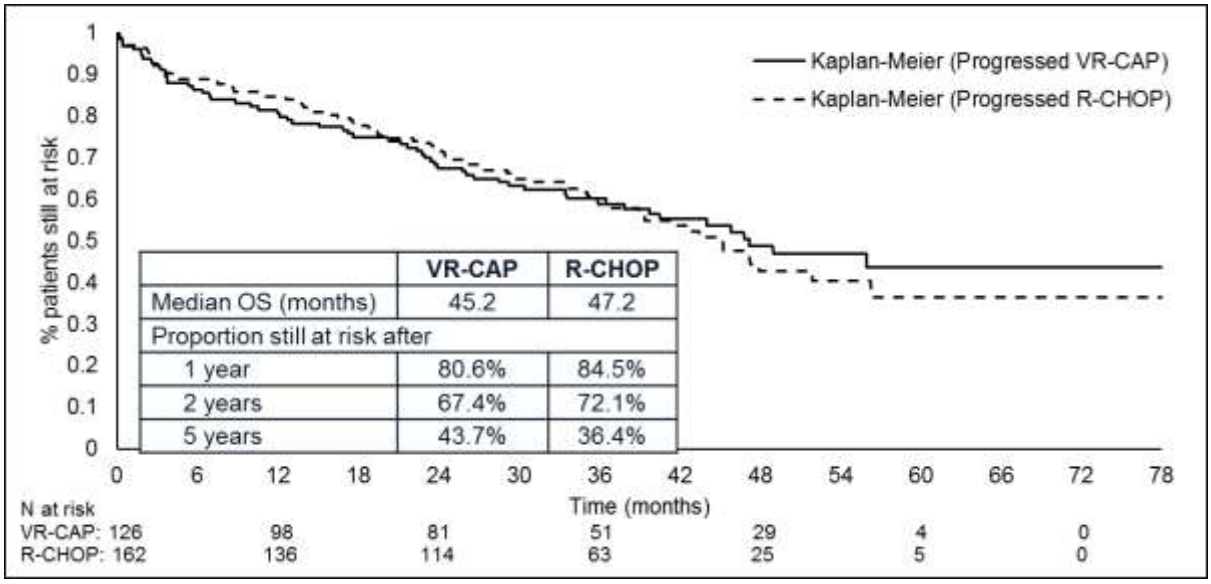
For the base case, parametric curves were fitted for three categories of patients: all patients who progressed from VR-CAP or R-CHOP during the trial, all patients who did not progress from VR-CAP, and all patients who did not progress from R-CHOP. This method assumed that patients who progressed had the same survival regardless of what treatment they received in first line.

Thus, in the base case, it was assumed that PPS was the same, regardless of the first-line therapy that had been received by the patient. This was justified by the observation that PPS was similar for the VR-CAP and R-CHOP arms in the LYM-3002 trial (see Figure 14), and was in line with the clinical guidance received at the UK advisory board: the differences in prior treatment would not be expected to impact PPS.[6]

In the model calculations, patients followed the curve for non-progressed patients until they progress. Subsequently, they followed the shape of the curve for patients who have progressed.

A scenario analysis exploring the model outcomes without assuming equal PPS in both treatment arms was conducted.

Figure 14: PPS in the LYM-3002 trial



	VR-CAP	R-CHOP
Median OS (months)	45.2	47.2
Proportion still at risk after		
1 year	80.6%	84.5%
2 years	67.4%	72.1%
5 years	43.7%	36.4%

Key: N, number; PPS, post-progression survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

Parametric curves were fitted to the clinical trial data using NICE Decision Support Unit guidance.[90] Too few data were available to fit individual models to the Kaplan–Meier data for PrePS; thus, proportional hazards were assumed. A scenario analysis that assumes equal PrePS in both arms of the model was conducted. The following parametric models were fitted for PrePS and PPS:

- Exponential
- Weibull
- Log-Normal
- Log-logistic
- Gamma
- Gompertz

The exponential model was applied for PrePS and PPS in the base case. This had the highest likelihood of providing the most reliable fit to the short- and long-term data (Figure 15 and Table 34), based upon AIC and BIC (Table 33), visual fit and long-term fit (Table 34). The Weibull curve also provided an appropriate fit. In Figure 15 and Figure 16, the time points from which fewer than 30 patients were still at risk

are marked; both the exponential and Weibull curves provided a good fit up to these points. After these points, Kaplan–Meier data were less reliable due to the small number of patients.

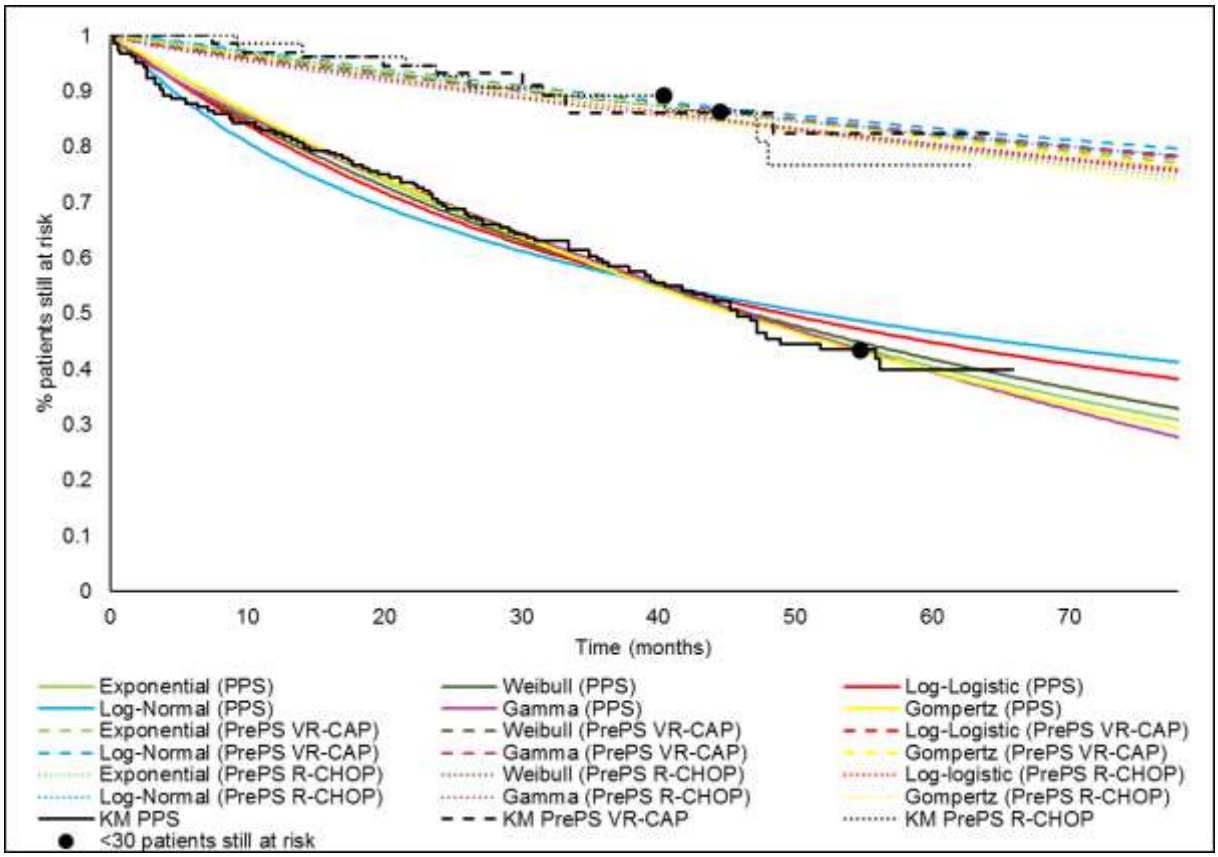
Table 33: Goodness of fit for OS curves

		Exponen-tial	Weibull	Log-Logistic	Log-Normal	Gamma	Gompertz
PPS combined	**AIC**	**913.62**	914.39	918.86	927.24	915.27	1715.60
	BIC	**926.19**	931.14	935.62	943.99	936.21	1732.36
PPS by trial arm	**AIC**	**915.60**	916.37	920.84	929.16	917.11	1717.58
	BIC	**932.35**	937.31	941.78	950.11	942.24	1738.52
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PPS, post-progression survival; OS, overall survival.							

Table 34: Goodness of fit of OS curves based on AIC/BIC, visual fit and long-term fit

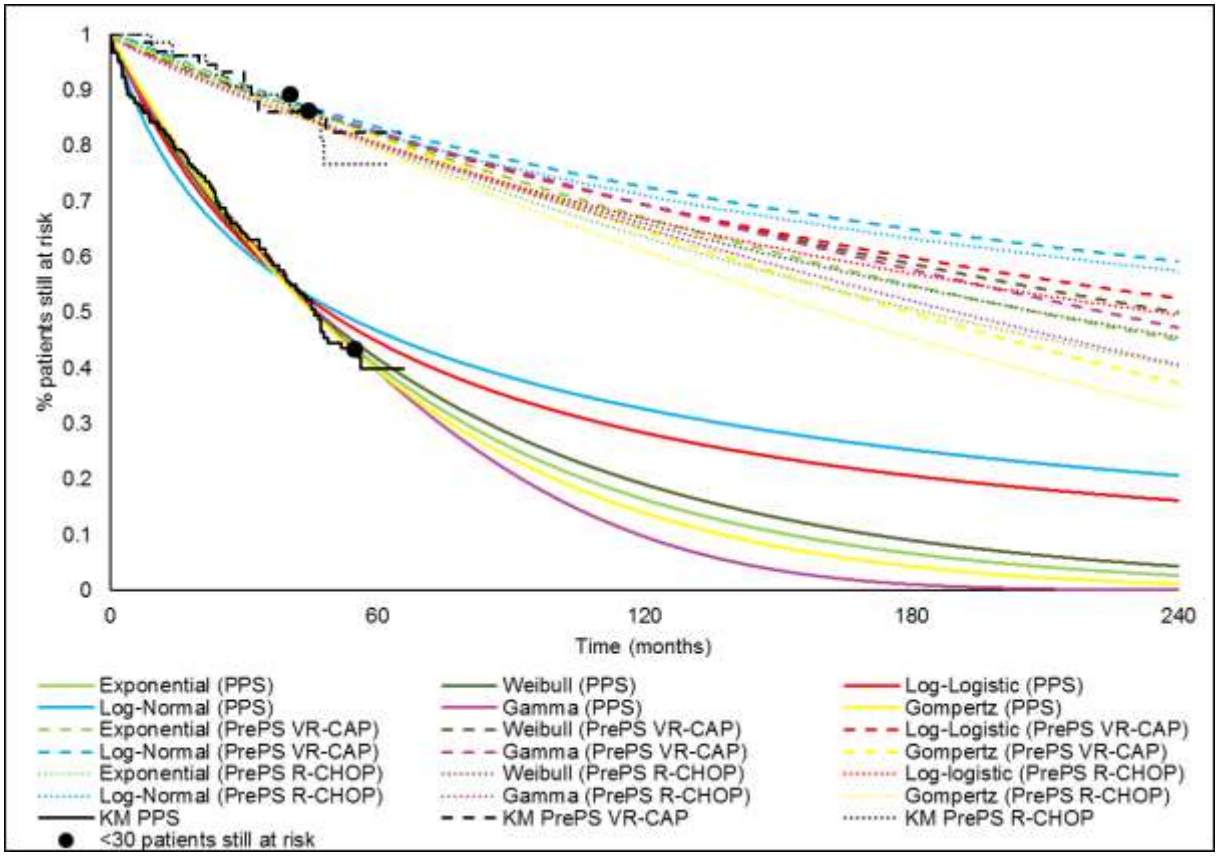
	AIC/BIC	Visual fit	Long term
Exponential	Best fit	Good fit	Good fit – quite low in the tail for the non-progressed, which was deemed plausible by clinical experts
Weibull	Quite good fit	Good fit	Good fit
Log-logistic	Not very good fit	Poor fit	Stays very high – not clinically plausible
Log-Normal	Very poor fit	Poor fit	Stays very high – not clinically plausible
Gamma	Not very good fit	Not very good fit	Good fit – quite low in the tail for the non-progressed, which was deemed plausible by clinical experts
Gompertz	Not comparable	Not very good fit	Good fit – quite low in the tail for the non-progressed, which was deemed plausible by clinical experts
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.			

Figure 15: Fit of parametric curves to OS (progression based on alternative IRC)



Key: IRC, independent review committee; KM, Kaplan–Meier; OS, overall survival; PrePS, pre-progression survival; PPS, post-progression survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

Figure 16: Long-term fit of parametric curves to OS (progression based on alternative IRC)



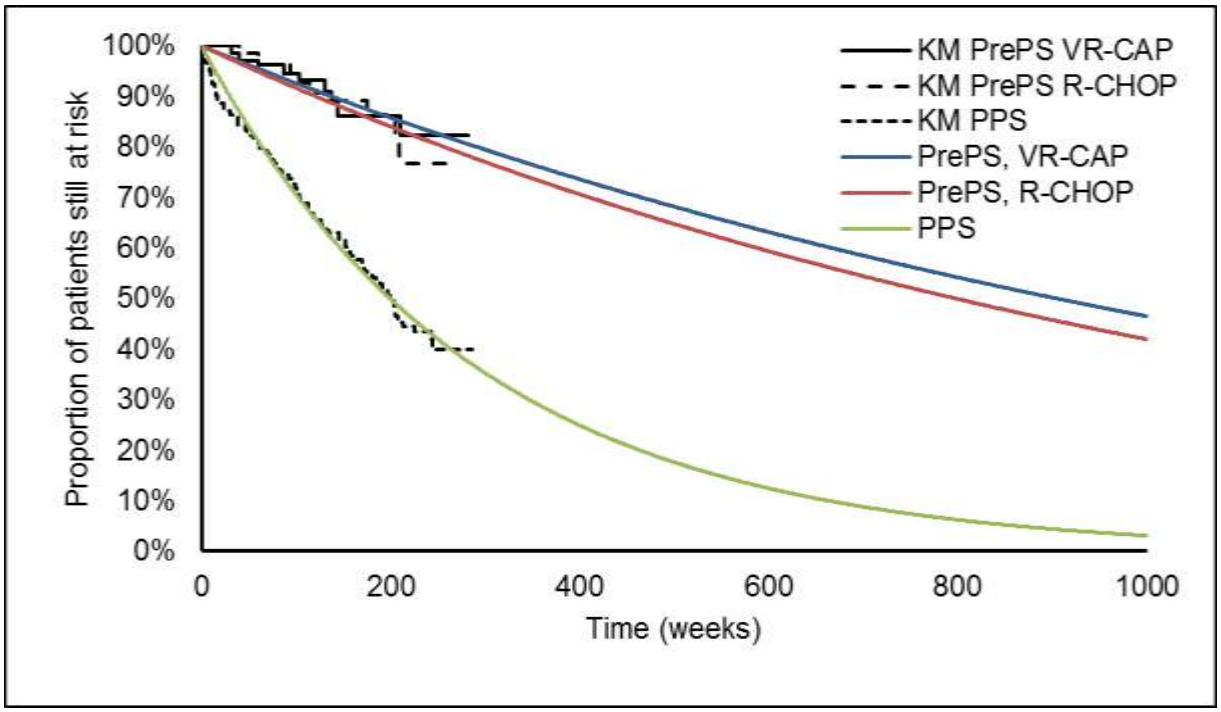
Key: IRC, independent review committee; KM, Kaplan–Meier; OS, overall survival; PrePS, pre-progression survival; PPS, post-progression survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

During the UK advisory board, it was noted that the long-term estimates of PrePS based on curve fitting were quite high. This was likely due to the relative immaturity of the data, meaning that the increase in background mortality with increasing age was not fully taken into account. Therefore, it was advised to add non-disease-specific mortality, based on age and gender, to the model to better capture long-term survival. This was included and based upon UK life tables.[91] In doing so, it was assumed that all deaths in the PrePS curves (prior to adjustment for background mortality) in the trial were deaths from MCL. This was a reasonable assumption as the number of deaths reported in the LYM-3002 trial that were not due to progression or toxicity was very low. Of the 69 deaths in total in the VR-CAP group, there were only eight deaths that were not due to progression or AEs. In the R-CHOP group, there were a total of 87 deaths, of which 14 were not due to progression or AEs. A

scenario analysis was conducted excluding non-disease-specific mortality from the model.

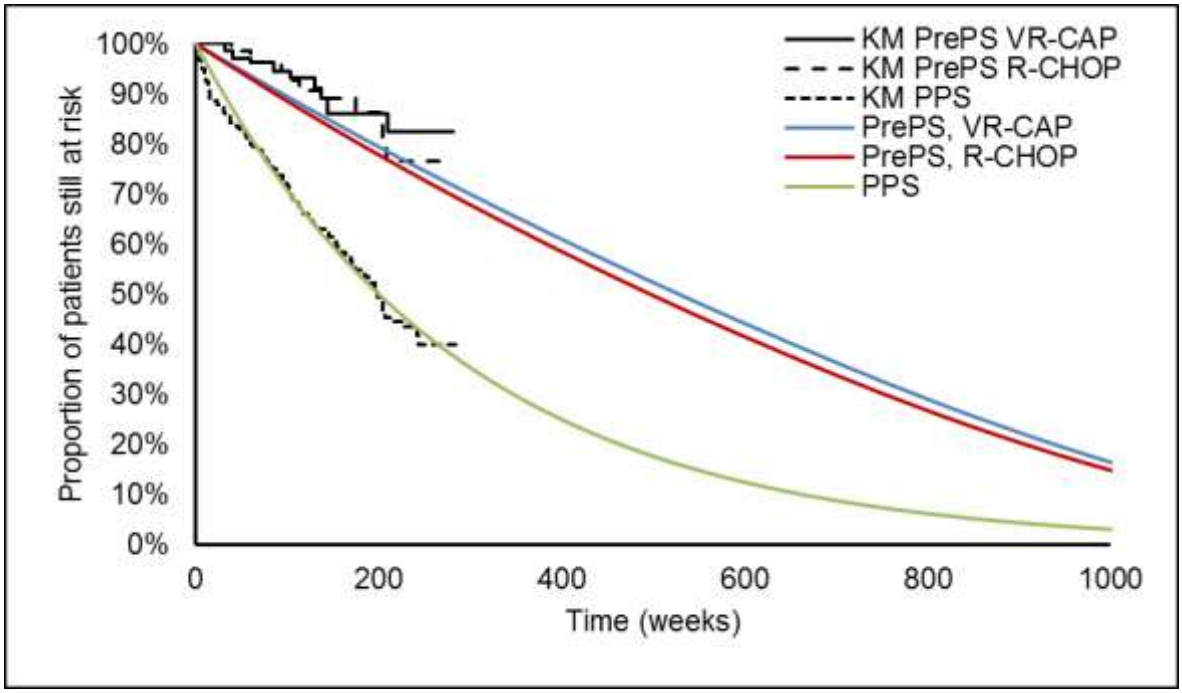
Figure 17 shows the base case survival estimates. Figure 18 shows the final base case survival estimates with general population mortality included in the curves for PrePS which are used in the model.

Figure 17: Base case exponential disease-specific OS curves



Key: KM, Kaplan–Meier; OS, overall survival; PrePS, pre-progression survival; PPS, post-progression survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

Figure 18: Base case exponential OS curves with general population mortality added to non-progressed curves



Key: KM, Kaplan–Meier; OS, overall survival; PrePS, pre-progression survival; PPS, post-progression survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

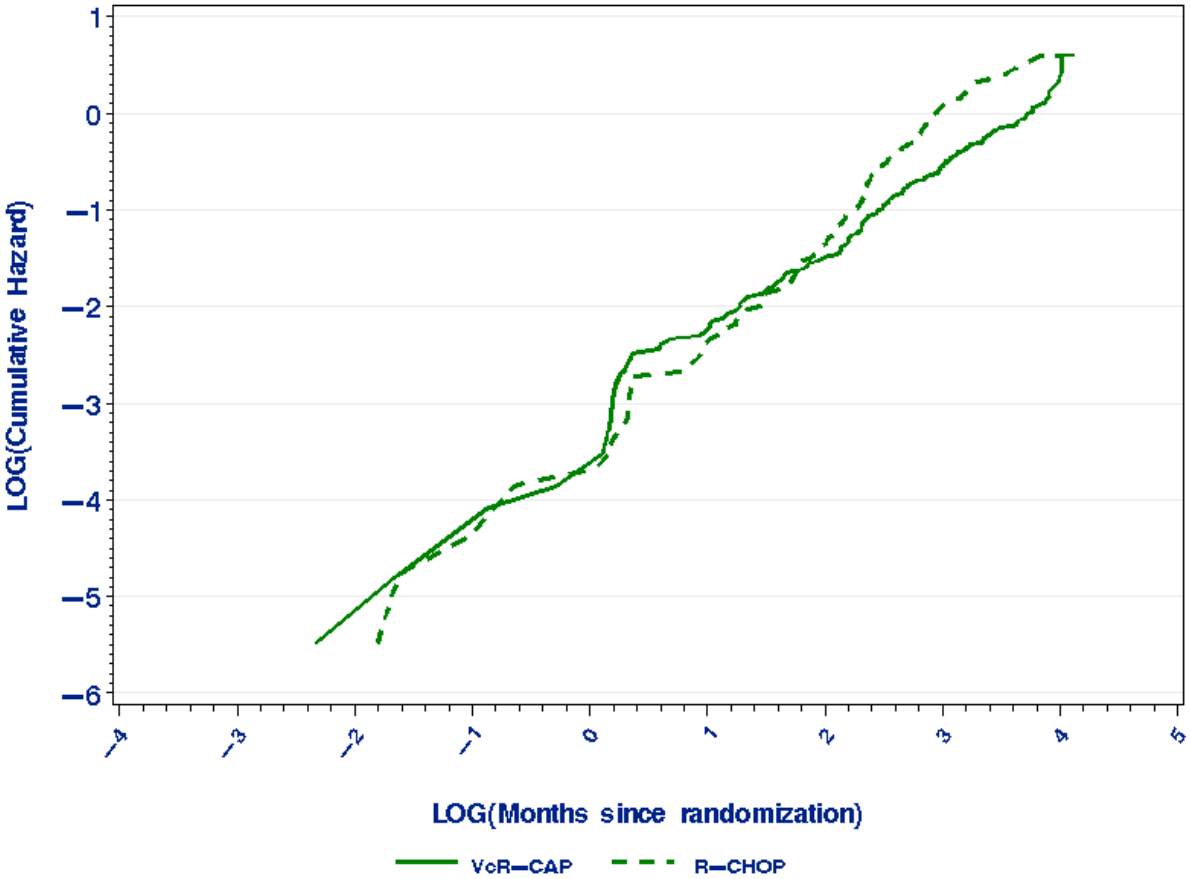
PFS

PFS was the primary endpoint of the LYM-3002 trial and was modelled using parametric models fitted to the LYM-3002 patient level data for R-CHOP and VR-CAP patients.

PFS was modelled by treatment arm of the clinical trial. Parametric curves were fitted to the clinical trial data using NICE Decision Support Unit guidance.[90] The chosen PFS curves dictate the rate at which patients transition from stable disease to progressive disease over time.

The log cumulative hazard plot (Figure 19) indicates that standard parametric curve fits are likely to be sufficient (plots are reasonably straight lines) and that the fitting of individual models is most appropriate (plots are not parallel).

Figure 19: Log cumulative hazard plots for PFS



Key: PFS, progression-free survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

The following parametric models were fitted for PFS:

- Exponential
- Weibull
- Lognormal
- Log-logistic
- Gamma
- Gompertz

The log-logistic model was applied in the base case. This has the highest likelihood of providing the most reliable fit to the data (Figure 20 and Figure 21), based upon the Akaike information criterion (AIC) and the Bayesian information criterion (BIC)

(Table 35), and visual fit and long-term fit (Table 36). Assessment of the long-term fit was based upon advice from clinical experts from the UK. In Figure 20 and Figure 21, the time point from which fewer than 30 patients were still at risk has been marked. After this point Kaplan–Meier data are less reliable due to the small number of patients. As noted in Table 36, the exponential curve also has a good fit.

Survival was subtracted from PFS in the model calculations to find the actual number of patients progressing, removing those that died before they had a chance to progress. Figure 22 shows the base case PFS used in the model.

Table 35: Goodness of fit of PFS curves

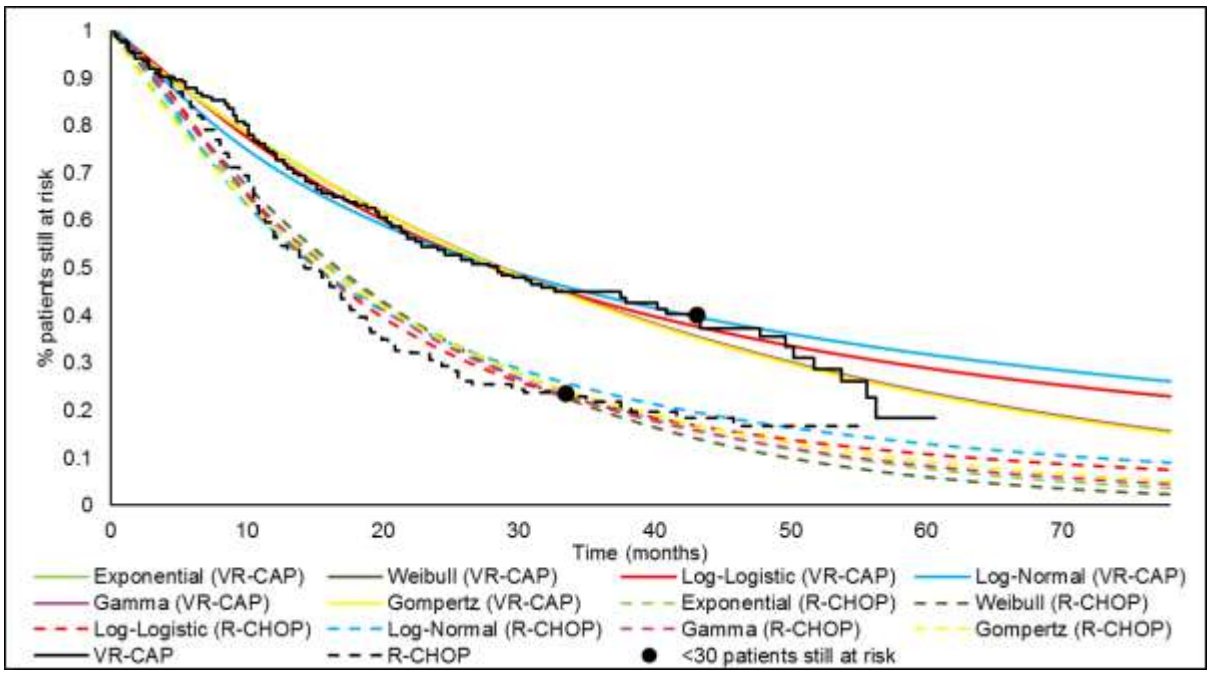
		Exponential	Weibull	Log-logistic	Log-Normal	Gamma	Gompertz
VR-CAP	**AIC**	**603.623**	605.604	608.385	616.888	607.603	1194.398
	BIC	**607.116**	612.590	615.371	623.874	618.082	1201.384
R-CHOP	**AIC**	634.079	634.075	**622.425**	636.948	630.674	1349.269
	BIC	637.576	641.070	**629.419**	643.942	641.166	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.

Table 36: Goodness of fit of PFS curves based on AIC/BIC, visual fit and long-term fit

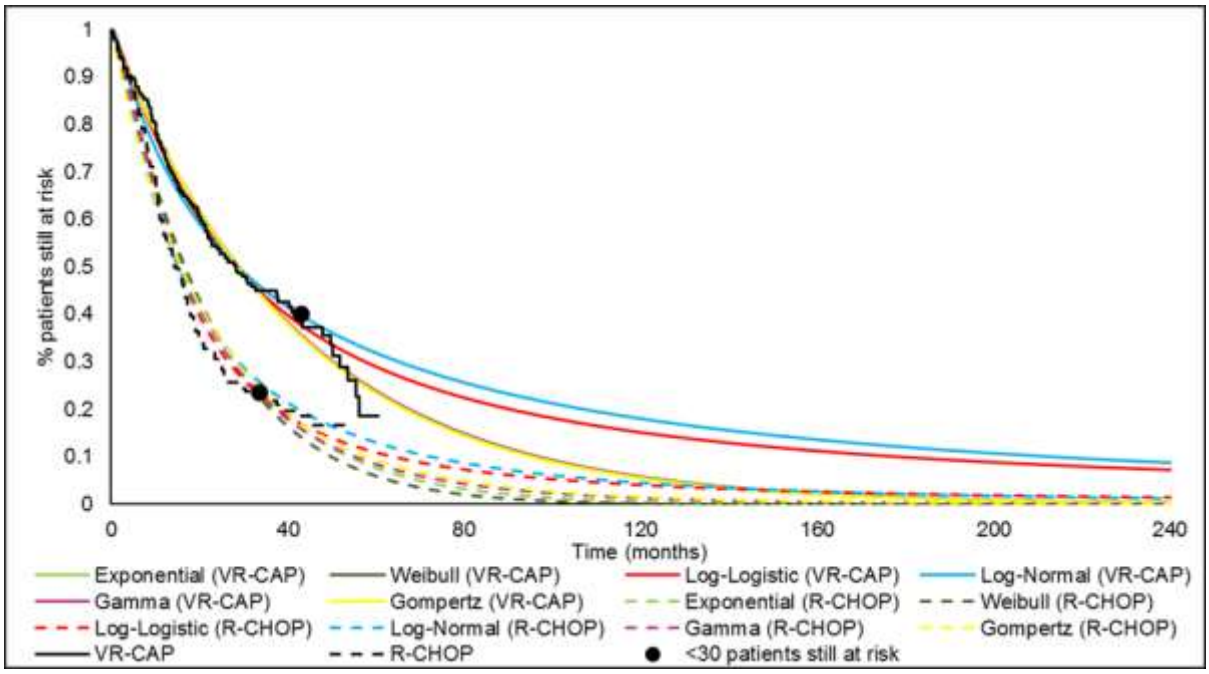
	AIC/BIC	Visual	Long term
Exponential	One of the best fits	All four of these curves exhibit a very similar fit; visual fit is relatively good	Steep drop in survival exhibited that is most likely informed by the areas of the KM curve where the fewest patients are available for analysis. Clinical experts felt PFS in LYM-3002 was generally shorter than expected, so preferred a curve that gives longer PFS at the tail.
Weibull	Reasonable fit		
Gamma	Worse fit		
Gompertz	Not comparable		
Log-logistic	One of the best fits	Good fit	Good fit – clinical experts felt PFS in LYM-3002 was generally shorter than expected, so preferred a curve that gives longer PFS at the tail.
Log-normal	Worse fit	Worse fit	Good fit – clinical experts felt PFS in LYM-3002 was generally shorter than expected, so preferred a curve that gives longer PFS at the tail.
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; KM, Kaplan–Meier; PFS, progression-free survival.			

Figure 20: Fit of parametric models to PFS based on alternative IRC assessment



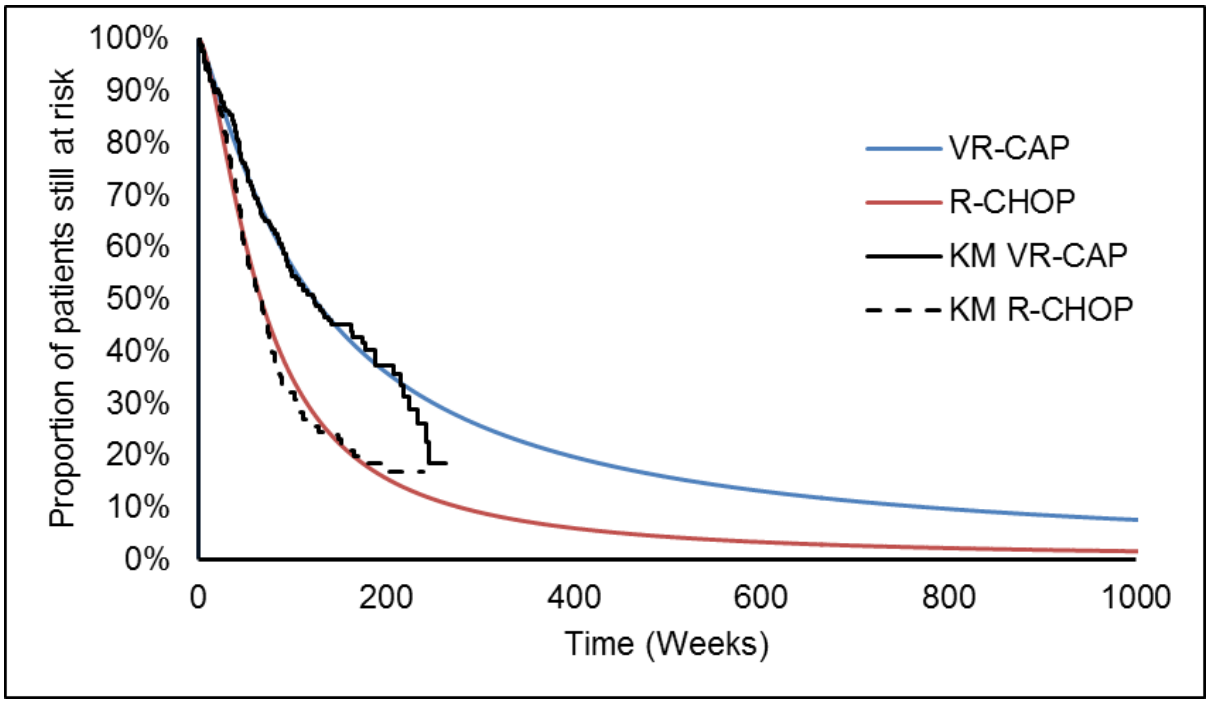
Key: IRC, independent review committee; PFS, progression-free survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

Figure 21: Long-term fit of parametric models to PFS based on alternative IRC assessment



Key: IRC, independent review committee; PFS, progression-free survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

Figure 22: Base case log-logistic PFS curves

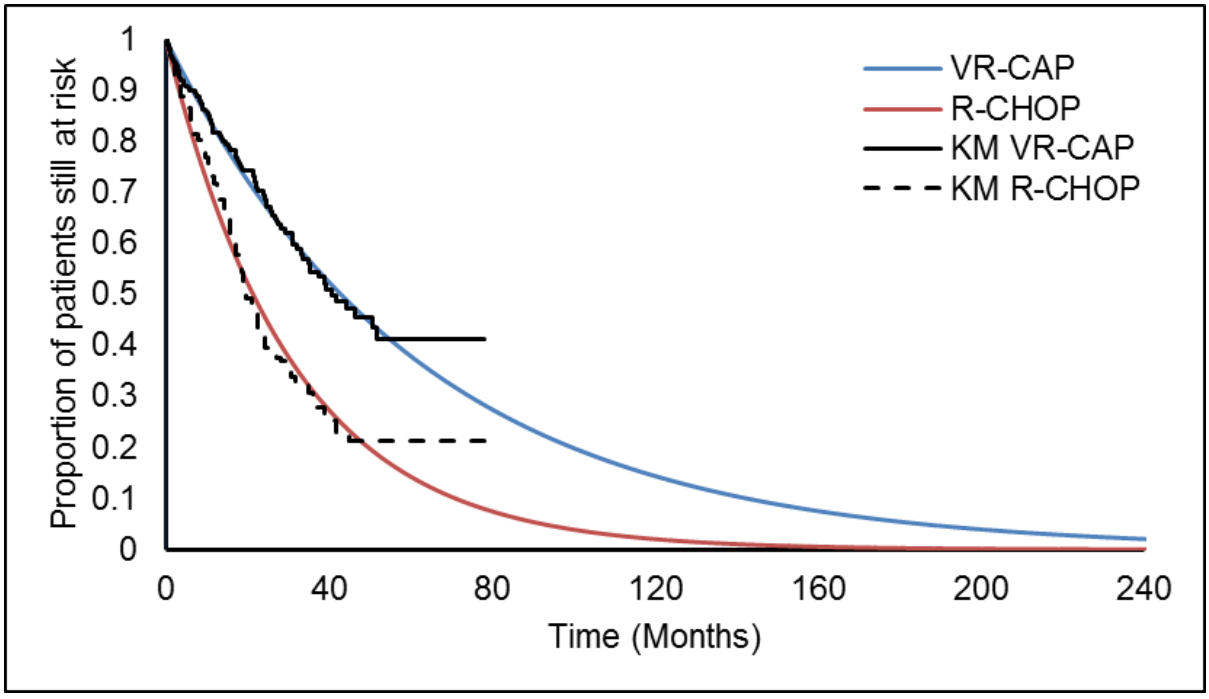


Key: KM, Kaplan–Meier; PFS, progression-free survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

Second-line treatment

After treatment with induction therapy was finalised (standard 6-8 cycles), a TFI generally followed in which the patient received no active treatment until a second-line treatment is initiated. To model time to second-line treatment, six curves (exponential, Weibull, lognormal, log-logistic, gamma and Gompertz) were fitted to the trial TFI data. The curve that fitted the data best, the exponential curve, was used to model the TFI (Figure 23). Fitting of all models to the TFI Kaplan–Meier curves and the AIC/BIC data is presented in Appendix 18.

Figure 23: TFI as observed in the LYM-3002 trial



Key: KM, Kaplan–Meier; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; TFI, treatment-free interval; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

The majority of patients in the UK receive a second-line treatment following progression on R-CHOP (estimated at 65-75% by English clinicians).[6] Within the model base case, the distribution of patients over the different second-line treatment regimens was based on the LYM-3002 trial, as shown in Table 37. All therapies received by 5% or more of either treatment arm were included, except if they were labelled ‘other’. All patients receiving treatments other than those included were redistributed over the included therapies. This table also specifies dosing regimens for second-line treatments included in the trial. A scenario analysis was conducted

using the mix of second-line treatments from the Haematological Malignancy Research Network (HMRN) registry, reflective of historical UK practice. Information on the distribution of treatments and dosing regimens for this dataset is included in Appendix 19.

Table 37: Distribution of patients over regimens at subsequent treatment lines

Subsequent treatment	VR-CAP (n=46) % (n)	R-CHOP (n=88) % (n)	Dosing
CHOP	7% (3)	12% (10)	Cyclophosphamide: 750 mg/m^2 on day 1 of 21-day cycle Doxorubicin: 50 mg/m^2 on day 1 of 21-day cycle Vincristine: 1.4 mg/m^2 (max 2 mg) on day 1 of 21-day cycle Prednisolone: 100 mg on days 1-5 of 21-day cycle[60]
R-bendamustine	11% (5)	23% (20)	Rituximab: 375 mg/m^2 on day 1 of 28-day cycle Bendamustine: 90 mg/m^2 on days 1 & 2 of 28-day cycle[52]
R-bortezomib	2% (1)	10% (9)	Rituximab: 375 mg/m^2 on day 1 of 21-day cycle Bortezomib: 1.3 mg/m^2 on days 1,4,8 and 11 of 21 day cycle[60]
R-CHOP	11% (5)	6% (5)	Rituximab: 375 mg/m^2 on day 1 of 21-day cycle Cyclophosphamide: 750 mg/m^2 on day 1 of 21-day cycle Doxorubicin: 50 mg/m^2 on day 1 of 21-day cycle Vincristine: 1.4 mg/m^2 (max 2 mg) on day 1 of 21-day cycle Prednisolone: 100 mg on days 1-5 of 21-day cycle[60]
Rituximab	13% (6)	18% (16)	375 mg/m^2 on day 1 of 21-day cycle[60]
Ibrutinib	19% (9)	9% (8)	560 mg/day for 7 days of 7-day cycle[92]
Lenalidomide	13% (6)	10% (9)	10 mg on days 1-21 of 28-day cycle[93]
Temsirolimus	9% (4)	9% (8)	75 mg on day 1 of 7-day cycle[94]
Bendamustine	15% (7)	4% (3)	90 mg/m^2 on days 1 & 2 of 28-day cycle[52]
Key: R, rituximab; R-bendamustine, rituximab with bendamustine; R-CHOP, rituximab with, cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.			

The proportion of patients receiving each therapy in the trial was slightly different between the trial arms (Table 37, Table 38). This could have had an impact on survival outcomes. A regression analysis was therefore performed to assess whether

the differences in types of subsequent lines of treatment between induction arms in the LYM-3002 trial were likely to have impacted survival outcomes. Subsequent therapies that were received by the patients in the trial were distributed over five categories for this analysis because of the small numbers of patients receiving some of the treatments. Clinical advice was received on how different treatments should be categorised. The distribution of patients over the five categories was not substantially different between the two arms of the trial, except for the use of experimental agents, shown in Table 38.

Table 38: Categories of second-line treatment used for regression analysis

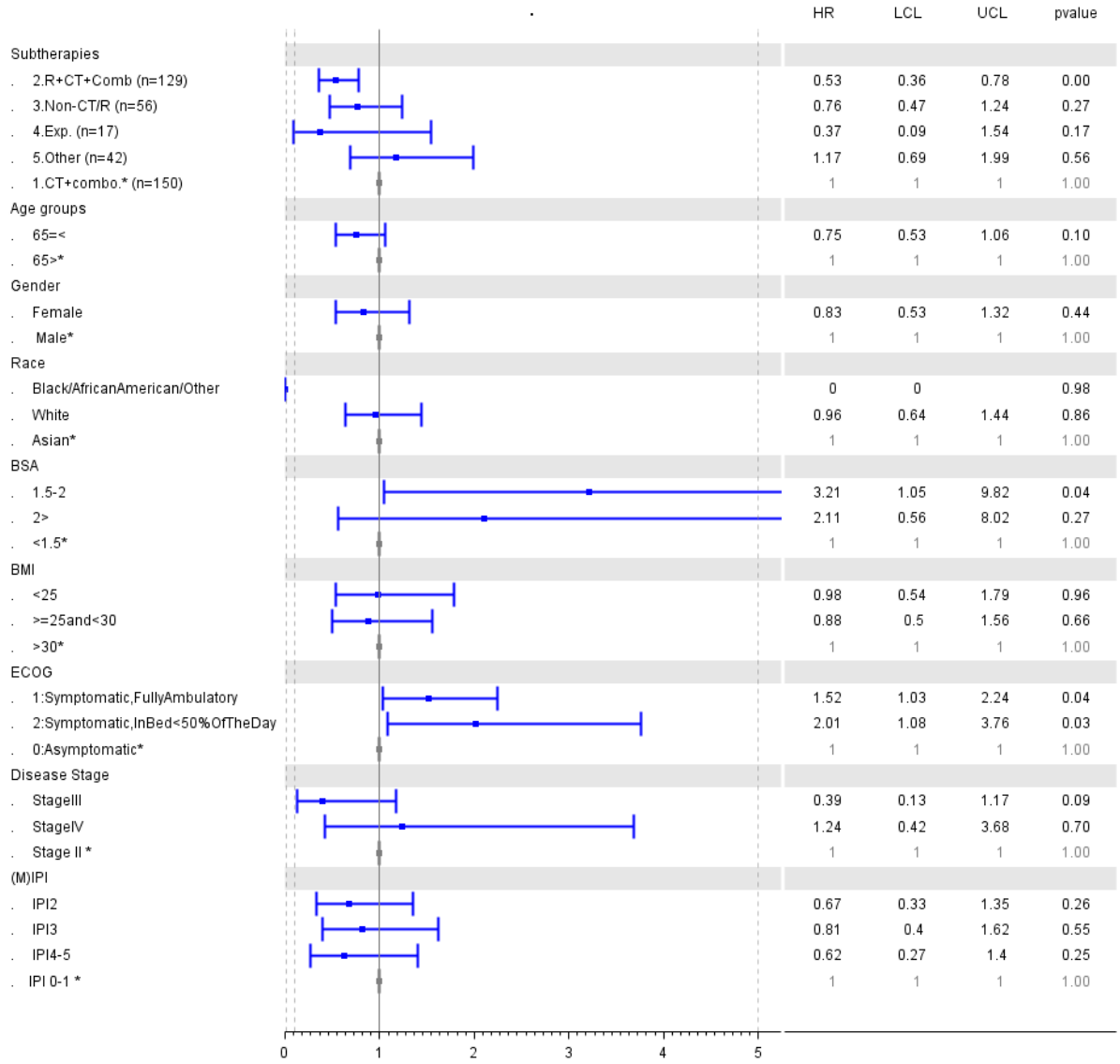
Category	**Includes**	**Number of patients in arm, n (%)**		
		VR-CAP	R-CHOP	Total
1. Chemotherapy agent-based treatment	Single agent or combination chemotherapy	60 (35%)	90 (43%)	150 (38%)
2. Rituximab + chemotherapy agents based treatment	Rituximab + single agent or combination chemotherapy	43 (31%)	86 (34%)	129 (33%)
3. Non-chemotherapy agents based treatment	e.g. lenalidomide, bortezomib, thalidomide, temsirolimus) with or without rituximab	14 (10%)	42 (16%)	56 (14%)
4. Experimental agents	e.g. ibrutinib, rituximab, targeted agents	9 (7%)	8 (3%)	17 (4%)
5. Other	e.g. steroids, radiotherapy	12 (9%)	30 (12%)	42 (11%)
Total		**138 (100%)**	**256 (100%)**	**394 (100%)**

A Cox proportional hazard model was used to conduct a multivariate regression analysis of OS from the start of subsequent treatment including key baseline patient characteristics and the categories of subsequent treatment included in Table 38 as covariates. Baseline characteristics considered to have a potential confounding impact were included as covariates in the model: age, gender, race, BMI, BSA, MIPI score, stage of disease and ECOG status. The output of the model was produced as a forest plot presented in Figure 24. By adding the baseline patient characteristics to the model adjustment for confounding was achieved and an adjusted treatment effect was estimated. The category ‘Chemotherapy (single agent or in combination)’ was used as the reference treatment, against which HRs for all other treatment categories were estimated. HRs in Figure 25 are unadjusted.

OS from the start of subsequent therapy has little variation across the five groups. Only the category of rituximab + chemotherapy had a significant impact on OS. The proportion of patients receiving rituximab + chemotherapy agent-based treatments

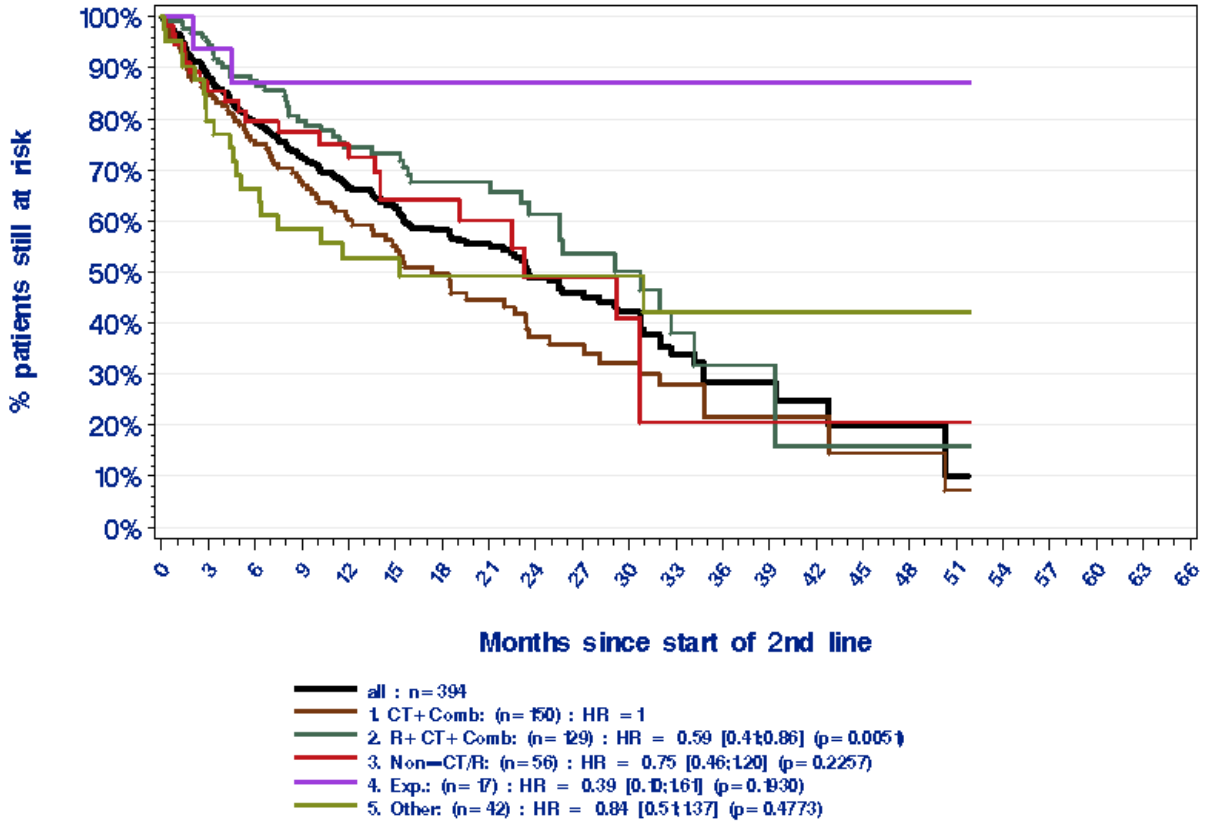
was similar between the two treatment arms, although slightly favouring R-CHOP (34% vs 31% for VR-CAP and R-CHOP, respectively). Therefore, the conservative assumption was made that there was no difference in survival based on second-line treatment received within the model. In this context, given the low proportion of usage, experimental treatments had no significant impact on results.

Figure 24: Regression analysis OS from start of subsequent treatment



Key: Chemo, chemotherapy; Combo, combination therapy; Exp, experimental, HR, hazard ratio, n, number; OS, overall survival; R, rituximab.

Figure 25: OS from start of second-line treatment



Key: Chemo, chemotherapy; Combo, combination therapy; Exp, experimental, HR, hazard ratio, n, number; OS, overall survival; R, rituximab.

The mean duration of second-line treatment and PFS from second-line treatment were derived from the LYM-3002 trial. Treatment duration and PFS for second-line treatment are displayed in Table 39. In the base case, model treatment duration and PFS were assumed to be the same for both arms, using data from both LYM-3002 trial arms combined.

To address any remaining uncertainty surrounding the efficacy of second-line treatments used in UK practice versus the LYM-3002 trial, scenario analyses are also provided excluding second-line treatment from the model. In another scenario analysis, equal costs for second-line treatment were assumed in both arms.

Table 39: Mean duration and PFS for second-line treatment

Second-line treatment:	VR-CAP	R-CHOP	Combined
Duration of treatment	90 days	90 days	90 days
PFS	226 days	234 days	231 days
Key: PFS, progression-free survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.			

Clinical evidence for other comparators in the NICE scope

Whilst it was possible to directly use data from the LYM-3002 trial to compare the effectiveness of VR-CAP and R-CHOP, comparing VR-CAP to the other comparators included in the NICE scope was more challenging.

Using the network of evidence described in section 4.10, the possibility of incorporating the results of indirect treatment comparison was investigated. As discussed earlier, limited data were available for both of the additional comparators included in the scope (R-FC and R-bendamustine).

- Conclusions from the indirect comparison supported the superiority of VR-CAP compared to R-FC, with R-FC resulting in worse outcomes than R-CHOP for OS; this result was likely driven by decreased possibility to use second-line treatment after R-FC.[6] Comparison of PFS was not possible with the available literature.
- Conclusions from the indirect comparison with R-bendamustine were unclear. OS was numerically but non-significantly worse with R-bendamustine than with VR-CAP (and R-CHOP), but PFS was numerically but non-significantly better within the small non-stratified sample of patients with MCL included in the one trial available.

Thus, it was concluded that indirect comparison to R-bendamustine was too unreliable given the heterogeneity described in section 4.10, particularly for PFS, to be used to assess comparative efficacy within the cost-effectiveness model. Rather, a simple assumption of equal efficacy (PFS and OS) to R-CHOP was used based on clinician feedback. This suggested that similar efficacy was expected for R-bendamustine compared to R-CHOP, with the main difference between the two regimens being tolerability.[6] This conclusion was supported by available non-RCT

evidence, which indicated comparable efficacy for R-CHOP and R-bendamustine once baseline confounders were adjusted for (section 4.11).

Given the limitations of the R-FC indirect comparison, an assumption of equal efficacy with R-CHOP was also made for R-FC. This assumption was likely conservative as UK clinician feedback and the indirect comparison indicated that lower survival was expected due to a lack of treatment options post-progression following R-FC. The long-term impact of R-FC on myelosuppression is thought to compromise the ability to deliver further treatment options at relapse.[6]

Scenario analyses were also conducted using the results of the indirect comparisons for R-FC and R-bendamustine, as presented in Table 24 in section 4.10.

R-maintenance

Two different scenario analyses were undertaken to test the impact of including R-maintenance within the model. These analyses should be viewed as purely exploratory as no clinical trial evidence is available assessing the effectiveness of R-maintenance compared to no maintenance therapy after any of the treatments used for MCL.

Two sources of evidence have been used to inform the potential effectiveness of MCL as shown in **Error! Reference source not found.**. There are considerable limitations with both available data sources; however, no more robust data are available for R-maintenance in MCL.

Table 40: Sources of data used for exploratory analysis of impact of inclusion of R-maintenance in the model

Source	NICE TA226[95]	European MCL Elderly trial[41]
Population	Follicular lymphoma	MCL
Comparison	R-maintenance vs observation after induction with rituximab plus chemotherapy	R-CHOP followed by R-maintenance vs R-CHOP followed by interferon
Results	HR 0.55 for PFS No significant effect on OS	HR 0.41 for PFS HR 0.48 for OS (see Appendix 9)
Key advantages	Comparison to no R-maintenance Two year treatment duration	Studied in MCL population Both OS and PFS presented
Key limitations	Not studied in an MCL population Open label OS is too immature as stated in the NICE appraisal Trial stopped early; there may be some bias in the HR for PFS, overestimating the benefit of R-maintenance	Not a comparison to observation Open label Duration of remission assumed equal to PFS R-maintenance given until progression rather than limited to 2 years as per UK practiceImbalanced drop out post randomisation between the arms (14% for IFN, 5% for rituximab) Differing results depending on initial treatment (R-FC vs R-CHOP)
Key: HR, hazard ratio; MCL, mantle cell lymphoma; NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; OS, overall survival; R, rituximab; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone.		

In addition to the testing of point estimates to quantify the expected impact of R-maintenance on the cost effectiveness of VR-CAP induction therapy, three threshold analyses are performed:

1. Threshold analysis for the HR for PFS; HR for OS is fixed at 1
2. Threshold analysis for the HR for OS; HR for PFS is fixed at 0.55
3. Threshold analysis where HR for PFS and OS are assumed equal and are varied together.

In all of the analyses performed, the cost of treatment is assumed, in line with UK practice, to be one dose of 375 mg/m^2 of rituximab administered subcutaneously every two weeks until 2 years after termination of induction therapy for those patients who responded to induction therapy (91.2% and 89.5% for VR-CAP and R-CHOP, respectively). HRs have also been applied until two years after termination of

induction therapy and only for the proportion of patients responding to induction therapy. Adverse events associated with R-maintenance were sourced from the European MCL Elderly Trial [41] and are presented in Appendix 17.

5.4 Measurement and valuation of health effects

The symptoms of MCL are similar to those of most other types of NHL, with the most common symptom being one or more painless swellings in the neck, armpit or groin.[20] There are generally few symptoms while a patient's disease is under control, and patients are expected to return to pre-progression HRQL within 3 months of completing chemotherapy, regardless of the line of therapy. For patients whose disease is not under control, however, HRQL considerably worsens. Patients may experience loss of appetite and weight loss; fever; night sweats; nausea and/or vomiting; indigestion, abdominal pain or bloating; a feeling of "fullness" or discomfort as a result of enlarged tonsils, liver or spleen; pressure or pain in the lower back that often extends down to one or both legs; or fatigue from developing anaemia.

Whilst VR-CAP, like all chemotherapy regimens, can cause a temporary side-effect-related reduction in HRQL in patients during their 4 months of treatment; VR-CAP has an important long-term role in improving patient HRQL by postponing disease progression, as suggested in section 5.3. Data presented in this section show the HRQL of patients with previously untreated MCL.

Health-related quality of life data from clinical trials

As noted in section 4.7, the EQ-5D was included as an exploratory endpoint in the LYM-3002 trial. Measurements were taken at baseline on day 1 of every treatment cycle and at the end-of-treatment visit, which was performed 30 days after the last dose of investigational product was administered. Long-term utility data, including utilities while on second-line treatment, were not captured. Compliance rates for EQ-5D completion were high across all time points, as shown in Table 41.

Table 41: EQ-5D compliance in the LYM-3002 trial

Visit	N expected	N received	Missing
Baseline	484	479	1.0%
Cycle 1, day 1	481	476	1.0%
Cycle 2, day 1	469	462	1.5%
Cycle 3, day 1	457	454	0.7%
Cycle 4, day 1	435	434	0.2%
Cycle 5, day 1	420	417	0.7%
Cycle 6, day 1	407	402	1.2%
Cycle 7, day 1	75	73	2.7%
Cycle 8, day 1	74	73	1.4%
End-of-treatment	435	399	8.3%
Total	3737	3669	1.8%
Key: EQ-5D, EuroQoL-5 Dimension Questionnaire; N, number of patients.			

The mean utility values for PrePS and PPS were estimated using a mixed model approach. Using the mixed model framework ensured that any correlations between repeated measurements from the same subject were properly taken into account. Therefore, the model accounted for the between- and within-subject variability, while the standard errors of the parameter estimates were estimated. Because mixed models have the ability to deal with missing values, they are preferred over more traditional approaches. The utility weights estimated using this mixed model approach are presented in Table 42. These utilities were used in the base case analysis. It should be noted that this methodology likely underestimated the impact of progression on patients' HRQL because utility was only assessed whilst patients were on treatment. This means that utility over the long-term in the post-progression state was not available from the trial. To limit the impact of this lack of data, HRQL during second-line treatment and after progression from second-line treatment were instead based upon clinician input and available published literature.

Table 42: Utilities from the LYM-3002 trial

Health state	Utility	n	SE	95% CI	Source
PFS	0.764	3,033	0.009	0.746-0.781	LYM-3002[60]
Progressed	0.693	162	0.094	0.639-0.744	LYM-3002[60]
Key: CI, confidence interval; PFS, progression-free survival; SE, standard error.					

Health-related quality of life studies

A systematic literature review was performed with the aim of finding utility values for input into the model.

Methods

To ensure that all potentially relevant studies were identified, specific search methods were used. These included both published peer-reviewed studies and abstracts from conference proceedings. There were no limits in terms of date or language.

Searches included search terms for adult patients with NHL as few studies reporting MCL-specific utility values were expected to be found. As MCL is a subtype of aggressive NHL, NHL was considered the best proxy for utility values in the absence of MCL-specific values.

The global electronic databases used were Medline, Medline in-Process (using Ovid platform), EconLit, Embase, Cochrane Library, HTA database and NHS EED. These were searched along with subject-specific conference proceedings of ASH, ASCO, ISPOR and the EHA.

In addition to the formal electronic searches, key international HTA websites (NICE, SMC, Zorginstituut Nederland, CADTH and AWMSG) were searched for relevant HTAs containing utility estimates. Moreover, reference lists of the included HRQL studies were hand searched and scanned for additional publications of relevance to the research question.

The full literature search strategies, including the terms used, are presented in Appendix 13.

To determine the studies eligible for the review, explicit pre-specified inclusion and exclusion criteria were applied to the literature search results (Table 43). In the first

round of filtering, the titles and abstracts of the studies were screened to assess possible eligibility. In the second round of filtering, the full text versions of the remaining studies were identified and screened for eligibility. This systematic approach to selecting studies ensured that the subsequent analysis provided an unbiased synthesis of the relevant research. The inclusion/exclusion criteria used are set out below (Table 43). If two hits had the same title and authors, and were published in the same issue of the same journal, they were considered duplicates, and one of them was excluded.

Primary and secondary filtering and data extraction was performed by one reviewer, and a second reviewer carried out quality control for both filtering and extraction.

Table 43: Inclusion criteria for utility studies

Types of studies	Utilities are not necessarily reported in cost–utility analyses. Additionally, standalone publications reporting on studies of HRQL specifically, and not in a cost-effectiveness context, are commonplace. As such, all studies were included barring reviews, letters and comment articles.
Types of participants	Searches included adult patients with NHL as few, if any, studies were expected to report utilities for MCL patients alone.
Types of intervention	Studies were not restricted by intervention.
Types of outcomes	Utilities derived from any instrument/methodology, including mapping.
Key: HRQL, health-related quality of life, MCL, mantle cell lymphoma; NHL, non-Hodgkin's lymphoma.	

Results

Searches were conducted between 7 and 18 July 2014 with a search update conducted between 11 and 26 March 2015. A total of 255 potentially relevant papers or abstracts were identified in the initial searches. In total, 24 studies were eligible and were included for data extraction (Figure 26).

Of the 24 eligible studies, four were primary utility studies reporting utilities in previously untreated patients with NHL in The Netherlands (Doorduijn et al. 2005; Uyl-de Groot et al. 1995; van Agthoven et al. 2001)[86, 96, 97] and Germany (Witzens-Harig et al. 2009).[98] The 20 remaining studies included 19 cost-effectiveness studies and one HRQL mapping study, Crott et al. 2013[99], which mapped EORTC QLQ-C30 to EQ-5D utilities in previously untreated patients with NHL.

The key characteristics of all included studies are presented in Table 44. Full data extraction tables are presented in Appendix 13.

Amongst the 19 cost-effectiveness studies reporting utility data, four source studies were identified that were not included in this literature review:

- The study by Pettengell et al.[100] had been identified in the searches but was excluded in primary filtering because it did not report utilities; it reports only Functional Assessment of Chronic Illness Therapy-General and -Lymphoma (FACT-G and FACT-LYM), Work Productivity and Activity Impairment Scale (WPAI) and Hospital Anxiety and Depression Scale (HADS), none of which have utilities as an outcome. We assume that the authors of the cost-effectiveness analysis had access to patient level data that were not reported.
- Edelman et al. (1997)[101] was referenced by Braga et al. (2010)[102] but does not include any information on utilities in the publication. It is likely that an incorrect reference was used in the paper published by Braga et al. (2010).[102]
- Wild et al. (2005 and 2006) were referenced in several of the included studies.
    - Wild et al. (2006)[103] was an abstract for a poster presented at the ISPOR European Meeting 2006 in Copenhagen. This abstract was not discovered in the hand searches. After identifying the abstract, it was confirmed that it did not report utility values and was therefore excluded.
    - Wild et al. (2005) was an unpublished report written for the manufacturer, which we were unable to access. However, as there are many studies using these utility values, a scenario analysis was conducted using these values, as reported by Deconinck et al. (2010).[104]

No studies reporting utilities specifically in MCL patients were identified. Of the five utility studies available for NHL (four primary utility studies and one mapping study)[46, 86, 96, 97, 99], an assessment was made as to which was suitable for utilisation within modelling for MCL. MCL is generally regarded as an aggressive form of NHL[105], and

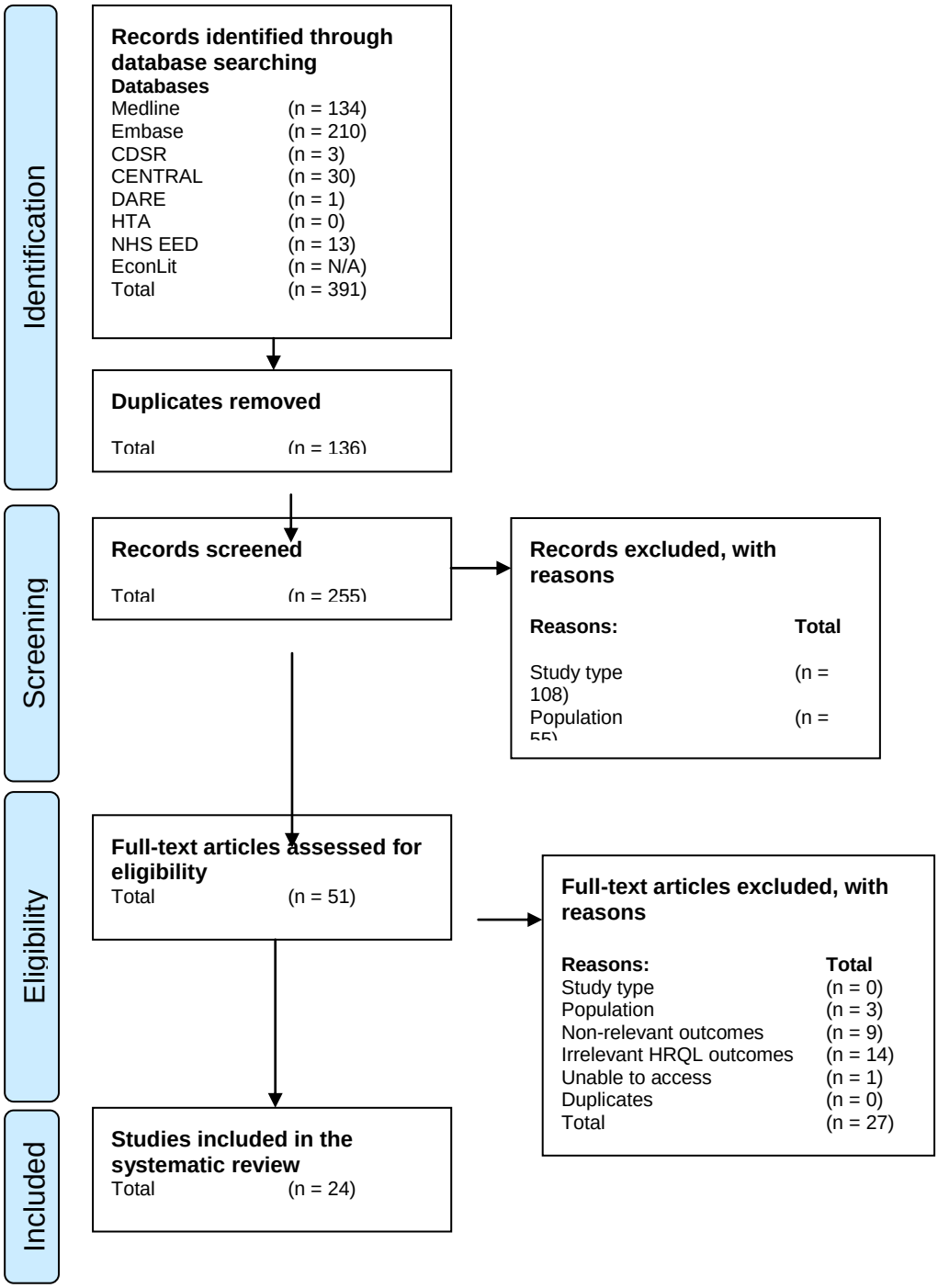
therefore, utilities measured in indolent forms, including follicular lymphoma (FL) are considered less reflective of MCL patients.

- Utilities from van Agthoven et al. (2001)[97] were measured in patients undergoing stem cell transplantation. The indication for VR-CAP is for the treatment of adult patients with previously untreated MCL who are unsuitable for HSCT; therefore, this study was not deemed appropriate to inform the utility values in the analysis.
- Witzens-Harig et al. (2009)[98] measured utilities in patients receiving R-maintenance treatment. This was not included in our model base case, and therefore, these utility values are not used.
- Crott et al. (2013)[99] reported only a mean utility value for patients with NHL based on a mapping from EORTC QLQ-C30 to EQ-5D utilities (0.68), and was therefore not useful for modelling change in utility by health state or over time.
- Of the remaining two papers, Doorduijn et al. (2005)[86] was the most applicable paper as it reported EQ-5D utilities by response and progression based health states for patients with aggressive NHL. This represented the most recent source and was used as a reference in many of the other included articles. As treatment for NHL (and MCL) has evolved over time, the use of a more recent study was preferred over an older study. Therefore, a scenario analysis was conducted using all the values reported by Doorduijn et al. (2005).[86]
- The alternative source (Uyl-de Groot et al. (1995)[96]) was a study conducted in a less clinically relevant patient population, that is, younger patients with less aggressive disease, and had a smaller (n=69 vs n=128) sample size. It was also not clear which method was used to evaluate the health states; the paper mentioned EuroHRQL but did not specify if the EQ-5D tariff or the VAS method was used.

Of the available secondary studies, Hayslip et al. (2008)[106] used utility values that appeared applicable to our model, and therefore, an additional scenario analysis was conducted using utility values from this publication. The same is true of Soini et al. (2012)[107], which provided the most detailed version of the unpublished utility values

from Pettengell et al.[100] Because both of these studies, as well as Deconinck et al.[104], were conducted with patients with FL, which is not deemed reflective of the HRQL impact of MCL, the utility decrements for progression reported in these three studies were applied to the utility for the progression-free health state from the LYM-3002 trial in scenario analyses.

Figure 26: PRISMA flow diagram of the utility studies



Key: HRQL, Quality of Life; N/A, not applicable.

Table 44: Key characteristics of the eligible utility studies

Reference	Location	Population	Study type	Utilities included
Doorduijn et al. (2005)[86]	The Netherlands	Previously untreated elderly patients with aggressive NHL	Primary utility study	Baseline aaPI 0-1: 0.74; aaPI 2-3: 0.44 Mean change scores during first-line CHOP treatment compared to baseline: *After 2nd CHOP cycle:* aaPI 0-1: -0.03 aaPI 2-3: +0.07 *After 4th CHOP cycle:* aaPI 0-1: -0.02 aaPI 2-3: +0.15 *After 6th CHOP cycle:* aaPI 0-1: -0.05 aaPI 2-3: +0.09 Mean change scores during follow-up compared to baseline: *PFS at 3 months:* aaPI 0-1: +0.07 aaPI 2-3: +0.23 *PFS at 6 months:* aaPI 0-1: +0.07 aaPI 2-3: +0.17 *PFS at 10 months:* aaPI 0-1: +0.04 aaPI 2-3: +0.14 *PFS at 18 months:* aaPI 0-1: +0.06 aaPI 2-3: +0.14 *At progression:* aaPI 0-1: -0.24 aaPI 2-3: -0.04
Uyl-de Groot et al. (1995)[96]	The Netherlands	Previously untreated patients aged 15-60 years with newly diagnosed intermediate- and high-grade malignant NHL	Primary utility study	EQ-5D unclear whether tariff or VAS Initial treatment: 0.60 Progression-free: 0.81 No complete response or progression: 0.60

Reference	Location	Population	Study type	Utilities included
Van Agthoven et al. (2001)[97]	The Netherlands	Patients with refractory or relapsed NHL or Morbus Hodgkin	Primary utility study	14 days after transplantation, PBSCT: 0.53 14 days after transplantation, ABMT: 0.42 3 months after discharge, PBSCT: 0.78 3 months after discharge, ABMT: 0.77
Witzens-Harig et al. (2009)[98]	Germany	Patients with CD20+ B cell non-Hodgkin's lymphoma	Primary utility study	Episode1, rituximab: 0.91 Episode2, rituximab: 1.38 Episode3, rituximab: 0.89 Episode4, rituximab: 0.82 Episode1, observation: 0.85 Episode2, observation: 0.91 Episode3, observation: 0.84 Episode4, observation: 0.92
Crott et al. (2013)[99]	Belgium, the Netherlands, Switzerland, UK, Canada	Patients with NHL	Primary: utility mapping study	Mapping EORTC QLQ-C30 to EQ-5D NHL: 0.68 (SD: 0.31)
Berto et al. (2004)[108]	Italy	Patients with aggressive NHL	Secondary: cost-effectiveness study containing utility values from a previous study by Doorduijn et al. (2001)	CR: 0.83 No CR: 0.38 Progression: 0.38
Best et al. (2005)[109]	France, Belgium, Switzerland	Patients aged 60-80 years with previously untreated DLBCL	Secondary: cost-effectiveness study containing utility values from a previous study by Doorduijn et al. (2001)	Disease free survival: 0.83 PPS: 0.39
Deconinck et al. (2010)[104]	France	Patients with relapsed/resistant FL	Secondary: cost-effectiveness study containing utility values from a previous study by Wild et al. (2005)	PFS: 0.805 Progressed disease: 0.618
Groot et al. (2005)[110]	The Netherlands	Previously untreated patients with DLBCL	Secondary: cost-effectiveness study containing utility values from a previous study by Doorduijn et al. (2003)	CR: 0.81 No CR or progression: 0.60

Reference	Location	Population	Study type	Utilities included
Hayslip et al. (2008)[106]	United States	Patients in their second remission from FL over 5 years	Secondary: cost-effectiveness study containing utility values from previous studies by van Agthoven 2005, Doorduijn 2001 and Doorduijn 2005	Disease free: 0.73 Salvage: 0.66 Subsequent remissions: 0.73 Transplantation: 0.65 Refractory: 0.43
Hill et al. (2014)[111]	United States	Patients with NHL	Secondary: cost-effectiveness study containing utility values from previous studies by Doorduijn 2005 and Uyl-de Groot 1995	Chemotherapy: 0.61 Hospitalisation for febrile neutropenia: 0.33 Post-chemotherapy (year 1): 0.79 Post-chemotherapy (year 2+): 0.89
Hornberger & Best (2005)[112]	United States	Patients aged 60-80 years with previously untreated DLBCL	Secondary: cost-effectiveness study containing utility values from a previous study by Doorduijn et al. (2001)	Event-free: 0.83 End of life: 0.38 Salvage or transplantation: 0.83
Kasteng et al. (2008)[113]	Sweden	Patients with relapsed/refractory FL	Secondary: cost-effectiveness study containing utility values from a previous study by Wild et al. (2005)	PFS: 0.805 Progressed disease: 0.618
Kymes et al. (2012)[114]	United States	Patients with DLBCL	Secondary: cost-effectiveness study containing utility values from a previous study by van Agthoven et al. (2005)	Undergoing apheresis: 0.75 High-dose chemotherapy or engraftment: 0.53 Post-engraftment: 0.78
Lathia et al. (2013)[115]	Canada	Patients with DLBCL receiving induction chemotherapy	Secondary: cost-effectiveness study containing utility values from a previous study by Doorduijn et al. (2005)	Baseline/no neutropenia: 0.59 Decrements: Hospitalisation febrile neutropenia: -0.15 Outpatient treatment febrile neutropenia: -0.1
Lyman et al. (2009)[116]	United States	Patients with aggressive NHL with a febrile neutropenia risk of ≥20%	Secondary: cost-effectiveness study containing utility values from previous studies by Doorduijn et al. (2003) and Uyl-de Groot et al. (1995)	During chemotherapy: 0.61 Hospitalisation for febrile neutropenia: 0.33 First year following treatment: 0.79 After the first year of treatment: 0.89

Reference	Location	Population	Study type	Utilities included
Braga et al. (2010)[102]	Portugal	Patients with previously untreated indolent NHL	Secondary: cost-effectiveness study and cost–utility study containing utility values from a previous study by Edelman et al. (1997)	PFS: 0.72 Progression: 0.45
Dewilde et al. (2014)[117]	England, Wales	Previously untreated patients with indolent NHL	Secondary: cost-effectiveness study containing utility values from a previous study by Wild et al. (2006)	Progression free at first-line: 0.805 (SE: 0.018) Progressive disease: 0.7363 (SE: 0.036815) Progression free at second-line assumed equal to PFS at first-line Adverse event: 0.018 (SE: 0.00)
Hornberger et al. (2008)[118]	United States	Previously untreated patients with FL	Secondary: cost-effectiveness study containing utility values from a previous study by Wild et al. (2006)	PFS: 0.802 Progressed: 0.618 Decrements: Chemotherapy: -0.18 Stem cell transplantation: -0.20 End-of-life: 0.30
Papaioannou et al. (2012)[119]	United Kingdom	Patients aged ≥ 60 years with previously untreated FL	Secondary: cost-effectiveness study containing utility values from previous studies by Wild et al. (2005, 2006)	PFS first-line treatment: 0.88 PFS second-line treatment: 0.79 Progressive disease: 0.62
Ray et al. (2010)[120]	United Kingdom	Previously untreated patients with advanced FL	Secondary: cost-effectiveness study containing utility values from a previous study by Pettengell et al. (2008)	PFS: 0.805 (SE: 0.018) Progression: 0.618 (SE: 0.056)
Pink et al. (2012)[121]	United Kingdom	Patients with FL	Secondary: cost-effectiveness study containing utility values from Ray et al. (2010)	PFS: 0.805 Progressed: 0.618
Soini et al. (2011)[122]	Finland	Patients with relapsed/refractory FL	Secondary: cost-effectiveness study containing utility values from a previous study by Pettengell et al. (2008)	PFS: 0.805 Progressed disease: 0.618 Serious drug-related adverse events: -0.19

Reference	Location	Population	Study type	Utilities included
Soini et al. (2012)[107]	Finland	Patients with FL	Secondary: cost-effectiveness study containing utility values from a previous study by Pettengell et al. (2008)	Progression free first-line treatment: 0.78 (SE: 0.03) Progression free second-line treatment: 0.78 (SE: 0.03) Progression: 0.62 (SE:0.06)
Key: ABMT, autologous bone marrow transplantation; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CR, complete response; DLBLC, diffuse large B-cell lymphoma; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, EuroQoL-5 Dimension Questionnaire HRQL, health-related quality of life; FL, follicular lymphoma; NHL, non-Hodgkin's lymphoma; PBSCT, peripheral blood stem cell transplantation; PFS, progression-free survival; PPS, post-progression survival; SE, standard error; VAS, visual analogue scale.				

Adverse events

Section 4.12 reported the incidence of Grade 3 or higher AEs in the LYM-3002 trial. All AEs that occurred at Grade 3 or higher in at least 5% of either treatment group were included in the model.[59, 60] Grade 2 peripheral sensory neuropathy and Grade 3 or higher alopecia and sepsis were also included in the model because these were deemed of clinical significance by the medical specialists attending the UK advisory board.[6]

The annual AE rate for each included AE was calculated from the number of events in the LYM-3002 trial and the total patient years on treatment from the separate treatment arms. This annual rate was then used to calculate the weekly probability of each AE, thus fitting the cost-effectiveness model cycle length.

The duration of AEs was also derived from the LYM-3002 trial, and the data used in the model are presented in Table 45. A scenario analysis was conducted where duration of AEs is assumed to be the same for both arms as, for most AEs, little difference was observed in the duration between the arms. AE durations for the combined model arms are presented in Appendix 20.

In a Phase III study comparing bortezomib administered intravenously versus subcutaneously in patients with multiple myeloma, the incidence of Grade ≥2 peripheral sensory neuropathy was reduced by 41% for subcutaneous administration, relative to IV administration.[1] Neurotoxicity can also be reduced using flexible dosing (see section 4.13).[7, 82, 83] No reduction rates for peripheral sensory neuropathy are available in MCL patients, but assuming that they are similar to those for multiple myeloma, these rates would be expected to reduce costs and improve quality of life (QoL) for patients treated with subcutaneous bortezomib compared to IV bortezomib, which would result in a reduced ICER.

A scenario analysis was conducted for the impact of subcutaneous administration. For this scenario analysis, it was assumed that subcutaneous administration costs were equal to oral administration costs. Because no data on reduction rates for peripheral sensory neuropathy for MCL patients were identified, the conservative assumption of no reduction was made when bortezomib was administered subcutaneously.

For exploratory comparisons with R-FC and R-bendamustine, data on adverse events were extracted from the literature. Where data on specific adverse events included in the model were not available in the published literature, a cycle probability of zero was assumed. If the paper did not specify the frequency of Grade 3 or 4 AEs, the same distribution over Grade 3 and Grade 4/5 as observed for the R-CHOP arm of LYM-3002 was assumed. The duration of AEs for R-FC and R-bendamustine was assumed to be the same as those observed for R-CHOP as no alternative data were available.

To account for the HRQL effects of AEs, utility decrements associated with AEs were derived from EQ-5D data reported in the LYM-3002 trial. Utility decrements were calculated by subtracting the utility value before developing an AE from the utility value with the AE, presented in Table 46**Error! Reference source not found.**. These were applied for the duration of the AE, as specified in Table 45. No AEs for second-line treatment were included as no EQ-5D data were available from the trial to do so.

The AE cycle probabilities and durations also informed the calculation of AE-related costs in the model in section 5.5.

Table 45: AEs, cycle probabilities and duration

Adverse event	VR-CAP		R-CHOP		R-FC[41]		R-bendamustine[72]		Duration (weeks)	
	Grade 3	Grade 4/5	Grade 3	Grade 4/5	Grade 3	Grade 4/5	Grade 3	Grade 4/5	VR-CAP	R-CHOP‡
Neutropenia	0.008	0.039	0.008	0.032					1.09	1.30
Thrombocytopenia	0.014	0.018	0.002	0.001	0.004	0.002			1.04	1.44
Anaemia	0.007	0.001	0.007	0.002	0.002	0.001			0.94	1.39
Leukopenia	0.008	0.017	0.011	0.007	0.007	0.005			1.10	1.35
Lymphopenia	0.007	0.009	0.005	0.001	0.010	0.002			1.19	2.39
Febrile neutropenia	0.006	0.003	0.004	0.004	0.001	0.001	0.002	0.002	0.95	1.19
Pneumonia	0.003	0.001	0.002	0.001			0.001	0.000	2.70	2.29
Fatigue	0.003	0.000	0.002	0.000	0.001	0.000	0.002	0.000	5.06	3.29
Diarrhoea	0.003	0.000	0.001	0.000			0.001	0.000	0.71	0.89
Peripheral sensory Neuropathy	0.007*	0.000	0.004*	0.000	0.000	0.000	0.001	0.000	8.19	21.24
Alopecia	0.000	0.000	0.001	0.000			0.001	0.000	46.43	10.68
Sepsis	0.001	0.001	0.000	0.000					1.81	0.50

Key: AE, adverse event; 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.

Notes: *Includes Grade 2 peripheral sensory neuropathy. ‡Duration of AEs with other comparators are assumed equal to R-CHOP AE durations. In case of missing data, a cycle probability of zero is assumed.

Table 46: Utility decrements for AEs from the LYM-3002 trial[60]

AEs	Utility decrement	n
Neutropenia	-0.000	367
Thrombocytopenia	0.010	152
Anaemia	-0.009	74
Leukopenia	-0.023	176
Lymphopenia	-0.026	88
Febrile neutropenia	0.090	70
Pneumonia	-0.059	28
Fatigue	-0.089	21
Diarrhoea	-0.000	17
Peripheral sensory neuropathy	-0.098	44
Sepsis	-0.171	6
Alopecia	-0.130	6
Key: AE, adverse event.		

Summary of HRQL data used in cost-effectiveness analysis

LYM-3002 EQ-5D data were used for HRQL 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. As no long-term utility values were available from the LYM-3002 trial, equal utility while progression free during first- and second-line treatments was assumed, based upon UK clinician feedback and previous NHL modelling.[6, 117] Utility associated with post-progression from second-line treatment was taken from the most robust source available for aggressive NHL, which is the most similar condition to MCL in terms of expected impact on health status.[86] Sensitivity analyses were carried out to test the impact of using various alternative sources of utility data. Table 47 provides a summary of the utility values used in the base case analysis.

Table 47: Summary of utility values for cost-effectiveness analysis

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 5.4 Table 42	LYM-3002 EQ-5D data.
Progressed from first-line	0.693	0.639; 0.745		

State	Utility value	95% CI	Reference in submission	Justification
treatment				PFS from second-line treatment assumed equal to PFS from first-line treatment[6, 117]
Progression free from second-line treatment	0.764	0.746; 0.781		
Progressed from second-line treatment	0.45*	0.206; 0.708	Section 5.4 Table 44	Most robust literature estimate[86]
Adverse event decrements				
Neutropenia	-0.032	-0.016; -0.052	Section 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		
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.

5.5 Cost and healthcare resource use identification, measurement and valuation

Resource identification, measurement and valuation studies

A systematic literature search for resource identification, measurement and valuation studies was conducted and is described in Appendix 14. No studies were identified that met the pre-specified inclusion criteria.

Intervention and comparator costs and resource use

Drug acquisition costs and administration costs are presented in Table 48 and Table 49, respectively.

Table 48: Drug acquisition costs for first- and second-line treatments

Drug	Unit	Unit cost	Source
Bortezomib	3.5mg	£762.38	MIMS online (Accessed April 2015)
Rituximab	100mg	£174.63	MIMS online (Accessed April 2015)
	500mg	£873.15	MIMS online (Accessed April 2015)
	1400mg	£1,344.65	MIMS online (Accessed April 2015)
Cyclophosphamide	500mg	£8.87	eMIT 201503
	1000mg	£16.49	eMIT 201503
Cyclophosphamide	50mg	£0.82	MIMS online (Accessed April 2015)
Doxorubicin	10mg	£1.72	eMIT 201503
	50mg	£4.41	eMIT 201503
	200mg	£19.09	eMIT 201503
Prednisone	5mg	£0.01	eMIT 201503
Vincristine	1mg	£3.09	eMIT 201503
	2mg	£6.16	eMIT 201503
Bendamustine	25mg	£69.45	MIMS online (Accessed April 2015)
	100mg	£275.81	MIMS online (Accessed April 2015)
Fludarabine	10mg	£20.17	MIMS online (Accessed April 2015)
Cytarabine	100mg	£3.56	eMIT 201503
	500mg	£4.74	eMIT 201503
	1000mg	£5.63	eMIT 201503
	2000mg	£16.81	eMIT 201503
Ibrutinib	140mg	£51.10	MIMS online (Accessed April 2015)
Lenalidomide	10mg	£180.00	MIMS online (Accessed April 2015)
Temsirolimus	30mg	£620.00	MIMS online (Accessed April 2015)

Table 49: Administration costs

Administration	Unit cost	Source
Intravenous administration	£245	NHS reference costs 2013-2014 – Total – HRGs; SB12Z; Deliver Simple Parenteral Chemotherapy at First Attendance – Daycase and Regular Day/Night
Oral administration	£136	NHS reference costs 2013-2014 – Total – HRGs; SB11Z; Deliver Exclusively Oral Chemotherapy – Outpatient
Administration by district nurse	£65	PSSRU 2014
Key: NHS, National Health Service; HRG, Healthcare Resource Group; PSSRU, Personal Social Services Research Unit.		

It was assumed that patients received only whole vials and that there was no vial sharing. Using LYM-3002 weight and height data (taken from the patients from Western countries in the model base case; Table 31), the average number of vials that would be required to satisfy one administration of each IV- or SC-administered drug based on BSA were calculated using method of moments techniques.[123] Table 50 shows the combination of vials on average per dose using an average BSA of 1.91m^2. No dose reductions were taken into account in these calculations.

Using the methods of moments technique, a normal distribution for the BSA within the trial was derived, based upon the mean and standard deviation of BSA. Then the normal distribution was used to predict what proportion of patients required each number of vials to administer the required dose. This method accounts for drug wastage. The number of vials needed per administration for the smallest available vial was calculated per drug. Based on this, the required number of vials of each available vial size was calculated. For rituximab, for example, patients use one vial of 500mg plus 2.66 vials of 100mg on average.

Table 50: Average number of vials required per administration of IV drugs dosed per m^2

Drug	Vial size (mg)	Mean number of vials per dose
Bortezomib	3.5	1
Rituximab	100	2.66
	500	1
	1400	0
Cyclophosphamide	500	1.33
	1000	1
Doxorubicin	10	0.05
	50	2
Vincristine	1	2
	2	0
Bendamustine	25	3.38
	100	1
Cytarabine	100	3.7
	500	1
	1000	1
	2000	1
Key: IV, intravenous.		

Table 51 describes the applied dosing regimens for VR-CAP, R-CHOP, exploratory comparators and second-line treatment regimens. Drug acquisition costs and dosing regimens for second-line treatments that were used in scenario analyses only are presented in Appendix 19:Table 77. For second-line treatment regimens, no maximum number of cycles was specified as the duration of second-line treatment of 90 days (Table 39) was applied for second-line treatment.

Table 51: Dosing regimens

Regimen	Drug	Dose	Cycle length (days)	Max number of cycles	Admins per dosing cycle	Admin type	Source
VR-CAP	Bortezomib	1.3mg/m^2	21	6 (or 8 if first response in cycle 6)	4	IV	LYM-3002[60]
	Rituximab	375mg/m^2			1	IV	
	Cyclophosphamide	750mg/m^2			1	IV	
	Doxorubicin	50mg/m^2			1	IV	
	Prednisone	100mg			5	Oral	
R-CHOP	Rituximab	375mg/m^2	21	6 (or 8 if first response in cycle 6)	1	IV	LYM-3002[60]
	Cyclophosphamide	750mg/m^2			1	IV	
	Doxorubicin	50mg/m^2			1	IV	
	Vincristine	1.4mg/m^2			1	IV	
	Prednisone	100mg			5	Oral	
R-FC	Rituximab	375mg/m^2	28	8	1	IV	SmPCs for cyclophosphamide and fludarabine[124, 125]
	Fludarabine	70mg			3	Oral	
	Cyclophosphamide	50mg			3	Oral	
R-bendamustine	Rituximab	375mg/m^2	28	6	1	IV	Rummel (2013)[52]
	Bendamustine	90mg/m^2			2	IV	
Ibrutinib	Ibrutinib	560mg	7	N/A	7	Oral	SmPC Ibrutinib (2014)[92]
R-cytarabine	Rituximab	375mg/m^2	21	N/A	1	IV	Forbes et al.(2013)[126]
	Cytarabine	200mg/m^2			4	IV	
Bendamustine	Bendamustine	90mg/m^2	28	N/A	2	IV	Rummel et al. (2013)[52]

Regimen	Drug	Dose	Cycle length (days)	Max number of cycles	Admins per dosing cycle	Admin type	Source
Cytarabine	Cytarabine	2000mg/m^2	21	N/A	4	IV	Forbes et al.(2013)[126]
Rituximab	Rituximab	375mg/m^2	21	N/A	1	IV	LYM-3002 (2014)[60]
Lenalidomide	Lenalidomide	10mg	28	N/A	21	Oral	SmPC Lenalidomide (2007)[93]
Temsirolimus	Temsirolimus	75mg	7	N/A	1	IV	SmPC Temsirolimus (2007)[94]
CHOP	Cyclophosphamide	750mg/m^2	21	N/A	1	IV	LYM-3002 (2014)[60]
	Doxorubicin	50mg/m^2			1	IV	
	Vincristine	1.4mg/m^2			1	IV	
	Prednisone	100mg			5	Oral	
Vincristine	Vincristine	1.4mg/m^2	21	N/A	1	IV	LYM-3002 (2014)[60]

Key: CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; IV, intravenous; R-bendamustine, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; R-cytarabine, rituximab with cytarabine; R-FC, rituximab with fludarabine and cyclophosphamide; SmPC, summary of product characteristics; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

Table 52 summarises the drug acquisition and administration costs associated with VR-CAP, R-CHOP, other comparators and second-line treatment options. The dosing, administration and vial info supporting these costs are presented in Table 48, Table 49, Table 50 and Table 51. For the first-line treatments that included an orally administered drug, one oral administration visit was assumed at the start of treatment. For second line, no oral administration visits were assumed for simplicity, as this would be expected to have a negligible impact on the results. Within scenario analysis assessing the impact of subcutaneous administration for bortezomib (and R-maintenance) the cost of subcutaneous administration is assumed equal to the cost of oral administration in the NHS reference costs.

Table 52: Drug acquisition and administration costs

Regimen	Drug	Drug costs		Administration costs per cycle
		Each component	Total per cycle	
VR-CAP	Bortezomib	£3,050	£4,426	Cycle 1: £1,116 Other cycles: £980
	Rituximab	£1,338		
	Cyclophosphamide	£28		
	Doxorubicin	£9		
	Prednisone	£1		
R-CHOP	Rituximab	£1,338	£1,383	Cycle 1: £381 Other cycles: £245
	Cyclophosphamide	£28		
	Doxorubicin	£9		
	Vincristine	£6		
	Prednisone	£1		
R-bendamustine	Rituximab	£1,338	£2,359	£490
	Bendamustine	£1,021		
R-FC	Rituximab	£1,338	£1,764	Cycle 1: £381 Other cycles: £245
	Fludarabine	£423		
	Cyclophosphamide	£2		
Ibrutinib	Ibrutinib	£1,431	£1,431	£0
R-Cytarabine	Rituximab	£1,338	£1,500	£490
	Cytarabine	£161		
Bendamustine	Bendamustine	£1,021	£1,021	£490
Cytarabine	Cytarabine	£161	£161	£490
Rituximab	Rituximab	£1,338	£1,338	£245
Lenalidomide	Lenalidomide	£5,040	£5,040	£0
Temsirolimus	Temsirolimus	£1,860	£1,860	£245
CHOP	Cyclophosphamide	£28	£45	£245
	Doxorubicin	£9		
	Vincristine	£6		
	Prednisone	£1		
Vincristine	Vincristine	£6	£6	£245

Key: CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; R-bendamustnie, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; R-cytarabine, rituximab with cytarabine; R-FC, rituximab with fludarabine and cyclophosphamide; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

Table 53 shows the number of patients receiving treatment per cycle informed by the LYM-3002 trial. Table 54 shows the relative dose reductions that were applied to the drug costs of all patients in the model, based on the relative dose intensity per cycle reported in the study. In the LYM-3002 trial, not all patients received the full dose of their treatment in all of the treatment cycles, in line with product SmPCs, which require modifications to dose levels in response to AEs.[60] Negative numbers are shown in Table 54 for cases where the actual dose was higher than the prescribed dose. This was assumed to be due to the rounding up of doses to the nearest decimal. Dose reductions were not included in the mean number of vials calculated using method of moments techniques.

Proportions of patients receiving each dose for the exploratory comparators were assumed equal to proportions of patients receiving R-CHOP. No dose reductions were applied due to a lack of data.

Table 53: Percentage of patients receiving first-line treatment per cycle (CSR table 20)[60]

	% receiving cycle	
Cycle	**VR-CAP**	**R-CHOP**
1	100.0%	100.0%
2	97.9%	96.7%
3	95.0%	94.2%
4	90.4%	90.5%
5	87.9%	86.0%
6	84.6%	83.9%
7	13.8%	17.4%
8	13.3%	17.4%

Key: CSR, clinical study report; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

Table 54: Difference between average dose received and per protocol dose per cycle in the LYM-3002 trial (CSR table TSS02B)[60]

		Cycle number							
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
VR-CAP	Bortezomib	11.35%	13.46%	13.85%	18.08%	22.31%	24.23%	25.77%	25.77%
	Rituximab	0.11%	0.03%	0.08%	0.13%	-0.05%	0.00%	0.11%	0.16%
	Cyclophosphamide	0.03%	4.69%	6.67%	9.03%	9.63%	10.95%	9.32%	11.51%
	Doxorubicin	0.20%	1.60%	2.60%	4.20%	6.40%	7.00%	3.60%	3.40%
	Prednisolone	3.64%	3.52%	4.04%	5.30%	6.48%	6.40%	2.10%	1.84%
R-CHOP	Rituximab	0.05%	-0.03%	0.11%	0.51%	-0.13%	-0.03%	0.16%	0.43%
	Cyclophosphamide	0.07%	1.12%	2.27%	1.61%	2.27%	2.85%	3.35%	4.52%
	Doxorubicin	0.00%	0.60%	0.80%	1.80%	1.80%	1.80%	0.80%	0.80%
	Vincristine	19.29%	19.29%	20.00%	19.29%	20.00%	20.00%	20.00%	19.29%
	Prednisolone	2.64%	4.00%	4.32%	3.50%	3.20%	3.52%	4.72%	4.64%

Key: CSR, clinical study report; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

Notes: Negative values represent average doses that were higher than per protocol doses.

Health-state unit costs and resource use

Costs associated with each health state are set out in Figure 12 and comprise treatment and disease-management costs as well as costs associated with the management of adverse events and palliative care at end of life.

The resource use and unit costs estimates attributed to disease management are described in Table 55 to Table 60. All resource use assumptions were validated during an advisory board with three UK clinical haematologists.[6]

Concomitant medications

In addition to the cost of hospital visits to treat AEs, drug acquisition costs associated with concomitant medications were also included in the model. Concomitant medications that were used in the LYM-3002 trial but which are not available in the UK were excluded from the analysis. Patients receiving therapies not used in the UK were assigned an average cost based upon therapies available in the UK, thus redistributing them over the therapies that are used in the UK. In the LYM-3002 trial, as in routine practice, concomitant medications were given to treat AEs or to avoid lowering the dose of chemotherapy. The concomitant medications presented in Table 56 were included in the model.

Using the total number of patients that received the category of concomitant medications per cycle and the proportion of patients receiving each concomitant drug in the LYM-3002 trial, the percentage of patients on treatment using concomitant medication per drug was calculated. Due to low patient numbers, the number of patients who received concomitant therapies in treatment cycles 6, 7 and 8 was assumed to be the same. These patients were calculated as an average of the numbers of patients receiving concomitant therapies in these three cycles. Dosage and number of doses per week were obtained from the SmPCs for the respective drugs and are presented in Table 56. Unit costs of concomitant drugs are presented in Table 57.

Based on clinical advice, no administration visits were included within the model for concomitant therapies to avoid double counting of these visits. Clinical advisors stated that these drugs are routinely administered during treatment administration or routine monitoring visits.

For concomitant drugs that are administered intravenously or subcutaneously, method of moments techniques were used to calculate the average number of vials needed per patient. Some of the concomitant drugs are dosed per kg body weight rather than per m^2 BSA. Patient weight was assumed to have a lognormal distribution. The results of the calculations for the concomitant drugs are shown in Table 58.

Based on clinical advice, it was assumed that patients self-administer G-CSFs. A scenario analysis was performed where administration was performed by a district nurse. Filgrastim and lenograstim were administered three times per treatment cycle.[127 128] Pegfilgrastim was given prophylactically and was given once per treatment cycle.[129]

Due to the lack of alternative information, it was assumed that exploratory comparators have the same concomitant medication requirements as R-CHOP which likely overestimated costs. However, the total cost of these medications is relatively low, and the assumption of equal efficacy to R-CHOP likely overestimated the benefits of these comparators.

Table 55: Medical resource use by health state

	On treatment (first- or second-line)	Stable disease (off treatment)	At time of progression	Progressed	Cost	Source
Full blood count	3 per treatment cycle	1 per 2-3 months*	1	0	£3.00	NHS Reference Costs 2013-2014[130]
Biochemistry	3 per treatment cycle	1 per 2-3 months*	1	0	£1.18	NHS Reference Costs 2013-2014[130]
Blood glucose	3 per treatment cycle	0	0	0	£1.18	NHS Reference Costs 2013-2014[130]
Computed tomography-scan	In treatment cycles 1, 3 and 6	0	1	0	£80.00	NHS Reference Costs 2013-2014[130]
Haematologist visit	In treatment cycles 1, 3 and 6	1 per 2-3 months*	1	1 per 2-3 months*	£150.06	NHS Reference Costs 2013-2014[130]

Key: NHS, National Health Service.

Notes: *This has been applied as once every 11 weeks

Table 56: Concomitant medication; percentage of patients using and dosing

	Percentage of patients receiving first-line treatment												Doses per week	Dose	
	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6, 7, 8				
	VR-CAP	R-CHOP	VR-CAP	R-CHOP	VR-CAP	R-CHOP	VR-CAP	R-CHOP	VR-CAP	R-CHOP	VR-CAP	R-CHOP			
G-CSFs															
Filgrastim	19%	16%	23%	19%	25%	20%	26%	24%	29%	24%	26%	19%	7	0.005	mg per kg[127]
Pegfilgrastim	6%	5%	7%	6%	8%	6%	8%	8%	9%	8%	8%	6%	0.33	6	mg[129]
Lenograstim	6%	4%	7%	4%	8%	5%	8%	6%	9%	6%	8%	4%	7	0.15	mg per m[2128]
Antibacterials for systemic use															
Ciprofloxacin	13%	14%	9%	7%	9%	7%	9%	6%	7%	5%	8%	6%	14	500	mg[131]
Levofloxacin	13%	6%	9%	3%	8%	3%	9%	3%	7%	2%	8%	2%	7	500	mg[132]
Moxifloxacin	6%	2%	4%	1%	4%	1%	4%	1%	3%	1%	4%	1%	7	400	mg[133]
Ceftazidime	6%	3%	4%	1%	4%	1%	4%	1%	3%	1%	3%	1%	7	4000	mg[134]
Ceftriaxone	6%	3%	4%	1%	4%	1%	4%	1%	3%	1%	3%	1%	7	2000	mg[135]
Meropenem	4%	3%	3%	2%	2%	2%	2%	1%	2%	1%	2%	1%	21	1000	mg[136]
Co-amoxiclav	10%	7%	7%	3%	7%	3%	7%	3%	6%	2%	6%	3%	21	625	mg[137]
Amoxicillin	3%	3%	2%	1%	2%	1%	2%	1%	2%	1%	2%	1%	14	750	mg[138]
Piperacillin + Tazobactam	6%	4%	4%	2%	4%	2%	4%	2%	3%	1%	4%	2%	28	4500	mg[139]
Co-trimoxazole	16%	12%	11%	6%	10%	6%	11%	5%	9%	4%	9%	5%	14	960	mg[140]
Vancomycin	3%	3%	2%	1%	2%	2%	2%	1%	2%	1%	2%	1%	14	1000	mg[141]
Amikacin	5%	3%	3%	1%	3%	1%	3%	1%	3%	1%	3%	1%	7	15	mg per kg[142]

	Percentage of patients receiving first-line treatment												Doses per week	Dose	
	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6, 7, 8				
	VR-CAP	R-CHOP	VR-CAP	R-CHOP	VR-CAP	R-CHOP	VR-CAP	R-CHOP	VR-CAP	R-CHOP	VR-CAP	R-CHOP			
Antivirals for systemic use															
Aciclovir	38%	27%	12%	6%	13%	4%	10%	6%	10%	4%	7%	5%	28	200	mg[143]
Valaciclovir	7%	3%	%	1%	3%	1%	2%	1%	2%	0%	1%	1%	21	1000	mg[144]
Key: G-CSFs, Granulocyte-colony stimulating agents; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.															

Table 57: Drug acquisition costs for concomitant therapies

Therapy	Unit dose (mg)	Published cost per pack (£)	Source
Filgrastim	0.12	£36.00	MIMS April 2015[145]
	0.3	£50.15	
	0.48	£79.90	
Pegfilgrastim	6	£686.38	
Lenograstim	0.105	£40.11	
	0.263	£62.54	
Moxifloxacin	400	£1.90	
Ciprofloxacin	500	£0.03	eMIT Dec 2014[146]
Levofloxacin	500	£0.26	
Ceftazidime	2000	£2.39	
Ceftriaxone	2000	£1.02	
Meropenem	1000	£3.57	
Co-amoxiclav	500	£0.11	
Amoxicillin	250	£0.01	
	500	£0.02	
Piperacillin + tazobactam	4500	£1.31	
Co-trimoxazole	480	£0.11	
Vancomycin	1000	£1.71	
Amikacin	500	£7.11	
Aciclovir	200	£0.03	
Valaciclovir	500	£0.17	
Key: eMIT, electronic Market Information Tool; MIMS, Monthly Index of Medical Specialities.			

Transfusions

Red blood cell (RBC) and platelet transfusions are administered to treat AEs and, prophylactically, to avoid having to decrease chemotherapy doses. Platelet transfusions are administered to avoid or treat thrombocytopenia, whereas RBC transfusions are used to avoid or treat anaemia.

The total number of transfusions per treatment cycle reported in the LYM-3002 trial was divided by the number of patients on treatment by trial arm to provide the number of transfusions per patient per treatment cycle for VR-CAP and R-CHOP. Due to low patient numbers, the number of transfusions per patient in treatment

cycles 6, 7 and 8 were assumed to be the same and calculated as an average of the numbers of transfusions in these three cycles. Transfusions were assumed to be administered in week 2 of each treatment cycle as, in the LYM-3002 trial, transfusions were observed to occur predominantly between day 10 and 14 (86% and 89% for R-CHOP and VR-CAP, respectively). One IV administration visit at the same cost as one chemotherapy administration visit was assumed for each transfusion as Minuk et al. (2008) reported that a chemotherapy administration chair is used for administering transfusions.[147] The rates applied in the model and the costs per unit are presented in Table 59.

It was assumed that exploratory comparators had the same transfusion requirements as R-CHOP. The total average cost per week of transfusions and concomitant medications is presented in Table 60. No transfusions or concomitant medication use was assumed for second-line treatment due to the lack of sufficient data.

Table 58: Average number of vials required per administration of drugs dosed per m^2 or kg

Drug	Vial size (mg)	Mean number of vials per dose
Filgrastim 0.005 mg/kg	0.12	1.30
	0.3	1
	0.48	0
Lenograstim 0.15 mg/m^2	0.105	0.67
	0.263	1
Amikacin 15 mg/kg	500	12.40

Table 59: Number of transfusions

	Transfusions per patient per model cycle			
	RBC		Platelet	
	VR-CAP	R-CHOP	VR-CAP	R-CHOP
Cycle 1	0.145	0.152	0.151	0.025
Cycle 2	0.121	0.137	0.126	0.023
Cycle 3	0.164	0.241	0.170	0.031
Cycle 4	0.102	0.128	0.106	0.021
Cycle 5	0.096	0.065	0.100	0.011
Cycle 6, 7 and 8	0.069	0.074	0.071	0.012
Cost per unit	£121.85[148]		£196.96[148]	

Key: R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; RBC; red blood cell; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

Table 60: Weekly costs of transfusions and concomitant medications by cycle

Cycle number	Transfusion costs		Concomitant medications costs	
	VR-CAP	R-CHOP	VR-CAP	R-CHOP
1	£64.66	£41.32	£54.49	£35.95
2	£54.26	£37.43	£57.58	£33.78
3	£73.65	£64.43	£60.18	£34.80
4	£46.36	£36.34	£62.76	£40.44
5	£44.92	£18.24	£67.39	£39.62
6, 7 and 8	£33.95	£21.85	£61.36	£32.91

Key: R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

Adverse event unit costs and resource use

The unit costs associated with the AEs included in the model, as described in section 5.4, were sourced from NHS reference costs and are presented in Table 61. Unit costs for AEs not presented in Table 61 were assumed to be zero to avoid double counting, as the events would be treated via the use of transfusions, concomitant medication or dose reductions, with no additional follow-up visit or resource use. These assumptions were made based on UK clinical expert advice.[6]

Table 61: Unit costs for adverse events (NHS Reference Costs 2013-2014)[130]

AE	Cost	Reference cost code
Febrile neutropenia Grade 3	£999.20	NEI-S; weighted average of PM45A, B, C and D; Febrile Neutropenia with Malignancy; Short Stay
Pneumonia Grade 3	£405.45	NEI_S; DZ19G; Other Respiratory Disorders with CC Score 0-5; Short Stay
Febrile neutropenia Grade 4/5	£5,379.59	NEI_L; Weighted average of PM45A, B, C and D; Febrile Neutropenia with Malignancy; Long stay
Pneumonia Grade 4/5	£1,182.95	EI_L; DZ19G; Other Respiratory Disorders with CC Score 0-5; Long Stay
Diarrhoea Grade 4/5	£579.21	NEI_S; Weighted average of PF26A&B; Other Gastrointestinal Disorders with CC Score 1+; Short Stay
Peripheral sensory neuropathy Grade 4/5	£458.86	NEI_S; AA26G; Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 3-5; Short Stay
Sepsis	£3,772.83	NEI_L; Weighted average of PW16A, B, C and D; Major infections with CC Score 1+; Long Stay
Key: AE, adverse event; NHS, National Health Service.		

Applying these costs to the cycle probability of each event, reported in Table 45 in section 5.4, produced cycle costs of £26.41 for VR-CAP and £28.81 for R-CHOP, as shown in Table 62.

Table 62: Weekly costs attributable to AEs

AE	Cost per cycle			
	VR-CAP	R-CHOP	R-FC	R-bendamustine
Febrile neutropenia	£20.90	£25.99	£5.34	£11.77
Pneumonia	£2.73	£1.72	£1.72	£0.81
Fatigue	£0.00	£0.00	£0.00	£0.00
Diarrhoea	£0.00	£0.15	£0.14	£0.11
Peripheral sensory neuropathy	£0.11	£0.00	£0.00	£0.00
Sepsis	£2.68	£0.95	£5.35	£5.35
Total	**£26.41**	**£28.81**	**£12.55**	**£18.04**

Key: AE, adverse event; 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.

End of life care

The cost of care immediately prior to death was taken from a King's Fund report on improving choice at end of life.[149] This provided the average cost of community and acute care for patients with cancer in the last 8 weeks of life, which was inflated to 2013/2014 levels.[150]

The cost for this end-of-life care was £6,018, which was applied upon the time of transition to the death state. Not all of these costs were direct NHS costs; some fell on 'third sector' healthcare organisations. However, their inclusion was relevant to the disease and did not introduce meaningful bias as the majority of patients died within the model time horizon.

5.6 Summary of base case de novo analysis inputs and assumptions

Summary of base case *de novo* analysis inputs

Appendix 21 summarises the base case economic model variables in terms of their point estimate value and their assumed distribution. This table guides the reader towards the sections of the submission in which the different variables are described. The scale of uncertainty around estimates was informed by data for key parameters, including all survival parameters, ORRs, and utility estimates for the "PFS, on Treatment" health state.

Assumptions

The base case analysis, which used data from the LYM-3002 trial to infer the relative economic value of VR-CAP versus R-CHOP and exploratory comparators, was subject to several key assumptions, as described and discussed throughout section 5. The assumptions are also listed here for reference:

Safety and effectiveness

- PFS was best characterised by log-logistic curves fitted to LYM-3002 data.
- OS was best characterised by exponential curves fitted to LYM-3002 data, categorised by progression status.
- PPS was assumed equal for both arms of the LYM-3002 trial.
- Second-line treatment started after a TFI informed by LYM-3002 data. TFI was best characterised by exponential curves fitted to these data.
- Average duration of second-line treatment and average PFS from second-line treatment were used based on LYM-3002 data. These were assumed equal across both trial arms.
- All AEs that occurred at Grade 3 or higher in at least 5% of patients in either arm of the trial plus Grade 2 peripheral sensory neutropenia and all grades sepsis and alopecia were included.
- Efficacy and safety of exploratory comparators was assumed equal to R-CHOP, except for AE rates reported in the literature.

Resource use and costs

- Patients were treated for the duration observed in the LYM-3002 trial.
- Resource use was dependent on treatment and progression status.
- Only concomitant medications available in the UK were included in the analysis. Patients receiving other concomitant medications were assigned an average cost based upon those available in the UK.

Quality of life

- Quality of life was dependent on progression status.
- The most suitable sources to estimate utilities were LYM-3002 EQ-5D data. For patients post-progression from second-line treatment, the EQ-5D utility reported by Doorduijn et al. (2005) was used in the model as the most suitable estimate.[86]

- Quality of life effects of adverse events were based on LYM-3002 EQ-5D data.

Scenario analysis summary

The key scenarios considered in the analyses are listed in Table 63. Comparisons of VR-CAP versus the exploratory comparators and exploratory analysis associated with R-maintenance treatment are presented separately from the listed scenarios.

Table 63: Key scenario analyses

Scenario		Description	Assumption tested
MOD1/2/3/4	Length of model time horizon	Four scenarios are presented for different time horizons of 10, 15, 25 and 30 years, to examine the sensitivity of results to the extrapolation of efficacy and costs.	Assessed the sensitivity to the level of extrapolation in the model, to examine the degree to which the time horizon affects the ICER.
EFF1	Model fit to PFS Kaplan–Meier curves	The exponential curve fit is used for PFS instead of the log-logistic curve fit. AIC and BIC data were similar for both curve fits. Other parametric models had a worse fit to the Kaplan–Meier data and are therefore tested in the secondary scenario analyses.	Assessed the impact on the model of using a different parametric model for the extrapolation of PFS trial data.
EFF2	Model fit to OS Kaplan–Meier curves	The Weibull curve fit is used for OS instead of the exponential curve fit. AIC and BIC data were similar for both curve fits. Other parametric models had a worse fit to the Kaplan–Meier data and are therefore tested in the secondary scenario analyses.	Assessed the impact on the model of using a different parametric model for the extrapolation of OS trial data.
EFF3	Same pre-progression OS across arms	The pre-progression OS is assumed equal for VR-CAP and R-CHOP.	Assessed the impact on the model of assuming no difference in OS between the two arms.
ASS1	IRC assessment	The primary IRC assessment of progression is used. The curves used are presented in Appendix 22.	Assessed the sensitivity of the model to the method of assessment of progression. The primary IRC assessment is used rather than the alternative IRC assessment.
ASS2	Investigator assessment	The investigator assessment of progression is used. The curves used for PFS are presented in Appendix 23.	Assessed the sensitivity of the model to the method of assessment of progression. The investigator assessment is used rather than the alternative IRC assessment.
QOL2	Utility for PFS from second line is equal to utility for progressed from first line	It is assumed that patients who have started second-line treatment and have not yet progressed from this line of treatment have the same utility as patients who have progressed from first-line treatment, reflecting that patients on second-line therapy will have more severe disease.	Assessed the sensitivity of the model to the assumptions made about the utility of patients who have started second-line treatment.
QOL3	Utility for progressed from second line is equal to utility for progressed from first line	It is assumed that patients who have progressed from second-line treatment have the same utility as patients who have progressed from first-line treatment.	Assessed the sensitivity of the model to the assumptions made about the utility of patients who have progressed from second-line treatment.
RES1	Subcutaneous administration of bortezomib	It is assumed that bortezomib is administered subcutaneously instead of intravenously.	Assessed the impact of the lower administration costs (assumed equal to oral administration costs) associated with subcutaneous administration of bortezomib.

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; ICER, incremental cost-effectiveness ratio; IRC, Independent Review Committee; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

Secondary scenario analyses were conducted to assess the sensitivity of the model to changes in a wider range of elements of the analysis, as shown in Table 64.

Table 64: Secondary scenario analyses

Model element	Base case	Alternative scenario(s)	Name
Model structure			
Second-line treatment	Patients receive second-line treatment following a treatment-free interval	Patients do not receive second-line treatment	**MOD5**
		Patients start second-line treatment immediately upon progression from first-line treatment	**MOD6**
		Equal costs of second-line treatment across arms	**MOD7**
		Duration of and PFS from second-line treatment by trial arm	**MOD8**
		HMRN data used to model cost of subsequent treatment lines	**MOD 9**
General population mortality	General population mortality is added to OS observed in LYM-3002	No general population mortality added	**MOR1**
Varying treatment efficacy assumptions			
PFS data source	LYM-3002 trial data log-logistic curve fit	Weibull	**EFF4**
		Lognormal	**EFF5**
		Gamma	**EFF6**
		Gompertz	**EFF7**
OS assumption	Equal OS for all progressed patients	OS post-progression by trial arm	**EFF8**
OS data source	LYM-3002 trial data exponential curve fit	Log-logistic	**EFF9**
		Lognormal	**EFF10**
		Gamma	**EFF11**
		Gompertz	**EFF12**
Treatment-free interval data source	LYM-3002 trial data exponential curve fit	Weibull	**EFF13**
		Log-logistic	**EFF14**
		Lognormal	**EFF15**
		Gamma	**EFF16**
		Gompertz	**EFF17**
Adverse events	Duration of adverse events based upon combined trial arms	Duration of events by trial arm	**EFF18**
Varying population assumptions			
Eligibility for HSCT	All patients included	Only patients who are clinically ineligible for HSCT	**POP1**
Demographic inputs	Western patients	ITT population	**POP2**

Model element	Base case	Alternative scenario(s)	Name
Age at baseline	69 years	65 years	**POP3**
		75 years	**POP4**
Patient weight	79 kg	70 kg	**POP5**
		85 kg	**POP6**
Patient BSA	1.91 m^2	1.8 m^2	**POP7**
		2.0 m^2	**POP8**
Varying the quality of life assumptions			
Health state utility values	LYM-3002 utility values	Doorduijn utility values	**QOL4**
		Utility decrement for progressing Soini	**QOL5**
		Utility decrement for progressing Hayslip	**QOL6**
		Utility decrement for progressing Deconinck	**QOL7**
Varying the resource use assumptions			
Administration of G-CSF	Self-administration	Administration by district nurse	**RES2**
Medical resource use post-progression	No medical resource use post-progression	Medical resource use post-progression equal to pre-progression	**RES3**
Key: BSA, body surface area; G-CSF, granulocyte-colony stimulating agent; HSCT, haematopoietic stem cell transplantation; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival.			

5.7 Base case results

Base case incremental cost-effectiveness analysis results

Base case results of the economic comparison between VR-CAP and R-CHOP are presented in Table 65. VR-CAP was estimated to generate 0.75 incremental LYs, 0.80 incremental QALYs and an incremental cost of £16,213 versus R-CHOP, leading to an ICER of £20,362. Given these results, VR-CAP was clearly a cost-effective alternative in comparison to R-CHOP for MCL patients for whom HSCT is unsuitable.

Table 65: Base case results, VR-CAP versus R-CHOP

	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

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.

Modelled clinical outcomes

Table 66 summarises the median results estimated by the model in comparison to median results observed in the LYM-3002 trial for the key clinical outcomes. The model predicted the median PFS accurately, if somewhat conservatively; below the trial PFS for VR-CAP but above the trial PFS for R-CHOP. Whilst median OS was not reached in the trial for VR-CAP, and the OS predicted for R-CHOP in the model was somewhat higher than reported in the trial, both results lay within the 95% confidence intervals reported in the trial.

Figure 27 and Figure 28 show the Markov trace for the VR-CAP and R-CHOP arms of the base case model. Survival benefits were clearly accrued pre-progression for VR-CAP versus R-CHOP.

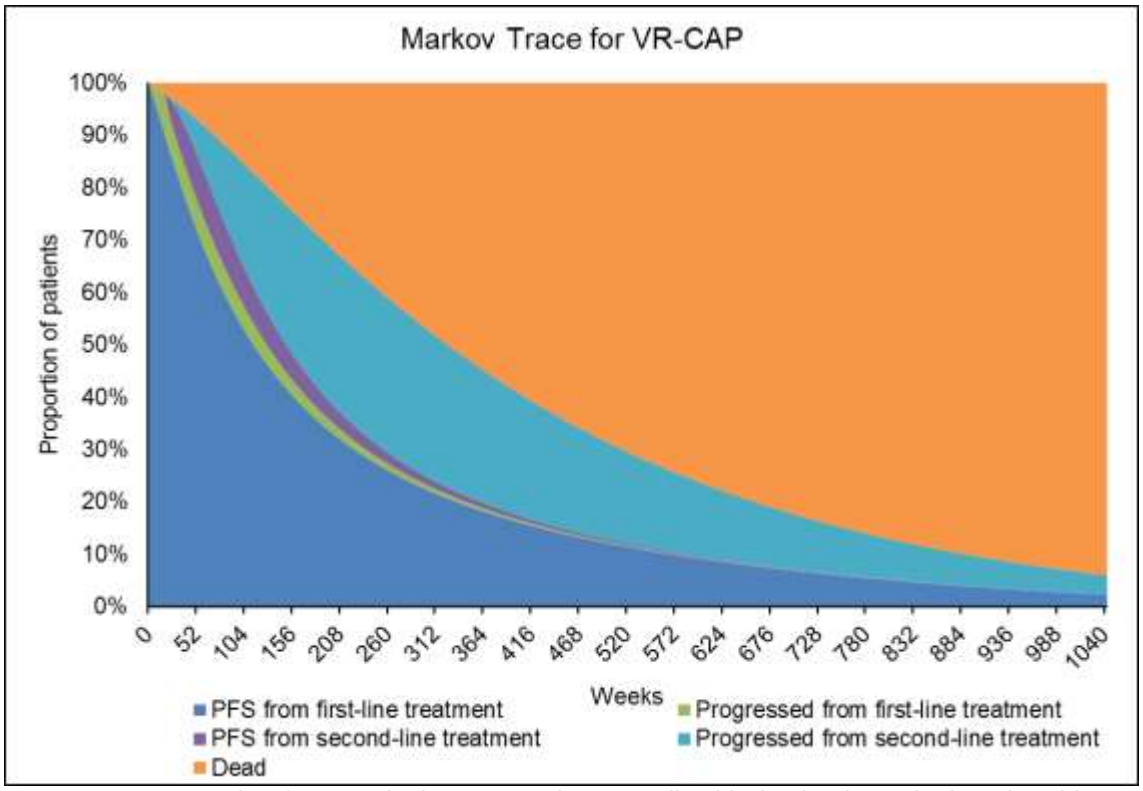
Figure 29 shows the cumulative uptake of second-line treatment. As already seen in the TFI curves, patients in the R-CHOP arm start second-line treatment sooner than patients in the VR-CAP arm. After 20 years 65.0% of the VR-CAP cohort starting the model has taken up second-line treatment versus 81.4% of the R-CHOP cohort.

Table 66: Summary of model results compared with clinical data (years)

Outcome	VR-CAP trial result	VR-CAP model result	R-CHOP trial result	R-CHOP model result
Median PFS	2.37 (1.82-3.16)	2.20	1.23 (1.00-1.41)	1.25
Median OS	NR (4.67-NR)	6.25	4.69 (3.93-NR)	5.21

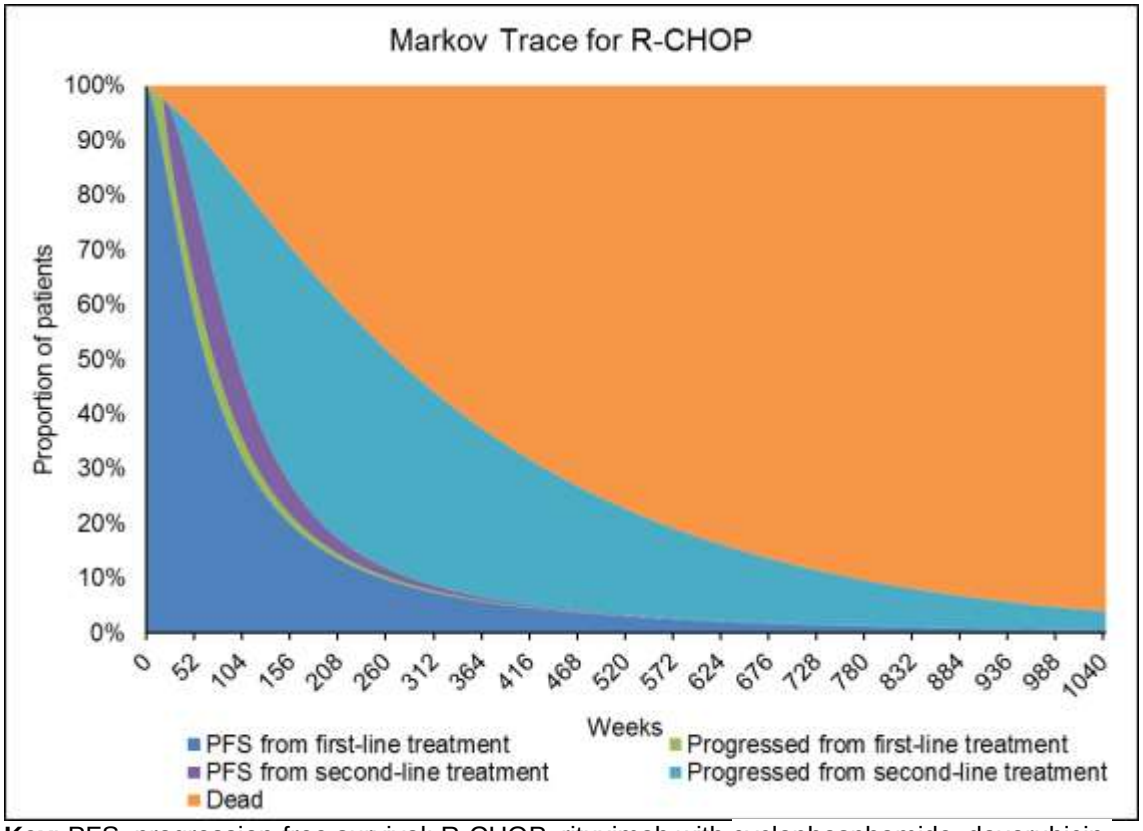
Key: NR, not reached; OS, overall survival; PFS, progression free survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

Figure 27: Markov trace for VR-CAP



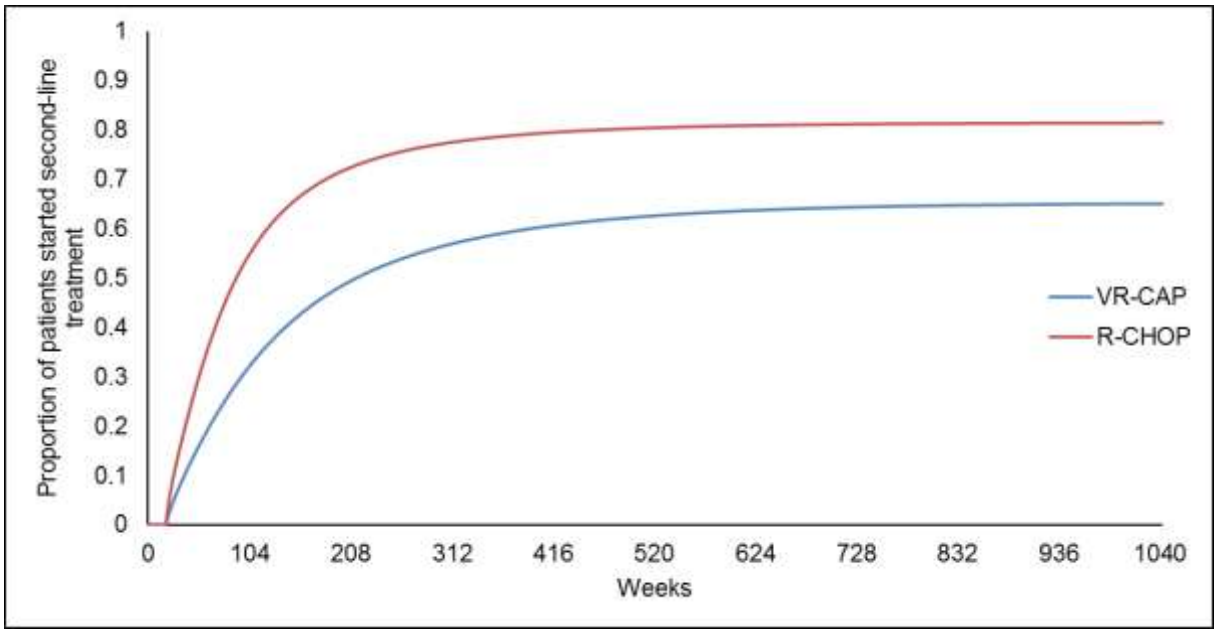
Key: PFS, progression-free survival; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

Figure 28: Markov trace for R-CHOP



Key: PFS, progression-free survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone.

Figure 29: Cumulative uptake of second-line treatment



Key: R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

Disaggregated results of the base case cost-effectiveness analysis

Table 67 summarises total QALYs for both arms of the base case model, disaggregated by model health states; Table 68 summarises total life years. As shown in Figure 27 and Figure 28, the predicted incremental LYs for VR-CAP were incurred in the pre-progression health states. This reflects the assumption of equal PPS. The same was seen for the QALY gain.

Table 69 shows the predicted total incremental costs for VR-CAP versus R-CHOP. Reflecting where the majority of treatment cost is incurred, 86% of the incremental total cost of VR-CAP was attributable to differences across model arms in the 'PFS from first-line treatment' health state. Table 70 shows these data further aggregated by category of costs.

Table 67: Summary of QALY gain by health state

Health state	QALYs VR-CAP	QALYs R-CHOP	Increment	Absolute increment	% absolute increment
PFS from first-line treatment	2.71	1.55	1.16	1.16	73%
Progressed from first-line treatment	0.14	0.10	0.03	0.03	2%
PFS from second-line treatment	0.22	0.29	-0.07	0.07	4%
Progressed from second-line treatment	1.09	1.42	-0.33	0.33	21%
Total	**4.15**	**3.35**	**0.80**	**1.59**	**100%**

Key: PFS, progression free survival; QALYs, quality-adjusted life years; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

Table 68: Summary of life years gained by health state

Health state	Life years VR-CAP	Life years R-CHOP	Increment	Absolute increment	% absolute increment
PFS from first-line treatment	3.54	2.02	1.52	1.52	64%
Progressed from first-line treatment	0.20	0.15	0.05	0.05	2%
PFS from second-line treatment	0.29	0.38	-0.09	0.09	4%
Progressed from second-line treatment	2.41	3.15	-0.73	0.73	31%
Total	**6.44**	**5.69**	**0.75**	**2.38**	**100%**

Key: PFS, progression free survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

Table 69: Disaggregated costs by health state, VR-CAP vs R-CHOP

Health state	Costs VR-CAP	Costs R-CHOP	Increment	Absolute increment	% absolute increment
PFS from first-line treatment	£31,374	£11,942	£19,433	£19,433	86%
Progressed from first-line treatment	£290	£294	-£4	£4	0%
PFS from second-line treatment	£7,729	£10,169	-£2,440	£2,440	11%
Progressed from second-line treatment	£6,445	£7,221	-£776	£776	3%
Total	**£45,838**	**£29,625**	**£16,213**	**£22,653**	**100%**

Key: PFS, progression free survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

Table 70: Disaggregated costs by cost category, VR-CAP vs R-CHOP

Health state	Costs VR-CAP	Costs R-CHOP	Increment	Absolute increment	% absolute increment
First-line therapy	£22,606	£8,041	£14,566	£14,566	66%
Administration	£5,817	£1,564	£4,253	£4,253	19%
AEs and concomitant medication	£1,472	£1,105	£367	£367	2%
Medical resource use	£4,186	£4,671	-£484	£484	2%
Second-line treatment	£7,152	£9,423	-£2,271	£2,271	10%
Terminal care	£4,605	£4,821	-£217	£217	1%
Total	**£45,838**	**£29,625**	**£16,213**	**£22,158**	**100%**

Key: AE, adverse event; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

5.8 Sensitivity analyses

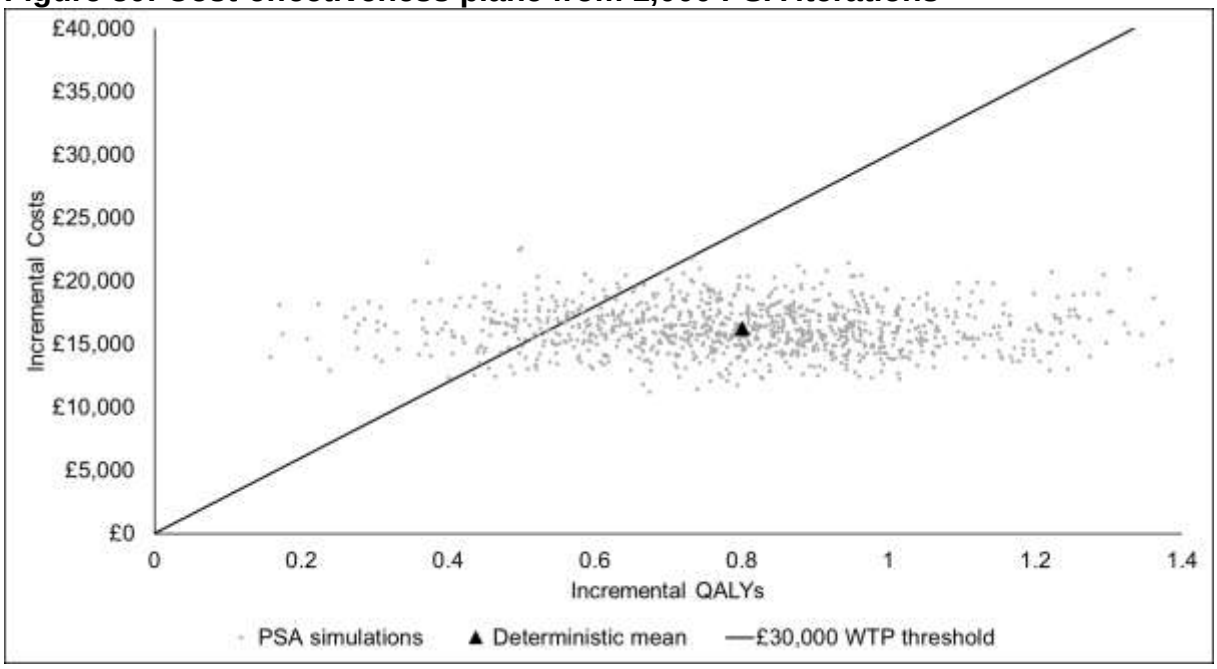
Probabilistic sensitivity analysis

Results from 1,000 probabilistic sensitivity analysis (PSA) iterations of VR-CAP versus R-CHOP are presented in Figure 30. This shows incremental QALYs and costs for VR-CAP versus R-CHOP. Incremental QALYs range from approximately 0.2 to 1.4, while incremental costs are approximately clustered between £11,000 and

£22,000. The mean cost difference is £16,234, and the mean difference in QALYs is 0.80, with a mean probabilistic ICER of £20,264.

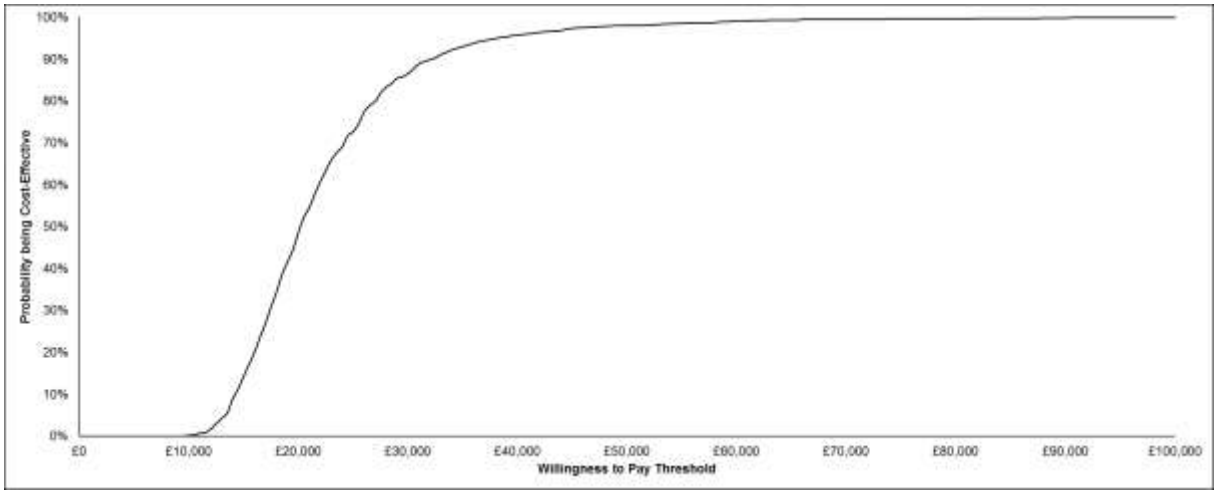
Based on 1,000 PSA iterations, the incremental cost-effectiveness acceptability curve versus R-CHOP (Figure 31) has been constructed. There is a 48.7% likelihood that VR-CAP is cost effective when compared to R-CHOP at a willingness to pay threshold of £20,000. At a threshold of £30,000, the likelihood is 86.5%.

Figure 30: Cost-effectiveness plane from 1,000 PSA iterations



Key: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 31: Incremental cost-effectiveness acceptability curve for VR-CAP versus R-CHOP



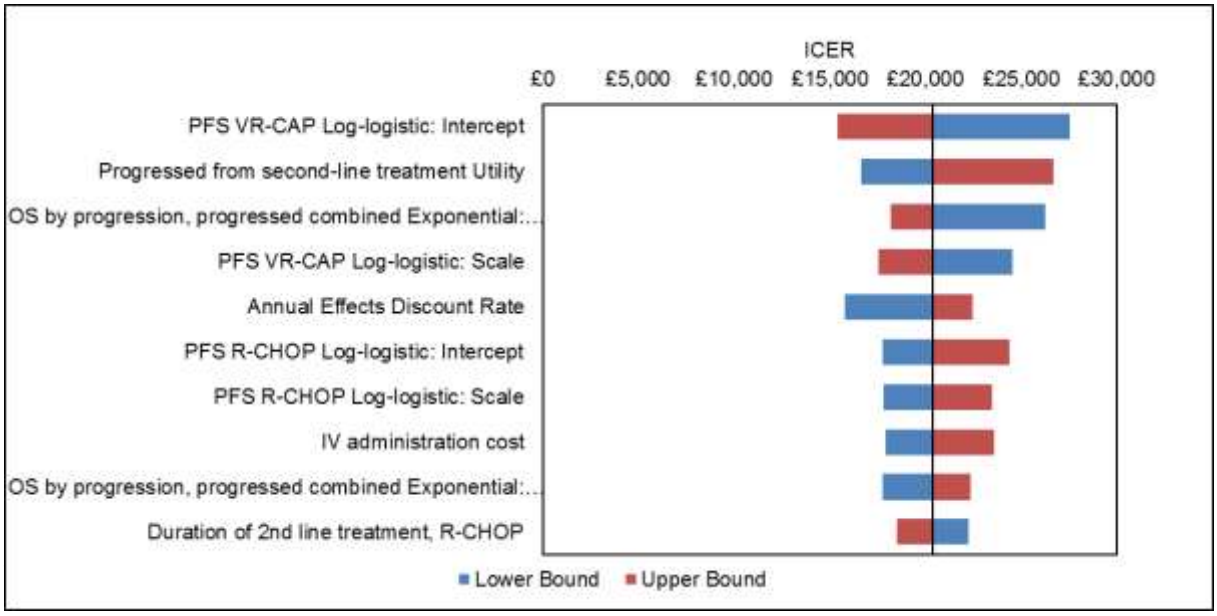
Key: R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

Deterministic sensitivity analysis

Figure 32 presents a tornado diagram showing the parameters with the greatest impact on the ICER, with descending ICER sensitivity.

The ICER is sensitive to variations within the fit of the parametric models for PFS and OS. The model outcomes depend 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 is the parameter with the second greatest ICER sensitivity, due to patients spending a relatively long time in this health state. The discount rate applied to QALYs also has a moderate impact on the ICER since the effect benefits for VR-CAP are spread over a reasonably long time horizon. Model results are comparatively insensitive to individual inputs not shown in Figure 32. A table with full one-way sensitivity analysis results is presented in Appendix 24. Overall, the variability around the ICER is minimal, with even extreme values of parameters still demonstrating cost-effective results below a £30,000 per QALY willingness to pay threshold.

Figure 32: Tornado diagram displaying the ICER sensitivity of the 10 most influential model inputs



Scenario analysis

Table 71 shows the results of the key scenario analyses. As expected, shorter time horizons give a higher ICER because benefits from VR-CAP are mainly accrued in the long term through improved survival. Nonetheless, even at a curtailed time horizon of 10 years, VR-CAP remains cost effective at a threshold of £30,000 per QALY. Using the exponential curve fit for PFS results in an ICER approximately £8,000 higher than with the log-logistic curve fit used in the base case. This is a key sensitivity of the model, but as outlined in section 5.3, the exponential curve may not reflect the clinical expectation of slightly longer PFS than observed in the LYM-3002 trial. Using the IRC assessment results in an increase of the ICER by approximately £1,500, and using the investigator assessment results in a decrease of the ICER by approximately £1,500. The model is insensitive to the utility assumptions for PFS on second-line treatment, but it is sensitive to the assumption regarding utility for post-progression from second-line treatment; this is because of the average time spent in these health states, which is short pre-progression and long post-progression from second-line treatment. However, even in the extreme scenario presented, which assumes no impact on utility despite a second relapse and potentially no further treatment, the ICER is still only £26,241.

Results of secondary scenario analyses are presented in Table 72. The ICER is below £30,000 for all but one of the scenarios tested (Gompertz curve fit for PFS with an ICER of £30,452). The Gompertz curve fit for PFS results in an ICER marginally above the cost-effectiveness threshold; however, this curve does not fit the data well. Excluding second line treatment from the model increases the ICER towards the £30,000 per QALY threshold, but not beyond it.

It should be noted that making changes to any of the assumptions around AEs has only a small impact on the model outcomes. Whilst the occurrence and management of AEs is highly important to patients and clinicians, the fixed duration of treatment means that the detrimental impact is outweighed by the longer term benefits of increased time off-treatment and improved survival.

Table 71: Results of key scenario analyses

	VR-CAP	R-CHOP	Difference	ICER
Base case analysis				
Costs	£45,838	£29,625	£16,213	£20,362
LYs	7.67	6.66	1.01	
QALYs	4.15	3.35	0.80	
MOD1: *Time horizon – 10 years*				
Costs	£44,298	£28,388	£15,910	£27,443
LYs	6.15	5.58	0.57	
QALYs	3.59	3.01	0.58	
MOD2: *Time horizon – 15 years*				
Costs	£45,419	£29,309	£16,109	£22,049
LYs	7.19	6.34	0.85	
QALYs	3.99	3.26	0.73	
MOD3: *Time horizon – 25 years*				
Costs	£45,993	£29,736	£16,258	£19,875
LYs	7.86	6.79	1.07	
QALYs	4.20	3.38	0.82	
MOD4: *Time horizon – 30 years*				
Costs	£46,044	£29,772	£16,271	£19,772
LYs	7.93	6.84	1.09	
QALYs	4.21	3.39	0.82	
EFF1: *Exponential curve fit for PFS*				
Costs	£47,233	£29,866	£17,367	£28,133
LYs	7.35	6.54	0.81	
QALYs	3.89	3.27	0.62	
EFF2: *Weibull curve fit for OS*				
Costs	£46,021	£29,732	£16,289	£20,683

	VR-CAP	R-CHOP	Difference	ICER
LYs	8.08	7.10	0.98	
QALYs	4.27	3.48	0.79	
EFF3: *Equal pre-progression OS across arms*				
Costs	£45,717	£29,700	£16,017	
LYs	7.61	6.69	0.92	£21,008
QALYs	4.12	3.36	0.76	
ASS1: *Independent Review Committee assessment*				
Costs	£45,638	£29,628	£16,010	
LYs	7.66	6.77	0.88	£21,766
QALYs	4.13	3.40	0.74	
ASS2: *Investigator assessment*				
Costs	£46,775	£30,188	£16,588	
LYs	8.02	6.79	1.23	£18,973
QALYs	4.30	3.42	0.87	
QOL1: *Utility for PFS on second-line equal to progressed from first-line*				
Costs	£45,838	£29,625	£16,213	
LYs	7.67	6.66	1.01	£20,209
QALYs	4.13	3.32	0.80	
QOL2: *Utility for progressed from second-line equal to progressed from first-line*				
Costs	£45,838	£29,625	£16,213	
LYs	7.67	6.66	1.01	£26,241
QALYs	4.73	4.11	0.62	
RES1: *Subcutaneous administration of bortezomib*				
Costs	£44,574	£29,625	£14,949	
LYs	7.67	6.66	1.01	£18,775
QALYs	4.15	3.35	0.80	

Key: ICER, incremental cost-effectiveness ratio; LY, life year; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisolone.

Table 72: Results of secondary scenario analyses

	VR-CAP	R-CHOP	Difference	ICER
Base case analysis				
Costs	£45,838	£29,625	£16,213	
LYs	7.67	6.66	1.01	£20,362
QALYs	4.15	3.35	0.80	
MOD5: *No second-line treatment*				
Costs	£38,191	£19,563	£18,629	
LYs	7.67	6.66	1.01	£29,858
QALYs	4.71	4.09	0.62	
MOD6: *Start second-line treatment upon progression from first-line treatment*				
Costs	£46,342	£29,995	£16,347	£20,811

	VR-CAP	R-CHOP	Difference	ICER
LYs	7.67	6.66	1.01	
QALYs	4.11	3.32	0.79	
MOD7: *Equal cost of second-line treatment across arms*				
Costs	£45,977	£29,625	£16,352	
LYs	7.67	6.66	1.01	£20,537
QALYs	4.15	3.35	0.80	
MOD8: *HMRN data for distribution of second-line treatments*				
Costs	£42,220	£25,209	£17,011	
LYs	7.67	6.66	1.01	£21,365
QALYs	4.15	3.35	0.80	
MOD9: *Duration of treatment and PFS from second-line treatment by trial arm*				
Costs	£45,838	£29,624	£16,214	
LYs	7.67	6.66	1.01	£20,508
QALYs	4.14	3.35	0.79	
MOR1: *No general population mortality*				
Costs	£46,109	£29,993	£16,116	
LYs	8.60	7.04	1.56	£15,028
QALYs	4.60	3.53	1.07	
EFF4: *PFS Weibull*				
Costs	£47,183	£30,127	£17,056	
LYs	7.36	6.51	0.85	£25,849
QALYs	3.90	3.24	0.66	
EFF5: *PFS Lognormal*				
Costs	£45,295	£29,373	£15,922	
LYs	7.77	6.72	1.05	£19,002
QALYs	4.24	3.40	0.84	
EFF6: *PFS Gamma*				
Costs	£47,193	£29,999	£17,194	
LYs	7.36	6.56	0.79	£27,697
QALYs	3.89	3.27	0.62	
EFF7: *PFS Gompertz*				
Costs	£47,236	£29,657	£17,579	
LYs	7.35	6.59	0.76	£30,452
QALYs	3.88	3.31	0.58	
EFF8: *OS post-progression by trial arm*				
Costs	£45,856	£29,609	£16,247	
LYs	7.71	6.62	1.09	£19,686
QALYs	4.16	3.34	0.83	
EFF9: *OS Log-logistic*				
Costs	£46,151	£29,909	£16,241	
LYs	9.59	8.85	0.75	£22,663
QALYs	4.71	3.99	0.72	

	VR-CAP	R-CHOP	Difference	ICER
EFF10: *OS Lognormal*				
Costs	£46,406	£30,148	£16,258	£24,117
LYs	10.41	9.80	0.61	
QALYs	4.96	4.29	0.67	
EFF11: *OS Gamma*				
Costs	£45,731	£29,398	£16,333	£19,777
LYs	6.86	5.77	1.09	
QALYs	3.90	3.08	0.83	
EFF12: *OS Gompertz*				
Costs	£45,648	£29,519	£16,128	£20,235
LYs	7.28	6.27	1.01	
QALYs	4.03	3.23	0.80	
EFF13: *TFI Weibull*				
Costs	£45,816	£29,600	£16,216	£20,372
LYs	7.67	6.66	1.01	
QALYs	4.15	3.35	0.80	
EFF14: *TFI Log-logistic*				
Costs	£45,724	£29,503	£16,221	£20,387
LYs	7.67	6.66	1.01	
QALYs	4.15	3.36	0.80	
EFF15: *TFI Lognormal*				
Costs	£45,757	£29,502	£16,255	£20,498
LYs	7.67	6.66	1.01	
QALYs	4.15	3.36	0.79	
EFF16: *TFI Gamma*				
Costs	£45,821	£29,601	£16,219	£20,382
LYs	7.67	6.66	1.01	
QALYs	4.15	3.35	0.80	
EFF17: *TFI Gompertz*				
Costs	£45,839	£29,620	£16,219	£20,381
LYs	7.67	6.66	1.01	
QALYs	4.15	3.35	0.80	
EFF18: *Duration of adverse events by trial arm*				
Costs	£45,838	£29,625	£16,213	£20,331
LYs	7.67	6.66	1.01	
QALYs	4.15	3.35	0.80	
POP1: *Patients clinically ineligible for SCT only*				
Costs	£45,549	£29,091	£16,458	£20,489
LYs	7.68	6.62	1.06	
QALYs	4.14	3.34	0.80	
POP2: *ITT population demographics*				
Costs	£45,387	£29,133	£16,254	£18,123

	VR-CAP	R-CHOP	Difference	ICER
LYs	8.01	6.80	1.21	
QALYs	4.32	3.42	0.90	
POP3: *Start age 65 years*				
Costs	£45,939	£29,749	£16,190	
LYs	7.95	6.78	1.17	£18,433
QALYs	4.28	3.41	0.88	
POP4: *Start age 75 years*				
Costs	£45,561	£29,327	£16,234	
LYs	7.07	6.40	0.67	£26,010
QALYs	3.85	3.22	0.62	
POP5: *Weight 70 kg*				
Costs	£45,773	£29,559	£16,214	
LYs	7.67	6.66	1.01	£20,363
QALYs	4.15	3.35	0.80	
POP6: *Weight 85 kg*				
Costs	£45,840	£29,619	£16,221	
LYs	7.67	6.66	1.01	£20,372
QALYs	4.15	3.35	0.80	
POP7: *BSA 1.8 m^2*				
Costs	£45,328	£29,047	£16,281	
LYs	7.67	6.66	1.01	£20,448
QALYs	4.15	3.35	0.80	
POP8: *BSA 2.0 m^2*				
Costs	£46,283	£30,123	£16,160	
LYs	7.67	6.66	1.01	£20,296
QALYs	4.15	3.35	0.80	
QOL3: *Doorduijn utility values*				
Costs	£45,838	£29,625	£16,213	
LYs	7.67	6.66	1.01	£28,746
QALYs	3.51	2.94	0.56	
QOL4: *Utility decrement for progressing Soini*				
Costs	£45,838	£29,625	£16,213	
LYs	7.67	6.66	1.01	£20,083
QALYs	4.19	3.38	0.81	
QOL5: *Utility decrement for progressing Hayslip*				
Costs	£45,838	£29,625	£16,213	
LYs	7.67	6.66	1.01	£20,191
QALYs	4.17	3.37	0.80	
QOL6: *Utility decrement for progressing Deconinck*				
Costs	£45,838	£29,625	£16,213	
LYs	7.67	6.66	1.01	£20,506
QALYs	4.12	3.33	0.79	

	VR-CAP	R-CHOP	Difference	ICER
QOL7: *No utility decrements for AEs*				
Costs	£45,838	£29,625	£16,213	£20,340
LYs	7.67	6.66	1.01	
QALYs	4.15	3.35	0.80	
RES2: *G-CSF administered by district nurse*				
Costs	£46,215	£29,968	£16,247	£20,405
LYs	7.67	6.66	1.01	
QALYs	4.15	3.35	0.80	
RES3: *Medical resource use post-progression equal to pre-progression*				
Costs	£45,889	£29,690	£16,199	£20,345
LYs	7.67	6.66	1.01	
QALYs	4.15	3.35	0.80	
RES4: *No costs for AEs*				
Costs	£45,380	£29,126	£16,254	£20,414
LYs	7.67	6.66	1.01	
QALYs	4.15	3.35	0.80	

Key: AE, adverse event; BSA; body surface area; G-CSF, granulocyte colony stimulating factor; HMRN, haematological malignancy research network; ICER, incremental cost-effectiveness ratio; ITT, intension to treat; LY, life year; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; SCT, stem cell transplant; TFI, treatment-free interval; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

Exploratory comparisons

Results of the exploratory comparisons between VR-CAP and other comparators specified in the scope are presented in Table 65. As noted previously, R-CHOP is the established standard of care at this point of the treatment pathway in UK practice; however, in line with the scope, exploratory analyses are also presented versus R-FC and R-bendamustine. In NHS England and Wales, these interventions are typically reserved for patients too frail to receive either R-CHOP or VR-CAP.

As would be expected, the ICERs presented are similar to those presented versus R-CHOP, given the assumptions of equal efficacy that were made due to the lack of robust data for these comparators. The absence of difference in QALYs, at 2 decimal places, between these treatments reflects the marginal impact of AEs.

A full incremental analysis of VR-CAP versus all three comparators is presented in Table 74. R-bendamustine is dominated by R-FC, and R-FC is extendedly dominated by VR-CAP.

Analyses of incremental costs and outcomes for these comparators are presented in Appendix 25.

Table 73: Base case results, VR-CAP versus exploratory comparators

	Costs	Life Years	QALYs	Incremental			ICER
				Costs	Life Years	QALYs	
VR-CAP	£45,838	6.44	4.15				
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-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.

Table 74: Full incremental analysis for VR-CAP and all three 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.

Model outcomes using HRs from the Bucher indirect comparison for PFS and OS with the exploratory comparators are presented in Table 75. Using results from the indirect comparison leads to a much lower ICER for VR-CAP versus R-FC due to curtailed overall survival with R-FC relative to the base case. This results in an increase in incremental QALYs from 0.78 in the base case to 1.56 in this scenario analysis, resulting in an ICER of £10,384.

It is highlighted that the results of the indirect comparison versus R-bendamustine did not generate statistically significant results. However, using the point estimates for PFS and OS results in a higher ICER for VR-CAP versus R-bendamustine. The number of life years gained is lower than in the base case, due to the HR of 0.63 for OS. However, the HR for PFS was 1.04 resulting in patients surviving longer than in

the base case analysis. This leads to only 0.50 incremental QALYs and an ICER of £30,640.

Table 75: Base case results, VR-CAP versus exploratory comparators using HRs from Bucher indirect comparison

	Costs	Life Years	QALYs	Incremental			ICER
				Costs	Life Years	QALYs	
VR-CAP	£45,838	6.44	4.15				
R-FC	£29,616	4.01	2.58	£16,222	2.43	1.56	£10,384
R-bendamustine	£30,612	5.34	3.65	£15,226	1.10	0.50	£30,640

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.

Threshold analysis is presented in Table 76, exploring the HR for PFS and OS for each comparator versus R-CHOP required to make VR-CAP cost effective at a threshold of £20,000 and £30,000. For comparison, available RCTs report a HR of death for R-FC versus R-CHOP as 1.50 (95% CI 1.13, 1.99) and a HR of death for R-bendamustine versus R-CHOP as 1.28 (0.69, 2.39). See section 4.10 and Appendix 9 for further details. In all cases, the HR required is lower than the published HRs for treatments for frailer patients, indicating that VR-CAP is highly likely to be cost effective versus these treatments as well as R-CHOP.

Table 76: Threshold analysis for exploratory comparators vs R-CHOP

First-line treatment	HR for ICER of £20,000	HR for ICER of £30,000
R-FC	0.95	0.79
R-bendamustine	0.83	0.73

Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; R-bendamustine, rituximab with bendamustine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; R-FC, rituximab with fludarabine and cyclophosphamide.

Rituximab maintenance

In the first scenario analysis testing the potential impact of including R-maintenance, a HR of 0.55 was applied to PFS, while no effect on OS was assumed. In the second scenario analysis, HRs of 0.40 and 0.39 were applied to PFS and OS, respectively. Model outcomes for these scenario analyses are presented in Table 77. In both scenario analyses, the ICER is higher than in the base case analysis. This is due to

the high cost of R-maintenance, which results in a large increase in costs in both model arms; £45,838 in the base case versus £58,781 with R-maintenance for VR-CAP and £29,625 versus £39,870 with the respective analyses for the R-CHOP arm. Conversely, effectiveness is less impacted by R-maintenance; QALYs in the VR-CAP arm are 4.15 in the base case versus 4.57 with R-maintenance included and 3.35 versus 3.73 for the respective analyses in the R-CHOP arm. Because there is a higher proportion of responding patients, and patients live progression-free for longer in the VR-CAP arm, this model arm experiences slightly more impact from the negative results of R-maintenance on cost effectiveness than the R-CHOP arm.

Table 77: Results of scenario analyses including R-maintenance

Scenario	Induction therapy	Costs	Life Years	QALYs	Incremental			ICER
					Costs	Life Years	QALYs	
HR: PFS: 0.55; OS: 1	VR-CAP	£58,781	6.86	4.57				
	R-CHOP	£39,870	6.07	3.73	£18,911	0.79	0.84	£22,518
HR PFS: 0.40; OS: 0.39	VR-CAP	£59,641	7.30	4.87				
	R-CHOP	£41,031	6.58	4.06	£18,610	0.72	0.81	£23,040

Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years; R, rituximab; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

The three threshold analyses that were performed for R-maintenance exploring what HR would be required for PFS, OS or both to make VR-CAP cost effective at a threshold of £20,000 and £30,000 are reported in Table 78. In the first and third threshold analysis, the ICER does not reduce below £20,000 at any HR. However, the HRs required to increase the ICER beyond £30,000 are greater than one, indicating that, as R-maintenance is highly unlikely to result in adverse efficacy outcomes, VR-CAP is highly likely to be cost effective if R-maintenance is given to patients after induction treatment.

In the threshold analysis of OS the ICER does not reach an ICER of £30,000 with any HR chosen. This means that if the HR for PFS is fixed at 0.55, VR-CAP will always be cost-effective versus R-CHOP at a £30,000 WTP threshold. In this analysis the ICER becomes lower with higher HR; the HR has to be as high as 3.20

to reach an ICER of £20,000. These results indicate that the efficacy of R-maintenance has little effect on the cost-effectiveness of VR-CAP.

Table 78: Threshold analysis for R-maintenance

Threshold analysis	HR for ICER of £20,000	HR for ICER of £30,000
PFS (HR OS fixed at 1)	ICER > £20,000 for all HRs	1.79
OS (HR PFS fixed at 0.55)	3.20	ICER < £30,000 for all HRs
Equal HR PFS and OS	ICER > £20,000 for all HRs	2.07
Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS; overall survival; PFS; progression-free survival; R, rituximab.		

Summary of sensitivity analyses results

Probabilistic analysis indicates that VR-CAP is highly likely to be a cost-effective treatment option versus R-CHOP at a willingness to pay threshold of £30,000 per QALY (86.5%).

Key uncertainties within the model results are the assumptions made regarding PFS and OS curve fits. However, using a different curve fit has only a moderate impact on the outcomes of the model. The model is also sensitive to assumptions regarding the utility for patients who have progressed from second-line treatment. This was not measured in the trial, and no data specific to MCL patients were identified in the literature; therefore, reasonable assumptions were made using the best available data from a study of aggressive NHL.

In all clinically plausible scenario analyses, the ICER remains below £30,000. Shorter time horizons give a higher ICER because benefits from VR-CAP are mainly accrued in the long term through improved survival. Nonetheless, VR-CAP remains cost effective at a time horizon of 10 years. Using the exponential curve fit for PFS results in a significant increase of the ICER, but the exponential curve may not reflect the clinical expectation of slightly longer PFS than observed in the LYM-3002 trial. Using the IRC assessment of PFS resulted in an increase of the ICER by approximately £1,500, whilst using the investigator assessment reduced the ICER by a similar degree. The model is insensitive to the utility assumptions for PFS on second-line treatment, but it is sensitive to the assumption regarding utility for post-progression from second-line treatment because of the average time spent in these health states, which is short pre-progression and long post-progression from second-

line treatment. However, even in the extreme scenario presented, which assumes no impact on utility despite a second relapse and potentially no further treatment, the ICER is only £26,241.

Results of the exploratory economic comparisons between VR-CAP and other comparators specified in the scope produced similar ICERs to those presented versus R-CHOP, given the assumptions of equal efficacy that were made due to the lack of robust data for these comparators. Threshold analysis indicated that, in all cases, for VR-CAP to be cost effective, the HR required for the exploratory comparators versus R-CHOP was lower than the published HRs for treatments for frailer patients, indicating that VR-CAP is highly likely to be cost effective versus these treatments as well as R-CHOP. Due to the short treatment duration and the long time horizon of the model, the better tolerability and, thus, the lower adverse events rates associated with the exploratory comparators are not drivers of the cost-effectiveness case.

Results of the exploratory analyses including R-maintenance after completion of induction therapy produced slightly higher ICERs than the base case ICER, but the uncertainty of the available data informing this analysis are noted. Threshold analysis confirmed that VR-CAP remains cost effective under clinically plausible assumptions around the efficacy of R-maintenance. Whilst R-maintenance was not included as a comparator in this decision problem, the exploratory analysis confirms the cost effectiveness of VR-CAP compared to R-CHOP in clinical practice where a maintenance regimen may follow the induction treatments under assessment in this appraisal.

5.9 Subgroup analysis

No subgroup analyses were explored as no subgroups were identified where the effectiveness of VR-CAP was significantly different from the ITT analysis. No subgroups of interest were listed in the scope.

5.10 Validation

Validation of *de novo* cost-effectiveness analysis

The model was quality-assured by the internal processes of the economists who produced the economic model. In these processes, an economist not involved in the model adaptation reviewed the model for coding errors, inconsistencies and the plausibility of inputs. The model was also put through an internal and external checklist of known modelling errors, and the assumptions were questioned.[151]

Further to this, the conceptual model and key assumptions were validated at an advisory board with practising UK haematologists and two UK health economic experts.[6] These individuals were selected as leading experts in health economic practice and methodology development in the UK: one of whom is a regular member of a NICE ERG, and the other is a regular SMC reviewer. The model was presented to the health economists during the advisory board. The shared content comprised the clinical trial data package, the model structure, the assumptions regarding the treatment pathway, the survival analysis undertaken, the preliminary EQ-5D analysis undertaken and the methodology used for costs and resource use. The opinions provided by these external health economists were used to determine the model base case in terms of survival analysis and utilities.

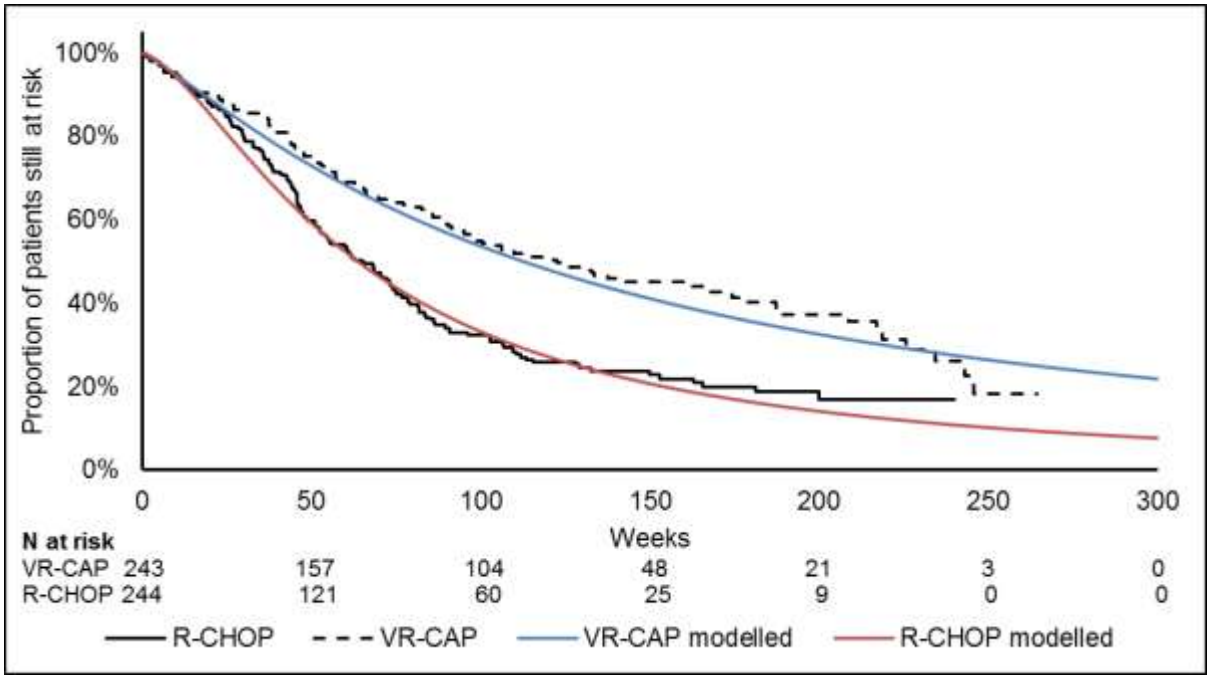
Clinical validity

Pham et al. (2003) demonstrated that bortezomib inhibits MCL tumour cell growth through two control mechanisms: cell cycle arrest and induction of cell death.[152] In the pivotal Phase III regulatory trial, LYM-3002, patients with MCL who were treated with VR-CAP demonstrated a prolonged response to initial therapy compared to patients treated with the current standard of care (R-CHOP). This translated into an improved PFS (primary endpoint).

Long-term trial projections compared well to the available Kaplan–Meier data (Figure 33 and Figure 34). In all cases, the modelled median lay within the confidence interval for the median presented from the trial (Table 66). Model projections for OS compared to the general population are shown in Figure 35; as expected, survival was lower for both arms of the model than in the general population.

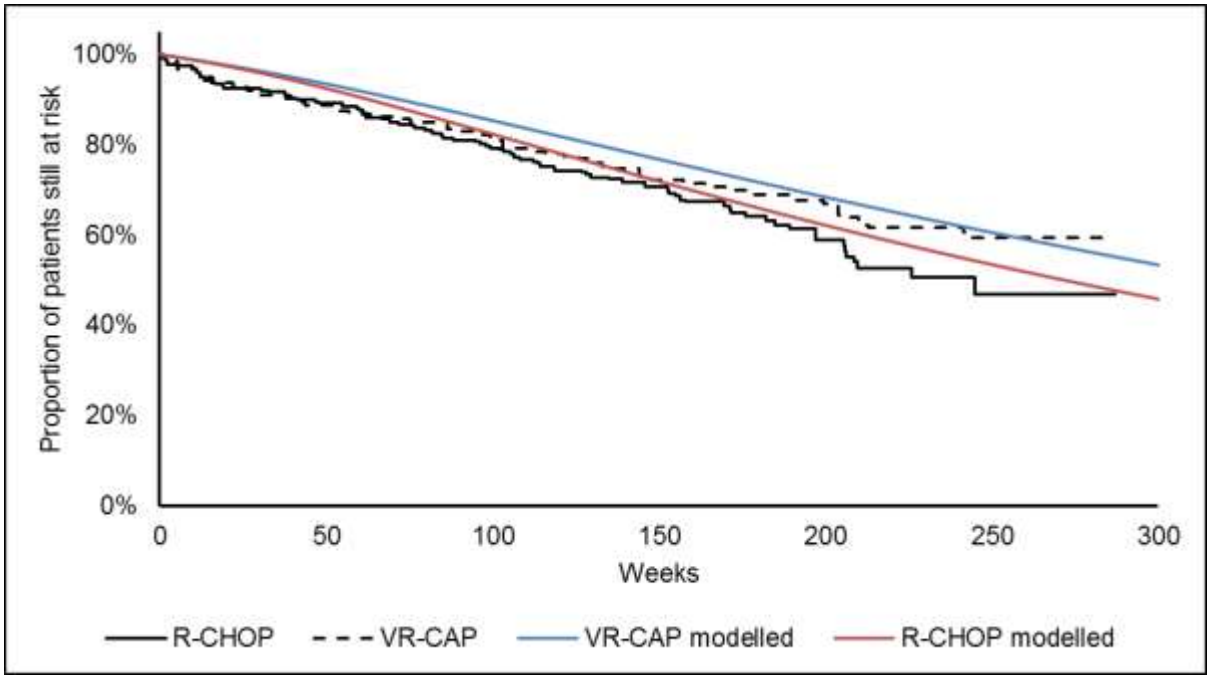
Utility values measured in the LYM-3002 trial that are used in the model base case (0.764 for PFS) are lower than the values of the UK general population of the same age (0.78 for persons aged 65-74).[153] This indicates that utility values are valid for the population in which they were measured.

Figure 33: Model PFS projections



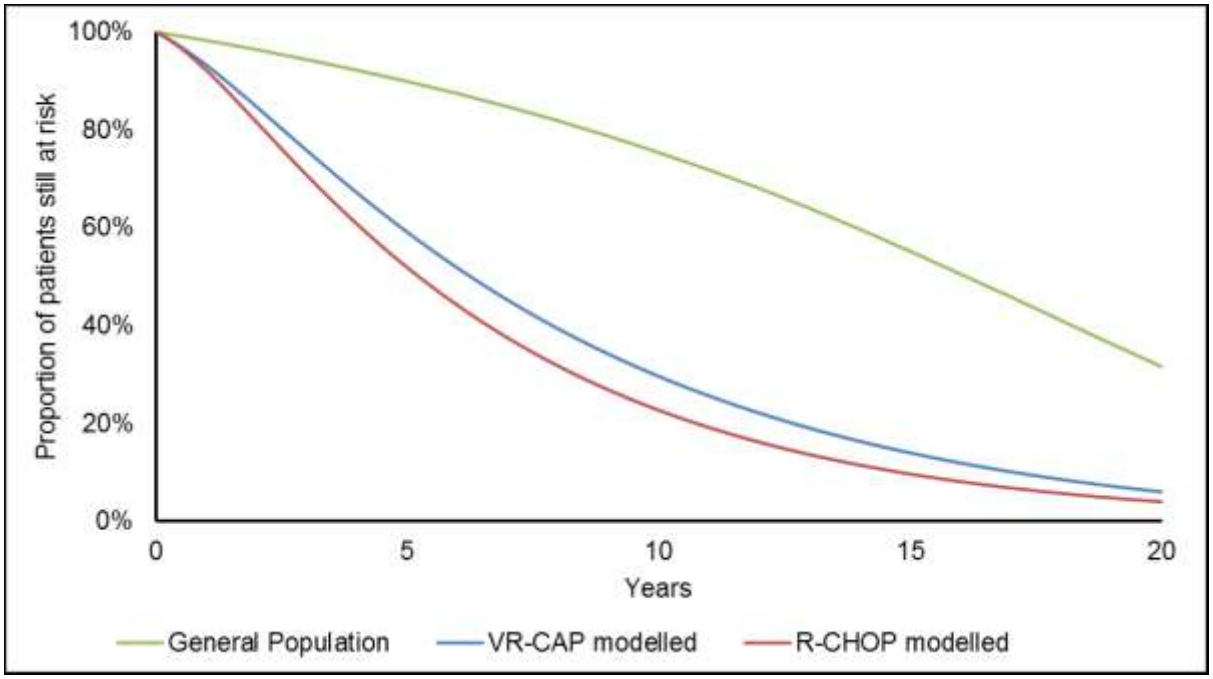
Key: N, number; PFS, progression-free survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

Figure 34: Model overall survival projections



Key: R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

Figure 35: Model estimates of OS by arm versus UK general population



Key: OS, overall survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

Generalisability

As is often the case in clinical trials, the mean age of participants in the ITT population was towards the younger end of the scale, with most patients presenting in clinical practice aged 65–75 in the UK (mean 70.6 in the HMRN database, median 71 in the Abrahamsson Swedish database, and median 68 in the US SEER database).[79, 154, 155] In light of this difference between the ITT population and UK practice demographic data for the cost-effectiveness analysis were taken from the Western Europe and North America subgroup of the LYM-3002 trial (median age 69) to better reflect a UK MCL population.

Thirty percent of patients enrolled in the clinical trial came from the European Union or North America. Whilst this could be perceived to limit the generalisability of some trial results, as treatment patterns may differ in other countries, key efficacy results showed consistency both in the size of benefit with VR-CAP and the absolute PFS for R-CHOP. It is therefore unlikely that the geographic spread of countries included in the trial had any relevant impact upon the results.

A pre-planned subgroup analysis for the LYM-3002 trial of the 91 subjects (49 in the R-CHOP group and 42 in the VR-CAP group) from Western Europe, the United States or Canada showed a higher median age at diagnosis (69 years), more subjects with an IPI score of 3, and more patients with Stage IV disease at diagnosis (see Table 31 in section 5.2). Similar observations of consistent HRs for the total US/Canada/Western European subgroup and the Western European subgroup were made for PFS by both IRC and investigator assessment; no significant difference was detected between patients from Western European or North American countries and patients from other countries in terms of OS and PFS.

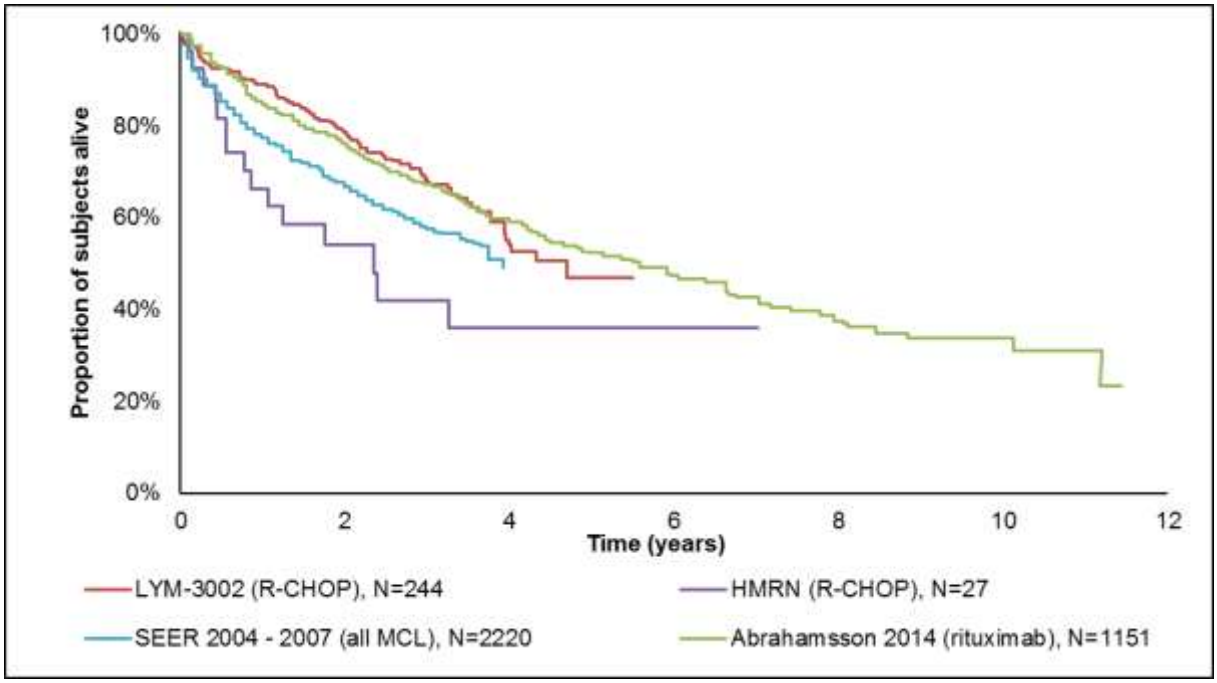
The median PFS and OS observed in the R-CHOP arm of the LYM-3002 trial were generally shorter than those observed in other clinical trials including R-CHOP but were in line with what was expected in a UK population (median 4-5 years).[7] It is important to note that PFS assessment in previous trials of MCL was less frequent than in LYM-3002 (approximately 6 monthly vs 6-8 weekly) and not undertaken by blinded assessors. Comparing the investigator assessments of LYM-3002 and other trials suggests a PFS more consistent with other studies.[49, 50] In general, the LYM-3002 trial data lay close to real-world data for trials where similar treatments and a

similar population were used, which indicated that the outcomes in the study were generalisable to the broader population (Figure 36).

In comparison to available observational datasets (SEER, Abrahamsson, HMRN), the survival in the LYM-3002 trial closely followed that seen by Abrahamsson but was greater than that of SEER and HMRN.[79, 154, 155] Abrahamsson was a recent publication (2014) that showed the OS of a European population (Swedish) and used a similar treatment to the LYM-3002 trial (rituximab based chemotherapy). In contrast, data from SEER were much older than data from the LYM-3002 trial (2004-2007); the study was conducted in the US and showed all MCL treatment (i.e. was likely to include treatments that were less efficacious than R-CHOP). Data from HMRN were from patients diagnosed between 2004 and 2012 and thus include older as well as more recent data. Furthermore, 46.8% of patients in this dataset were treated first-line with either FC or R-FC, indicating that this dataset does not reflect current UK practice. OS for responders is closer to the LYM-3002 R-CHOP OS suggesting that the OS for all patients in the HMRN database may be influenced by a low response to first-line therapy (58% response rate to first-line therapy in the HMRN database versus 89.5% overall response rate to R-CHOP in the LYM-3002 trial).

PFS in the HMRN dataset was longer than in the LYM-3002 trial. This is due to two key differences in measurement of PFS. In the HMRN data, PFS is measured in responding patients only, from the date of response, while in the LYM-3002 trial, non-responding patients are also included in the analysis with PFS measured from date of randomisation. Additionally, in the LYM-3002 trial, patients were frequently assessed for signs of progression, whereas patients that are not participating in a clinical trial typically have less frequent check-ups.

Figure 36: Comparison of R-CHOP survival in the LYM-3002 trial to available observational datasets



Key: HRMN, Haematological Malignancy Research Network; MCL, mantle cell lymphoma; R-CHOP with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone.

5.11 Interpretation and conclusions of economic evidence

The economic analysis presented here demonstrates the cost effectiveness of VR-CAP for patients with previously untreated MCL for whom HSCT is unsuitable from the perspective of NHS England and Wales. It is supported by RCT data from a large regulatory quality trial, and key model inputs and assumptions were validated by UK clinicians and economists. The availability of VR-CAP as a first-line treatment offers a 59% improvement in PFS relative to R-CHOP, as demonstrated in the LYM-3002 trial. These benefits were modelled to translate to substantial and meaningful improvements in survival. In the absence of licensed treatment options and a current standard of care for previously untreated MCL, and the limited OS benefit for R-CHOP and other comparators, the introduction of the clinically effective and cost-effective VR-CAP regimen offers an important treatment option for this orphan disease.

Key uncertainties of the model were the assumptions made regarding PFS and OS curve fits. However, the use of different curve fits had only a moderate impact on the outcomes of the model. The model was also sensitive to assumptions regarding the

utility for patients who progressed from second-line treatment. This was not measured in the trial, and no data specific to MCL patients were identified in the literature. Therefore, reasonable assumptions were made using the best available data from studies of aggressive NHL. Despite the fact that higher adverse event rates were reported for VR-CAP compared to R-CHOP, assumptions around AE rates had only a minimal impact on the ICER reflecting that, whilst important to patients and clinicians in the short term, this adverse impact is outweighed by the long term benefit of a more effective treatment.

This analysis indicated that VR-CAP is a cost-effective treatment option for patients with MCL who have not received previous treatment and for whom HSCT is not an option, with a base case ICER of £20,362. The sensitivity analyses performed showed that there was only minor uncertainty around the base case results and that VR-CAP was still cost effective even when assumptions were varied to the extreme.

As discussed in section 3.2, practicing haematologists confirmed that, in NHS England and Wales, R-CHOP is the preferred therapy option for patients with previously untreated MCL for whom HSCT is unsuitable, with the majority of patients receiving R-CHOP in the front-line setting. Only patients not deemed fit enough to receive CHOP-like therapies such as R-CHOP and VR-CAP would receive alternative rituximab-chemotherapy regimens first line in England and Wales. R-CHOP is therefore seen as the established standard of care at this place in the treatment pathway in UK clinical practice.

To fulfil the NICE scope requirements, additional exploratory comparison was presented with R-FC and R-bendamustine and for the inclusion of R-maintenance. These comparisons should be viewed as purely exploratory because, in addition to R-FC and R-bendamustine not being used in the same placement in the treatment pathway as VR-CAP, no robust comparison could be made with the available clinical trial data for these two comparators as well as for the inclusion of subsequent R-maintenance post induction therapy, as discussed in section 4.10. Therefore, assumptions of equal effectiveness to R-CHOP were required for these treatments; assumptions which were likely to underestimate the benefits of VR-CAP compared to these therapies given that each of these therapies is reserved for frailer patients.

As is the case for the clinical evidence for R-FC and R-bendamustine, the cost-effectiveness results including R-maintenance are limited by the lack of inclusion of R-maintenance in the LYM-3002 trial. At the time the trial was initiated, R-maintenance therapy was not commonly adopted. Unfortunately, there are no trials exploring the effect of R-maintenance versus no maintenance in an MCL population; therefore, exploratory analyses were performed with the limited data available. UK haematologists believe R-maintenance therapy results in similar benefit post any CHOP-like induction regimen and would expect to be able to give R-maintenance after VR-CAP induction with a similar extension to median survival times, as observed with R-maintenance after R-CHOP induction. It is also noted that the decision problem does not include R-maintenance and the focus of the decision is the clinical and cost effectiveness of the induction regimens used in previously untreated MCL. Notwithstanding that this analysis exceeds the NICE scope of this appraisal, including R-maintenance in the model using the limited data that are available did not lead to major differences in cost-effectiveness outcomes.

Previously untreated MCL is an orphan disease, with an estimated incidence of 0.9 per 100,000[53] and fewer than 250 patients are expected to be eligible for treatment with VR-CAP. Thus, given the rare nature of MCL, the base case ICER of £20,362 and the relative insensitivity of the ICER to modelling assumptions, VR-CAP has been demonstrated to be a cost-effective use of NHS resources.

6 Assessment of factors relevant to the NHS and other parties

VR-CAP is licensed for the treatment of adult patients with previously untreated MCL who are unsuitable for HSCT..

An incidence of MCL of 0.9 per 100,000 was recently reported by HMRN.[53] In this analysis it was assumed that the incidence of MCL remains constant for the time horizon of the budget impact model. Of these incident patients, 67% were expected to be ineligible for HSCT.[6] Of this subpopulation, 67% were expected to be eligible for treatment with R-CHOP.[6]

All costs for the first year as specified in section 5.5, were combined to give the total cost per patient. Unit costs were sourced from eMIT and Monthly Index of Medical Specialities (MIMS) online and from NHS Reference Costs 2013-2014, and are also described in more detail in section 5.5.[130, 145] Cost per patient per year was calculated by setting the time horizon of the cost-effectiveness model to 1 year and using cost-outcomes. This means that average patient weight and dose adjustments are taken into account as per the cost-effectiveness analysis. This results in a cost per patient of £15,355 for R-CHOP and £33,329 for VR-CAP. For simplicity, no attempt has been made to estimate the impact of loss of exclusivity of bortezomib in 2019 on future drug acquisition costs.

Estimates of current market share are presented in Table 79. As patients for whom R-CHOP is unsuitable would not be expected to receive other alternatives in the first-line setting, R-CHOP is assumed to be used in 100% of patients currently. The future market share of VR-CAP, amongst patients suitable for CHOP-like therapy, was estimated according to Janssen internal assumptions as 25% in year 1, 50% in year 2 and 75% in years 3 to 5.

Table 80 presents the total and net budget impact of VR-CAP in patients with previously untreated MCL for whom HSCT is unsuitable. In year 1, the budget impact in NHS England was estimated to be less than £1 million, rising to just over £3 million from year 3 which is driven by increased uptake. The estimates for NHS Wales are presented in Table 81.

It is possible that the assumptions in this analysis overestimate the expected budget impact of VR-CAP:

- The impact of a longer time to second-line treatment has not been included. For simplicity, treatment costs are restricted to induction therapies only.
- If the distribution of current treatments is different to the assumption in Table 79, the inclusion of higher cost regimens would reduce the net budget impact of VR-CAP.
- As in the cost effectiveness analysis, the cost of subcutaneous administration of bortezomib in the VR-CAP regimen is expected to be lower than the IV costs included in this analysis.

Table 79: Current market share in the population eligible for VR-CAP

	Market shares
R-CHOP	100%
R-FC	0%
R-bendamustine	0%
Key: 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 prednisone.	

Table 80: Budget impact of VR-CAP in NHS England

	2015	2016	2017	2018	2019
Total number of patients eligible for VR-CAP	215	215	215	215	215
Patients expected to receive VR-CAP	54	108	162	162	162
Costs without VR-CAP					
Total cost of current treatments (R-CHOP)	£3,301,370	£3,301,370	£3,301,370	£3,301,370	£3,301,370
Costs with VR-CAP					
Cost of VR-CAP	£1,799,750	£3,599,500	£5,399,250	£5,399,250	£5,399,250
Cost of other treatments (R-CHOP)	£2,472,114	£1,642,958	£813,802	£813,802	£813,802
Total cost of future treatments	£4,271,864	£5,242,458	£6,213,051	£6,213,051	£6,213,051
Net budget impact	**£970,594**	**£1,941,187**	**£2,911,781**	**£2,911,781**	**£2,911,781**

Key: R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

Table 81: Budget impact of VR-CAP in NHS Wales

	2015	2016	2017	2018	2019
Total number of patients eligible for VR-CAP	12	12	12	12	12
Patients expected to receive VR-CAP	4	7	10	10	10
Costs without VR-CAP					
Total cost of current treatments (R-CHOP)	£184,257	£184,257	£184,257	£184,257	£184,257
Costs with VR-CAP					
Cost of VR-CAP	£133,315	£233,301	£333,287	£333,287	£333,287
Cost of other treatments (R-CHOP)	£122,838	£76,774	£30,709	£30,709	£30,709
Total cost of future treatments	£256,153	£310,075	£363,997	£363,997	£363,997
Net budget impact	**£71,896**	**£125,818**	**£179,740**	**£179,740**	**£179,740**

Key: R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone.

7 References

1. Janssen-Cilag International NV. Velcade 3.5 mg powder for solution for injection. Summary of Product Characteristics (SPC). May 2015. Available at: http://www.medicines.org.uk/EMC/medicine/17109/SPC/Velcade+3.5mg+powder+for+solution+for+injection/ Accessed: 26 May 2015.

2. Holkova B and Grant S. Proteasome inhibitors in mantle cell lymphoma. *Best practice & research Clinical haematology*. 2012; 25(2):133-41.

3. National Institute for Health and Care Excellence (NICE). TA129: Bortezomib monotherapy for relapsed multiple myeloma. 2007. Available at: https://www.nice.org.uk/guidance/ta129 Accessed: 9 April 2015.

4. National Institute for Health and Care Excellence (NICE). TA228: Bortezomib and thalidomide for the first-line treatment of multiple myeloma. 2011. Available at: https://www.nice.org.uk/guidance/ta228 Accessed: 9 April 2015.

5. National Institute for Health and Care Excellence (NICE). TA311: Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation. 2014. Available at: https://www.nice.org.uk/guidance/ta311 Accessed: 9 April 2015.

6. Janssen-Cilag Ltd. Velcade MCL HTA Advisory Board Summary 2014.

7. McKay P, Leach M, Jackson R, et al. Guidelines for the investigation and management of mantle cell lymphoma. *Br J Haematol*. 2012; 159(4):405-26.

8. Cancer Research UK. Worldwide cancer incidence statistics. 2014. Available at: http://www.cancerresearchuk.org/cancer-info/cancerstats/world/incidence/#Common Accessed: 15 January 2015.

9. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010; 127(12):2893-917.

10. The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. *Blood*. 1997; 89(11):3909-18.

11. Argatoff LH, Connors JM, Klasa RJ, et al. Mantle cell lymphoma: a clinicopathologic study of 80 cases. *Blood*. 1997; 89(6):2067-78.

12. Zhou Y, Wang H, Fang W, et al. Incidence trends of mantle cell lymphoma in the United States between 1992 and 2004. *Cancer*. 2008; 113(4):791-8.

13. Akiyama N, Tsuruta H, Sasaki H, et al. Messenger RNA levels of five genes located at chromosome 11q13 in B-cell tumors with chromosome translocation t(11;14)(q13;q32). *Cancer Res*. 1994; 54(2):377-9.

14. Campo E, Raffeld M and Jaffe ES. Mantle-cell lymphoma. *Semin Hematol*. 1999; 36(2):115-27.

15. Jares P, Colomer D and Campo E. Genetic and molecular pathogenesis of mantle cell lymphoma: perspectives for new targeted therapeutics. *Nat Rev Cancer*. 2007; 7(10):750-62.

16. Caballero D, Campo E, Lopez-Guillermo A, et al. Clinical practice guidelines for diagnosis, treatment, and follow-up of patients with mantle cell lymphoma. Recommendations from the GEL/TAMO Spanish Cooperative Group. *Annals of hematology*. 2013; 92(9):1151-79.

17. Cortelazzo S, Ponzoni M, Ferreri AJ, et al. Mantle cell lymphoma. *Crit Rev Oncol Hematol*. 2012; 82(1):78-101.

18. National Institute for Health Research (NIHR). Bortezomib (Velcade) for newly diagnosed mantle cell lymphoma – first line. 2012. Available at: http://www.hsc.nihr.ac.uk/topics/bortezomib-velcade-for-newly-diagnosed-mantle-cell/ Accessed: 2 April 2015.

19. Lenz G, Dreyling M and Hiddemann W. Mantle cell lymphoma: established therapeutic options and future directions. *Annals of hematology*. 2004; 83(2):71-7.

20. Leukemia & Lymphoma Society. Mantle cell lymphoma facts. 2014. Available at: http://www.lls.org/content/nationalcontent/resourcecenter/freeeducationmaterials/lymphoma/pdf/mantlecelllymphoma.pdf Accessed: 5 December 2014.

21. Amin A, Taylor R, Alonso A, et al. Progression-free survival as a surrogate endpoint for overall survival in relapsed-refractory mantle cell lymphoma. 19th European Hematology Association Congress. Milan, Italy. 12-15 June 2014. Abstract P456.

22. Shah BD, Martin P and Sotomayor EM. Mantle cell lymphoma: a clinically heterogeneous disease in need of tailored approaches. *Cancer control : journal of the Moffitt Cancer Center*. 2012; 19(3):227-35.

23. Smedby KE and Hjalgrim H. Epidemiology and etiology of mantle cell lymphoma and other non-Hodgkin lymphoma subtypes. *Semin Cancer Biol*. 2011; 21(5):293-8.

24. Abrahamsson A, Dahle N and Jerkeman M. Marked improvement of overall survival in mantle cell lymphoma: a population based study from the Swedish Lymphoma Registry. *Leukemia & lymphoma*. 2011; 52(10):1929-35.

25. Ambinder AJ, Shenoy PJ, Nastoupil LJ, et al. Using primary site as a predictor of survival in mantle cell lymphoma. *Cancer*. 2013; 119(8):1570-7.

26. Aschebrook-Kilfoy B, Caces DB, Ollberding NJ, et al. An upward trend in the age-specific incidence patterns for mantle cell lymphoma in the USA. *Leukemia & lymphoma*. 2013; 54(8):1677-83.

27. Leux C, Maynadie M, Troussard X, et al. Mantle cell lymphoma epidemiology: a population-based study in France. *Annals of hematology*. 2014; 93(8):1327-33.

28. Sant M, Allemani C, Tereanu C, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. *Blood*. 2010; 116(19):3724-34.

29. Smith A, Howell D, Patmore R, et al. Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network. *Br J Cancer*. 2011; 105(11):1684-92.

30. Lymphoma Association. Mantle cell lymphoma. 2014. Available at: http://www.nhs.uk/ipgmedia/National/Lymphoma%20Association/assets/Mantlecellllymphoma.pdf Accessed: 5 December 2014.

31. Eve HE, Furtado M, Hamon MD, et al. Time to treatment does not influence overall survival in newly diagnosed mantle-cell lymphoma. *Journal of Clinical Oncology*. 2009; 27(32):e189-e90.

32. Nygren L, Baumgartner Wennerholm S, Klimkowska M, et al. Prognostic role of SOX11 in a population-based cohort of mantle cell lymphoma. *Blood*. 2012; 119(18):4215-23.

33. Sarkozy C, Terre C, Jardin F, et al. Complex karyotype in mantle cell lymphoma is a strong prognostic factor for the time to treatment and overall survival, independent of the MCL international prognostic index. *Genes Chromosomes Cancer*. 2014; 53(1):106-16.

34. Dreyling M, Geisler C, Hermine O, et al. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2014; 25 Suppl 3(Supplement 3):iii83-92.

35. Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. *Blood*. 2008; 111(2):558-65.

36. Klapper W, Hoster E, Determann O, et al. Ki-67 as a prognostic marker in mantle cell lymphoma-consensus guidelines of the pathology panel of the European MCL Network. *Journal of hematopathology*. 2009; 2(2):103-11.

37. Tiemann M, Schrader C, Klapper W, et al. Histopathology, cell proliferation indices and clinical outcome in 304 patients with mantle cell lymphoma (MCL): a clinicopathological study from the European MCL Network. *Br J Haematol*. 2005; 131(1):29-38.

38. Campo E and Rule S. Mantle cell lymphoma: evolving management strategies. *Blood*. 2015; 125(1):48-55.

39. Dreyling M, Kluin-Nelemans HC, Bea S, et al. Update on the molecular pathogenesis and clinical treatment of mantle cell lymphoma: report of the 11th annual conference of the European Mantle Cell Lymphoma Network. *Leukemia & lymphoma*. 2013; 54(4):699-707.

40. Dreyling M, Thieblemont C, Gallamini A, et al. ESMO Consensus conferences: guidelines on malignant lymphoma. part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2013; 24(4):857-77.

41. Kluin-Nelemans HC, Hoster E, Hermine O, et al. Treatment of older patients with mantle-cell lymphoma. *N Engl J Med*. 2012; 367(6):520-31.

42. NHS England. National Cancer Drugs Fund list V4.2. 2015. Available at: http://www.england.nhs.uk/wp-content/uploads/2015/05/ncdf-list-may15-upd.pdf Accessed: 02 June 2015.

43. National Institute for Health and Care Excellence (NICE). Bortezomib for previously untreated mantle cell lymphoma: Response to consultee and

commentator comments on the draft remit and draft scope (pre-referral). 2015. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-tag495/documents Accessed: 7 May 2015.

44. Geisler CH, Kolstad A, Laurell A, et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. *Blood*. 2008; 112(7):2687-93.

45. Romaguera JE, Fayad LE, Feng L, et al. Ten-year follow-up after intense chemoimmunotherapy with rituximab-HyperCVAD alternating with rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. *Br J Haematol*. 2010; 150:200-8.

46. Witzig TE. Current treatment approaches for mantle-cell lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2005; 23(26):6409-14.

47. Herrmann A, Hoster E, Zwingers T, et al. Improvement of overall survival in advanced stage mantle cell lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2009; 27(4):511-8.

48. Hoster E, Unterhalt M, Wormann B, et al. The addition of rituximab to first-line chemotherapy (R-CHOP) results in superior response rates, time to treatment failure and response duration in patients with advanced stage mantle cell lymphoma: Long term results of a randomized GLSG trial [Abstract no. 3049]. *Blood*. 2008; 112:1048.

49. Howard OM, Gribben JG, Neuberg DS, et al. Rituximab and CHOP induction therapy for newly diagnosed mantle-cell lymphoma: molecular complete responses are not predictive of progression-free survival. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2002; 20(5):1288-94.

50. Lenz G, Dreyling M, Hoster E, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantiy improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: Results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). *Journal of Clinical Oncology*. 2005; 23(9):1984-92.

51. Moller MB, Pedersen NT and Christensen BE. Mantle cell lymphoma: prognostic capacity of the Follicular Lymphoma International Prognostic Index. *Br J Haematol*. 2006; 133(1):43-9.

52. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013; 381(9873):1203-10.

53. Haematological Malignancy Research Network (HMRN). Statistics: Incidence. 2015. Available at: https://www.hmrn.org/statistics/incidence Accessed: 27 February 2015.

54. Office for National Statistics. Population estimates for UK, England and Wales, Scotland and Northern Ireland, Mid-2013. 2014. Available at:

http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/2013/index.html Accessed: 7 May 2015.

55. National Institute for Health and Care Excellence (NICE). NICE Pathways: Blood and bone marrow cancers. 2015. Available at: http://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers Accessed: 2 April 2015.

56. National Institute for Health and Care Excellence (NICE). NICE Guidelines: Improving outcomes in haemato-oncology cancer. 2003. Available at: http://www.nice.org.uk/guidance/csgho Accessed: 2 April 2015.

57. National Institute for Health and Care Excellence (NICE). Lymphoma (mantle cell) - bendamustine (1st line, with rituximab) [ID609]. 2012. Available at: http://www.nice.org.uk/guidance/indevelopment/gid-tag321 Accessed: 2 April 2015.

58. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med*. 2009; 6(7):e1000097.

59. Robak T, Huang H, Jin J, et al. Bortezomib-based therapy for newly diagnosed mantle-cell lymphoma. *N Engl J Med*. 2015; 372(10):944-53.

60. 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). 27 May 2014. Data on file.

61. Rummel M. MCL subgroup analyses of the randomised Phase III study of the Study Group Indolent Lymphomas (StiL). 2014.

62. Drach J, Huang H, Samoilova O, 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). 56th American Society of Heamatology (ASH) Annual Meeting and Exposition. San Francisco, CA, USA. December 6-9, 2014. Abstract 3064.

63. Robak T, Jin J, Zhu J, et al. Bortezomib (btz) dose intensity is the strongest predictor for overall survival (OS) in mantle cell lymphoma (MCL) patients (pts) not considered for transplantation, receiving frontline btz plus rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) therapy in the Phase 3 LYM-3002 study. 56th American Society of Hematology (ASH) Annual Meeting and Exposition. San Francisco, CA, USA. 6-9 December 2014. Abstract 4412.

64. Shipp MA and The International Non-Hodgkin’s Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med*. 1993; 329(14):987-94.

65. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2007; 25(5):579-86.

66. Belch A, Kouroukis CT, Crump M, et al. A phase II study of bortezomib in mantle cell lymphoma: the National Cancer Institute of Canada Clinical Trials Group trial IND.150. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2007; 18(1):116-21.

67. Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1998; 16(1):139-44.

68. Walters SJ and Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation*. 2005; 14(6):1523-32.

69. Pickard AS, Neary MP and Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes*. 2007; 5:70.

70. Eve HE, Linch D, Qian W, et al. Toxicity of fludarabine and cyclophosphamide with or without rituximab as initial therapy for patients with previously untreated mantle cell lymphoma: results of a randomised phase II study. *Leukemia & lymphoma*. 2009; 50(2):211-5.

71. Rule S, Burton C, Waleski J, et al. A randomized phase II study of fludarabine/cyclophosphamide +/- rituximab in patients with untreated mantle cell lymphoma *Annals of Oncology*. 2005; 16 Suppl. 5(Abstract 198):197.

72. Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/C-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. *Blood*. 2014; 123(19):2944-52.

73. Rule S, Smith P, Johnson PW, et al. The addition of rituximab to fludarabine and cyclophosphamide (FC) improves overall survival in newly diagnosed mantle cell lymphoma (MCL): Results of the randomised UK national cancer research institute (NCRI) trial. 53rd Annual Meeting and Exposition of the American Society of Hematology (ASH), . San Diego, CA, USA. 10-13 December 2011. Abstract 440.

74. Rummel M, Maschmeyer G, Ganser A, et al. Bendamustine plus rituximab (B-R) versus CHOP plus rituximab (CHOP-R) as first-line treatment in patients with indolent and mantle cell lymphomas (MCL) – 7 Year updated results from the StiL NHL1 study. 56th American Society of Hematology (ASH) Annual Meeting and Exposition. San Francisco, CA., USA. December 6-9, 2014. Abstract 4407.

75. World Health Organisation (WHO). WHO handbook for reporting results of cancer treatment. 1979. Available at: http://whqlibdoc.who.int/offset/WHO_OFFSET_48.pdf Accessed: 3 November 2014.

76. Bucher HC, Guyatt GH, Griffith LE, et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol*. 1997; 50(6):683-91.

77. Warsch S, Hosein PJ, Maeda LS, et al. A retrospective study evaluating the efficacy and safety of bendamustine in the treatment of mantle cell lymphoma. *Leukemia & lymphoma*. 2012; 53(7):1299-305.

78. Visco C, Finotto S, Zambello R, et al. Combination of rituximab, bendamustine, and cytarabine for patients with mantle-cell non-Hodgkin lymphoma ineligible for intensive regimens or autologous transplantation. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2013; 31(11):1442-9.

79. Abrahamsson A, Albertsson-Lindblad A, Brown PN, et al. Real world data on primary treatment for mantle cell lymphoma: a Nordic Lymphoma Group observational study. *Blood*. 2014; 124(8):1288-95.

80. Dimopoulos MA, Mateos MV, Richardson PG, et al. Risk factors for, and reversibility of, peripheral neuropathy associated with bortezomib-melphalan-prednisone in newly diagnosed patients with multiple myeloma: subanalysis of the phase 3 VISTA study. *European journal of haematology*. 2011; 86(1):23-31.

81. Richardson PG, Sonneveld P, Schuster MW, et al. Reversibility of symptomatic peripheral neuropathy with bortezomib in the phase III APEX trial in relapsed multiple myeloma: impact of a dose-modification guideline. *Br J Haematol*. 2009; 144(6):895-903.

82. Furtado M, Johnson R, Kruger A, et al. Addition of bortezomib to standard dose chop chemotherapy improves response and survival in relapsed mantle cell lymphoma. *Br J Haematol*. 2015; 168(1):55-62.

83. Bonthapally V, Lafeuille M-H, Fortier J, et al. Retrospective analysis of treatment patterns and outcomes with subcutaneous bortezomib in patients with relapsed mantle cell lymphoma. American Society of Clinical Oncology. Chicago, IL USA. May 30 - June 3 2014. Abstract 8554.

84. Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. *The Lancet Oncology*. 2011; 12(5):431-40.

85. European Medicines Association (EMA). EPAR Summary for the public: Velcade. 2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000539/WC500048136.pdf Accessed: 2 April 2015.

86. Doorduijn J, Buijt I, Holt B, et al. Self-reported quality of life in elderly patients with aggressive non-Hodgkin's lymphoma treated with CHOP chemotherapy. *European journal of haematology*. 2005; 75(2):116-23.

87. Drummond MF and Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ*. 1996; 313(7052):275-83.

88. National Institute for Health and Care Excellence (NICE). National Institute for Health and Care Excellence (NICE). 2014. Available at: www.nice.org.uk Accessed: 12 December 2014.

89. Pan L, Guthrie KA, Till BG, et al. The mantle cell lymphoma international prognostic index (MIPI) at diagnosis is associated with survival of mantle cell lymphoma patients undergoing autologous hematopoietic stem cell transplantation.

50th American Society of Hematology (ASH) Annual Meeting & Exposition. San Fransisco, CA, USA. 6-9 December 2008. Abstract 1143.

90. Latimer N. National Institute for Health and Clinical Excellence (NICE) DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011. Available at: http://www.nicedsu.org.uk/NICE%20DSU%20TSD%20Survival%20analysis.updated%20March%202013.v2.pdf Accessed: 2 March 2015.

91. Office for National Statistics. England and Wales National Life Tables, 1980-82 to 2010-12. 2014. Available at: http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-352834 Accessed: 6 May 2014.

92. Janssen-Cilag International NV. Imbruvica 140mg hard capsules. Summary of Product Characteristics (SPC). October 2014. Available at: http://www.medicines.org.uk/emc/medicine/29383 Accessed: 2 March 2015.

93. Celgene Europe Limited. Revlimid 10mg. Summary of Product Characteristics (SPC). June 2007. Available at: http://www.medicines.org.uk/emc/medicine/29491 Accessed: 2 March 2015.

94. Pfizer Limited. Torisel 30mg concentrate and diluent for solution for infusion. Summary of Product Characteristics (SPC). 19 November 2012. Available at: http://www.medicines.org.uk/emc/medicine/21260 Accessed: 2 March 2015.

95. National Institute for Health and Care Excellence (NICE). TA226: Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma. 2011. Available at: http://www.nice.org.uk/guidance/TA226 Accessed: 8 October 2014.

96. Uyl-de Groot CA, Hagenbeek A, Verdonck LF, et al. Cost-effectiveness of ABMT in comparison with CHOP chemotherapy in patients with intermediate- and high-grade malignant non-Hodgkin's lymphoma (NHL). *Bone marrow transplantation*. 1995; 16(3):463-70.

97. van Agthoven M, Vellenga E, Fibbe WE, et al. Cost analysis and quality of life assessment comparing patients undergoing autologous peripheral blood stem cell transplantation or autologous bone marrow transplantation for refratory or relapsed non-Hodgkin's lymphoma or Hodgkin's disease: a prospective randomised trial. *Eur J Cancer*. 2001; 37(14):1781-9.

98. Witzens-Harig M, Reiz M, Heiss C, et al. Quality of life during maintenance therapy with the anti-CD20 antibody rituximab in patients with B cell non-Hodgkin's lymphoma: results of a prospective randomized controlled trial. *Annals of hematology*. 2009; 88(1):51-7.

99. Crott R, Versteegh M and Uyl-de-Groot C. An assessment of the external validity of mapping QLQ-C30 to EQ-5D preferences. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation*. 2013; 22(5):1045-54.

100. Pettengell R, Donatti C, Hoskin P, et al. The impact of follicular lymphoma on health-related quality of life. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2008; 19(3):570-6.

101. Edelman MJ, Meyers FJ and Siegel D. The utility of follow-up testing after curatice cancer therapy. *J Gen Intern Med*. 1997; 12(5):318-31.

102. Braga P, Carvalho S, Gomes M, et al. [Economic analysis of rituximab in combination with cyclophosphamide, vincristine and prednisolone in the treatment of patients with advanced follicular lymphoma in Portugal]. *Acta medica portuguesa*. 2010; 23(6):1025-34.

103. Wild D, Walker M, Pettengell R, et al. Pcn62 Utility Elicitation in Patients with Follicular Lymphoma. *Value in Health*. 2006; 9(6):A294.

104. Deconinck E, Miadi-Fargier H, Pen CL, et al. Cost effectiveness of rituximab maintenance therapy in follicular lymphoma: long-term economic evaluation. *PharmacoEconomics*. 2010; 28(1):35-46.

105. Hancock S, Wake B and Hyde C. Fludarabine as first line therapy for chronic lymphocytic leukaemia. A West Midlands Health Technology Assessment Collaboration report. 2002. Available at: http://www.birmingham.ac.uk/Documents/college-mds/haps/projects/WMHTAC/REPreports/2002/Fludarabine.pdf Accessed: 13 January 2015.

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

107. Soini EJ, Martikainen JA, Vihervaara V, et al. Economic evaluation of sequential treatments for follicular non-hodgkin lymphoma. *Clinical therapeutics*. 2012; 34(4):915-25 e2.

108. Berto P, Morsanutto A, Lopatriello S, et al. Analisi costo-efficacia di rituximab + CHOP versus CHOP in soggetti affetti da linfoma non-Hodgkin aggressivo. *PharmacoEconomics - Italian Research Articles*. 2004; 6(3):151-60.

109. Best JH, Hornberger J, Proctor SJ, et al. Cost-effectiveness analysis of rituximab combined with chop for treatment of diffuse large B-cell lymphoma. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2005; 8(4):462-70.

110. Groot MT, Lugtenburg PJ, Hornberger J, et al. Cost-effectiveness of rituximab (MabThera) in diffuse large B-cell lymphoma in The Netherlands. *European journal of haematology*. 2005; 74(3):194-202.

111. Hill G, Barron R, Fust K, et al. Primary vs secondary prophylaxis with pegfilgrastim for the reduction of febrile neutropenia risk in patients receiving chemotherapy for non-Hodgkin's lymphoma: cost-effectiveness analyses. *Journal of medical economics*. 2014; 17(1):32-42.

112. Hornberger JC and Best JH. Cost utility in the United States of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone for the treatment of elderly patients with diffuse large B-cell lymphoma. *Cancer*. 2005; 103(8):1644-51.

113. Kasteng F, Erlanson M, Hagberg H, et al. Cost-effectiveness of maintenance rituximab treatment after second line therapy in patients with follicular lymphoma in Sweden. *Acta Oncol*. 2008; 47(6):1029-36.

114. Kymes SM, Pusic I, Lambert DL, et al. Economic evaluation of plerixafor for stem cell mobilization. *Am J Manag Care*. 2012; 18(1):33-41.

115. Lathia N, Isogai PK, De Angelis C, et al. Cost-effectiveness of filgrastim and pegfilgrastim as primary prophylaxis against febrile neutropenia in lymphoma patients. *Journal of the National Cancer Institute*. 2013; 105(15):1078-85.

116. Lyman G, Lalla A, Barron R, et al. Cost-effectiveness of pegfilgrastim versus 6-day filgrastim primary prophylaxis in patients with non-Hodgkin's lymphoma receiving CHOP-21 in United States. *Current medical research and opinion*. 2009; 25(2):401-11.

117. Dewilde S, Woods B, Castaigne JG, et al. Bendamustine-rituximab: a cost-utility analysis in first-line treatment of indolent non-Hodgkin's lymphoma in England and Wales. *Journal of medical economics*. 2014; 17(2):111-24.

118. Hornberger J, Reyes C, Lubeck D, et al. Economic evaluation of rituximab plus cyclophosphamide, vincristine and prednisolone for advanced follicular lymphoma. *Leukemia & lymphoma*. 2008; 49(2):227-36.

119. Papaioannou D, Rafia R, Rathbone J, et al. Rituximab for the first-line treatment of stage III-IV follicular lymphoma (review of Technology Appraisal No. 110): a systematic review and economic evaluation. *Health technology assessment (Winchester, England)*. 2012; 16(37):1-253, iii-iv.

120. Ray JA, Carr E, Lewis G, et al. An evaluation of the cost-effectiveness of rituximab in combination with chemotherapy for the first-line treatment of follicular non-Hodgkin's lymphoma in the UK. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2010; 13(4):346-57.

121. Pink J, Lane S and Hughes DA. Mechanism-based approach to the economic evaluation of pharmaceuticals: pharmacokinetic/pharmacodynamic/pharmacoeconomic analysis of rituximab for follicular lymphoma. *PharmacoEconomics*. 2012; 30(5):413-29.

122. Soini EJ, Martikainen JA and Nousiainen T. Treatment of follicular non-Hodgkin's lymphoma with or without rituximab: cost-effectiveness and value of information based on a 5-year follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2011; 22(5):1189-97.

123. Hatswell AJ, Porter J, Hertel N, et al. The cost of costing treatments incorrectly: errors in the application of drug prices in economic models due to differing patient weights. ISPOR 17th Annual European Congress. Amsterdam, The Netherlands. 8-12 November 2014. Presentation CN4.

124. Pharmacia Limited. Cyclophosphamide tablets. Summary of Product Characteristics (SPC). August 2002. Available at: http://www.medicines.org.uk/emc/medicine/10550 Accessed: 2 March 2015.

125. Schering Health Care Ltd. TA119 Manufacturer's Submission: Fludarabine phosphate for the first-line treatment of chronic lymphocytic leukaemia. 2006. Accessed: September 2014.

126. Forbes A, Farrell K, McKay P, et al. High dose cytarabine with rituximab is an effective first-line therapy for mantle cell lymphoma and produces ample stem cell harvest yields after multiple chemotherapy cycles. *Leukemia & lymphoma*. 2013; 54(10):2303-5.

127. Amgen Europe. Neupogen 30 MU (0.3mg/ml) solution for injection. Summary of Product Characteristics (SPC). April 2008. Available at: https://www.medicines.org.uk/emc/medicine/27485 Accessed: 4 December 2014.

128. Chugai Pharma UK. Granocyte. Summary of Product Characteristics (SPC). November 1993. Available at: https://www.medicines.org.uk/emc/medicine/8347 Accessed: 4 December 2014.

129. Amgen Europe. Neulasta® 6mg solution for injection. Summary of Product Characteristics (SPC). July 2007. Available at: https://www.medicines.org.uk/emc/medicine/11783 Accessed: 4 December 2014.

130. National Health Service (NHS). Department of Health reference costs 2013-14. 2013. Available at: https://www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014 Accessed: 2 March 2015.

131. Accord Healthcare Limited. Ciprofloxacin 500mg film-coated tablets. Summary of Product Characteristics (SPC). July 2003. Available at: http://www.medicines.org.uk/emc/medicine/25756 Accessed: 2 March 2015.

132. Beacon Pharmaceutical Ltd. Evoxil (levofloxacin) 500mg film-coated tablets. Summary of Product Characteristics (SPC). June 2013. Available at: http://www.medicines.org.uk/emc/medicine/27508 Accessed: 2 March 2015.

133. Actavis UK Ltd. Moxifloxacin 400 mg film-coated tablets. Summary of Product Characteristics (SPC). December 2013. Available at: http://www.medicines.org.uk/emc/medicine/29040 Accessed: 2 March 2015.

134. Stravencon Ltd. Ceftazidime 2.0g powder for solution for injection or infusion. Summary of Product Characteristics (SPC). July 2011. Available at: http://www.medicines.org.uk/emc/medicine/28576 Accessed: 2 March 2015.

135. Stravencon Ltd. Ceftriaxone Sodium 2g injection. Summary of Product Characteristics (SPC). July 2011. Available at: http://www.medicines.org.uk/emc/medicine/26466 Accessed: 2 March 2015.

136. AstraZeneca UK Limited. Meronem IV. Summary of Product Characteristics (SPC). April 2012. Available at: http://www.medicines.org.uk/emc/medicine/11215 Accessed: 2 March 2015.

137. GlaxoSmithKline UK. Augmentin 625mg tablets. Summary of Product Characteristics (SPC). October 2005. Available at: http://www.medicines.org.uk/emc/medicine/19191 Accessed: 2 March 2015.

138. Accord Healthcare Limited. Amoxicillin 500 mg capsules BP. Summary of Product Characteristics (SPC). November 2010. Available at: http://www.medicines.org.uk/emc/medicine/25942 Accessed: 2 March 2015.

139. Sandoz Limited. Piperacillin/Tazobactam 2g/0.25 g powder for solution for infusion. Summary of Product Characteristics (SPC). November 2008. Available at: http://www.medicines.org.uk/emc/medicine/28877 Accessed: 2 March 2015.

140. Actavis UK Ltd. Co-Trimoxazole tablets 80/400mg. Summary of Product Characteristics (SPC). September 1998. Available at: http://www.medicines.org.uk/emc/medicine/23909 Accessed: 2 March 2015.

141. Actavis UK Ltd. Vancomycin powder for infusion 1g. Summary of Product Characteristics (SPC). August 2011. Available at: http://www.medicines.org.uk/emc/medicine/9549 Accessed: 2 March 2015.

142. Hospira UK Ltd. Amikacin 250mg/ml injection. Summary of Product Characteristics (SPC). May 2001. Available at: http://www.medicines.org.uk/emc/medicine/619 Accessed: 2 March 2015.

143. Actavis UK Ltd. Aciclovir tablets BP 200mg. Summary of Product Characteristics (SPC). June 2002. Available at: http://www.medicines.org.uk/emc/medicine/23720 Accessed: 2 March 2015.

144. Actavis UK Ltd. Valaciclovir 500mg tablets. Summary of Product Characteristics (SPC). October 2013. Available at: http://www.medicines.org.uk/emc/medicine/24175 Accessed: 2 March 2015.

145. Monthly Index of Medical Specialities (MIMS). 2015. Available at: http://www.mims.co.uk/.

146. Department of Health. Drugs and pharmaceutical electronic market information (eMit). 2014. Available at: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit Accessed: 4 March 2015.

147. Minuk L, Chin-Yee I, Hibbert A, et al. Red blood cell transfusion and chemotherapy administration: a study of resource utilization. *Community Oncol*. 2008; 5:598-603.

148. National Health Service (NHS). NHS blood and transplant price list 2014-2015. 2014. Available at: http://hospital.blood.co.uk/products/ Accessed: 2 March 2015.

149. Curtis L. Unit costs of health and social care 2014. 2014. Available at: http://www.pssru.ac.uk/project-pages/unit-costs/2014/ Accessed: 2 March 2015.

150. Addicot R and Dewar S. Improving choice at the end of life: a descriptive analysis of the impact and costs of the Marie Curie Delivering Choice programme in Lincolnshire. 2008. Available at: http://www.kingsfund.org.uk/sites/files/kf/improving-choice-end-of-life-descriptive-analysis-impact-costs-marie-curie-choice-programme-lincolnshire-rachael-addicot-steve-dewar-april-2008.pdf Accessed: 12 June 2015.

151. University of Glasgow. Critical appraisal checklist for economic evaluations. 1997. Available at: http://www.gla.ac.uk/media/media_64048_en.pdf Accessed: 14 April 2014.

152. Pham LV, Tamayo AT, Yoshimura LC, et al. Inhibition of constitutive NF-kappa B activation in mantle cell lymphoma B cells leads to induction of cell cycle arrest and apoptosis. *J Immunol*. 2003; 171(1):88-95.

153. Kind P, Hardman G and Macran S. UK Populations norms for EQ-5D. 1999. Available at: http://www.york.ac.uk/media/che/documents/papers/discussionpapers/CHE%20Discussion%20Paper%20172.pdf Accessed: 12 June 2015.

154. Chandran R, Gardiner SK, Simon M, et al. Survival trends in mantle cell lymphoma in the United States over 16 years 1992-2007. *Leukemia & lymphoma*. 2012; 53(8):1488-93.

155. Haematological Malignancy Research Network (HMRN). Clinical Management and Outcome in Mantle Cell Lymphoma. 2014.