NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]

Contents:

NICE National Institute for Health and Care Excellence

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Pre-meeting briefing

PART 1

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

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

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

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

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Abbreviation	In full
Del(17p)	Deletion of the short arm of chromosome 17
AIC	Akaike information criteria
AEs	Adverse events
BR	Bendamustine plus rituximab
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
CR	Complete response rate
EFS	Event-free survival
EQ-5D-3L	EuroQoL five-dimension 3-level version
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IDELA+R	Idelalisib in combination with rituximab
IRC	Independent review committee
KM	Kaplan-Meier
MAIC	Matched adjusted indirect comparison
MRD	Minimal residue disease
NMA	Network meta-analysis
ORR	Overall response rate
OS	Overall survival
PFS	Progression free survival
QALY	Quality-adjusted life year
R/R	Relapsed or refractory
TP53	Mutation in the TP53 gene
VEN+R	Venetoclax in combination with rituximab

Key Issues - clinical

Clinical Pathway:

- Is restricting the population to those post chemoimmunotherapy appropriate since this might exclude CLL patients with del(17p) and/or TP53 mutation?
- Is a two year stopping rule for VEN+R appropriate?

Clinical evidence

- Are the results generalisable to UK clinical practice since most patients in trials recruited outside of UK?
- Are data used from MAIC appropriate to use?

Cancer drugs fund:

- Will further data collection on OS reduce uncertainty?
- Will ongoing studies provide useful data?

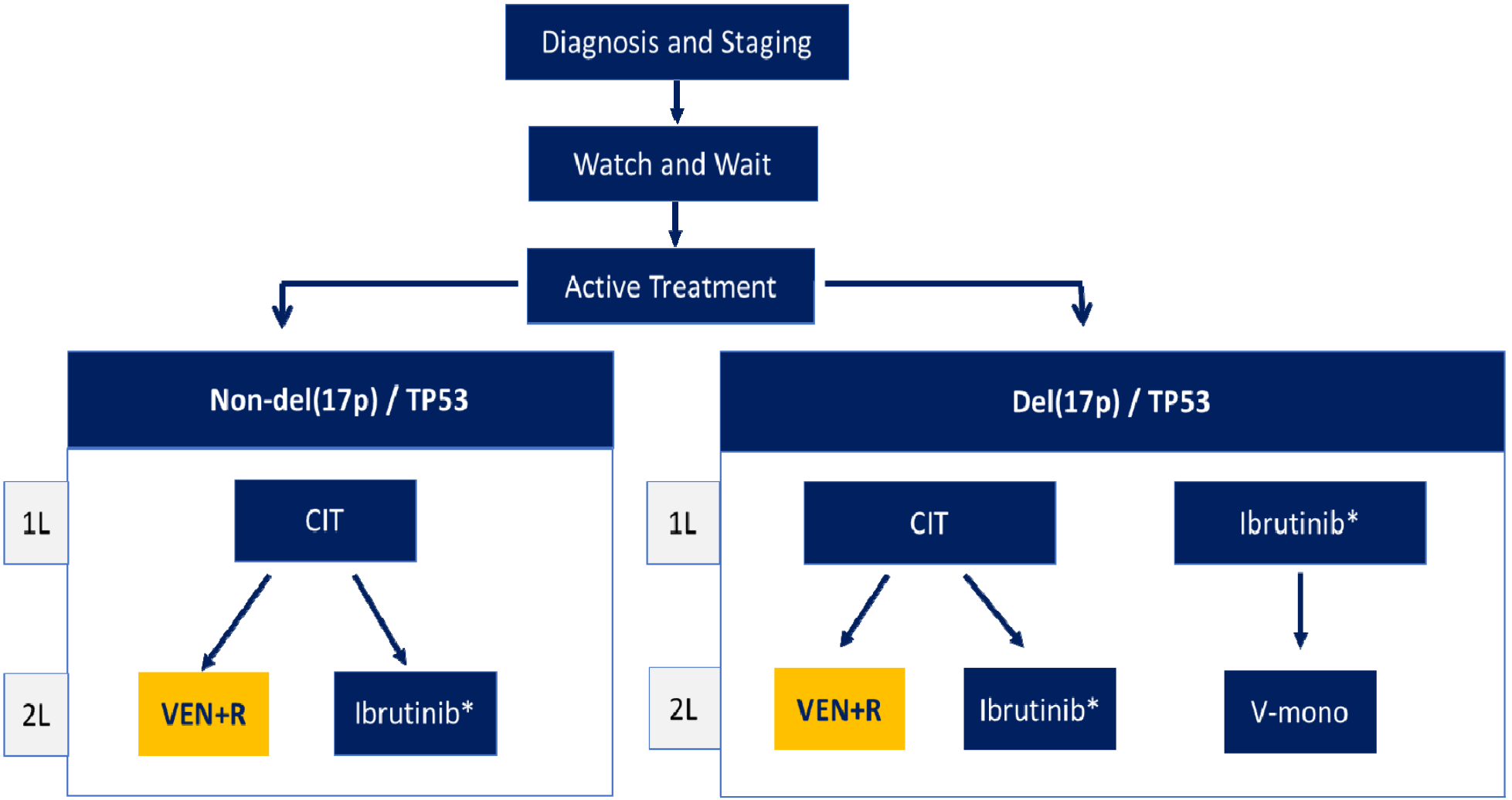
Other:

- Is VEN+R an innovative treatment?
- Are there any equality issues?

Disease Background

- Chronic lymphocytic leukaemia (CLL) is a common form of leukaemia, with an estimated 3,515 new diagnoses in England each year.
- Risk increases with age and is more common in men
- 5%-10% of people are considered to have ‘high risk’ disease
- British Committee for Standards in Haematology defines people as ‘high-risk’, if:
  - they have **17p deletion** or **TP53 mutation** (this increases the rate of cell growth and the resistance of the disease to treatment)
  - their disease relapses/is refractory to chemotherapy
- The most common symptoms encountered by patients are fatigue, swollen lymph nodes, weakness or breathlessness, night sweats, weight loss, fever and repeated infections.

Clinical pathway of care



*Ibrutinib is depicted in this figure as it is the preferred B-cell receptor inhibitor therapy because of its effectiveness and because of the AE associated with idelalisib with rituximab (idela+R) as per clinical experts' opinion as stated in NICE TA429.

NICE

Related NICE Guidance (1)

TA487

Venetoclax is recommended for use within the Cancer Drugs Fund, within its marketing authorisation, as an option for treating chronic lymphocytic leukaemia, that is, in adults:

- with a 17p deletion or TP53 mutation and when a B-cell receptor pathway inhibitor is unsuitable, or whose disease has progressed after a B-cell receptor pathway inhibitor **or**
- without a 17p deletion or TP53 mutation, and whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor **and**
- only if the conditions in the managed access agreement are followed

TA429

Ibrutinib alone is recommended within its marketing authorisation as an option for treating chronic lymphocytic leukaemia in adults:

- who have had at least 1 prior therapy or
- who have a 17p deletion or TP53 mutation, and in whom chemo-immunotherapy is unsuitable and
- only when the company provides ibrutinib with the discount agreed in the patient access scheme.

Related NICE Guidance (2)

TA359

Idelalisib with rituximab is recommended:

- for untreated chronic lymphocytic leukaemia in adults with a 17p deletion or TP53 mutation or
- for chronic lymphocytic leukaemia in adults when the disease has been treated but has relapsed within 24 months.
- Idelalisib is recommended only if the company provides the drug with the discount agreed in the simple discount agreement.

Comments from patient and professional groups

- Patient groups
  - Extremely poor prognosis and no recent progress in treatment
  - CLL places huge emotional strain on patients, families and carers especially during 'Watch and Wait' stage
  - The average age of a CLL patient is 72, so many treatments unsuitable or not tolerated
  - The most common symptoms encountered by patients are fatigue, swollen lymph nodes, weakness or breathlessness, night sweats, weight loss, fever and repeated infections
- Professional groups
  - Venetoclax in combination with rituximab has shown greater achievement of minimal residual disease compared with chemoimmunotherapy and other novel agents
  - There is a fixed duration of therapy, compared with using therapy until progression
  - Venetoclax and rituximab should be available as an option in relapsed /refractory CLL or in patients with 17p Deletion or TP53 mutation unsuitable for B-cell receptor inhibitor
  - The impact of high remission rates and prolonged survival is a substantial shift in prognosis compared with either supportive care or chemoimmunotherapy such as bendamustine and rituximab

Venetoclax, AbbVie

Marketing authorisation	CHMP not yet received. Anticipated wording of marketing authorisation is: venetoclax in combination with rituximab is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy
Mechanism of action	Selective small molecule inhibitor of B-cell lymphoma 2, anti- apoptotic protein overexpressed in 95% of people with CLL

Administration and dose	• **Titration phase**
	  • Venetoclax, taken orally, dose escalates from 20 mg/day to 400 mg/day over 5 weeks
	• **Post-titration phase**
	  • Venetoclax, taken orally, 400 mg/day
	  • Rituximab 375 mg/m^2 IV on day one of one cycle (a cycle is 28 days) followed by 500 mg/m^2 on day one of cycles two to six

List price	Venetoclax: 112 tab pack (100 mg) = £4,789.47 (Week five onwards, 400 mg per day for 28 days) The company has a confidential commercial access agreement with NHS England which makes venetoclax available at a reduced cost Rituximab: 500 mg/50 ml concentrate for solution for infusion vial = £785.84 The average cost of VEN+R for the course of 2-years when assuming 100% compliance and no progression or mortality events is £129,513

Decision problem

	Final scope issued by NICE	Company submission
Population	Adults with relapsed or refractory chronic lymphocytic leukaemia who have had at least 1 therapy	Adults with relapsed or refractory chronic lymphocytic leukaemia in the following population: • Post CIT
Intervention	Venetoclax with rituximab	Venetoclax with rituximab
Comparator	• Ibrutinib • Idelalisib with rituximab • Best supportive care (including but not limited to regular monitoring, blood transfusions, infection control, corticosteroids with or without rituximab and psychological support).	• Ibrutinib • Idelalisib with rituximab • BSC is not an appropriate comparator for this appraisal
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • disease-free survival • minimal residual disease negative rate • adverse effects of treatment • health-related quality of life	Same as final scope issued by NICE

ERG's comments on decision problem

Area	ERG's comments
Population	• Restricting the target population to patients post chemo-immunotherapy potentially excludes CLL patients with del(17p) and/or TP53 mutation • Patients may never receive chemoimmunotherapy, given that they receive ibrutinib as first-line in clinical practice
Comparator	• Single-agent ibrutinib or idelalisib-rituximab combination (IDELA+R) are the main comparators • No head-to-head trials comparing VEN+R against single-agent ibrutinib or IDELA+R were identified • BSC is not relevant in this appraisal
Outcome	• Data from the key trial evidence (MURANO) was not mature enough to estimate the overall survival, so progression free survival was a reasonable primary endpoint • The company did not provide MAIC analyses of the MRD status

Clinical evidence: MURANO

Design	• Phase 3 open-label parallel-arm RCT
Location (sites)	• 109 sites in 20 countries: 4 sites in the UK
Population	• Adults (18yrs +) with R/R CLL treated with at least one but not more three lines of therapy
Intervention and comparator	• ITT=389: VEN+R (n=194) and BR (n=195) • Patients from UK: VEN+R (n=6) and BR (n=4) • BR was selected as the comparator arm for the MURANO trial as it was considered the most effective regimen for relapsed CLL when the study was initiated • VEN+R is given for a maximum of 2 years, or until disease progression or unacceptable toxic effects, whichever occurred sooner
Primary outcome measures	• Investigator-assessed PFS median follow-up at recent data cut: 23.8
Secondary outcome measures	• IRC-assessed PFS, investigator- and IRC–assessed PFS in patients with del(17p), protocol-defined investigator and IRC–assessed ORR, MRD, Duration of response, OS, event-free survival and time to next anti-CLL treatment, HRQoL

Baseline characteristics in MURANO trial (1)

Characteristic	VEN+R (n=194)	BR (n=195)
Age, years, median (range)	64.5 (28-83)	66.0 (22–85)
Male n (%	136 (70.1)	151 (77.4)
ECOG score, n (%)		(n=194)
0	111(57.2)	108 (55.7)
1	82 (42.3)	82 (42.3)
2	1 (0.5)	2 (1.0)
Del(17p) status, n (%)	(n=173)	(n=169)
Present	46 (26.6)	46 (27.2)
Absent	127 (73.4)	123 (72.8)
TP53 mutation status, n (%)	(n=192)	(n=184)
Mutated	48 (25.0)	51 (27.7)
Unmutated	144 (75.0)	133 (72.3)
Del(17p) vs.TP53 mutation, n/N (%)	(n=192)	(n=192)
Only del(17p)	24 (14.0)	18 (11.4)
TP53 mutation only	19 (11.1)	23 (14.6)
Del(17p) and TP53 mutated	22 (12.9)	22 (13.9)
Del(17p) and TP53 mutated	53 (27.8)	50 (26.6)[d]
Non-del(17p) andTP53 mutated[d]	141 (72.7)	138 (73.4)[d]
[d] Outcomes based on n=188.		

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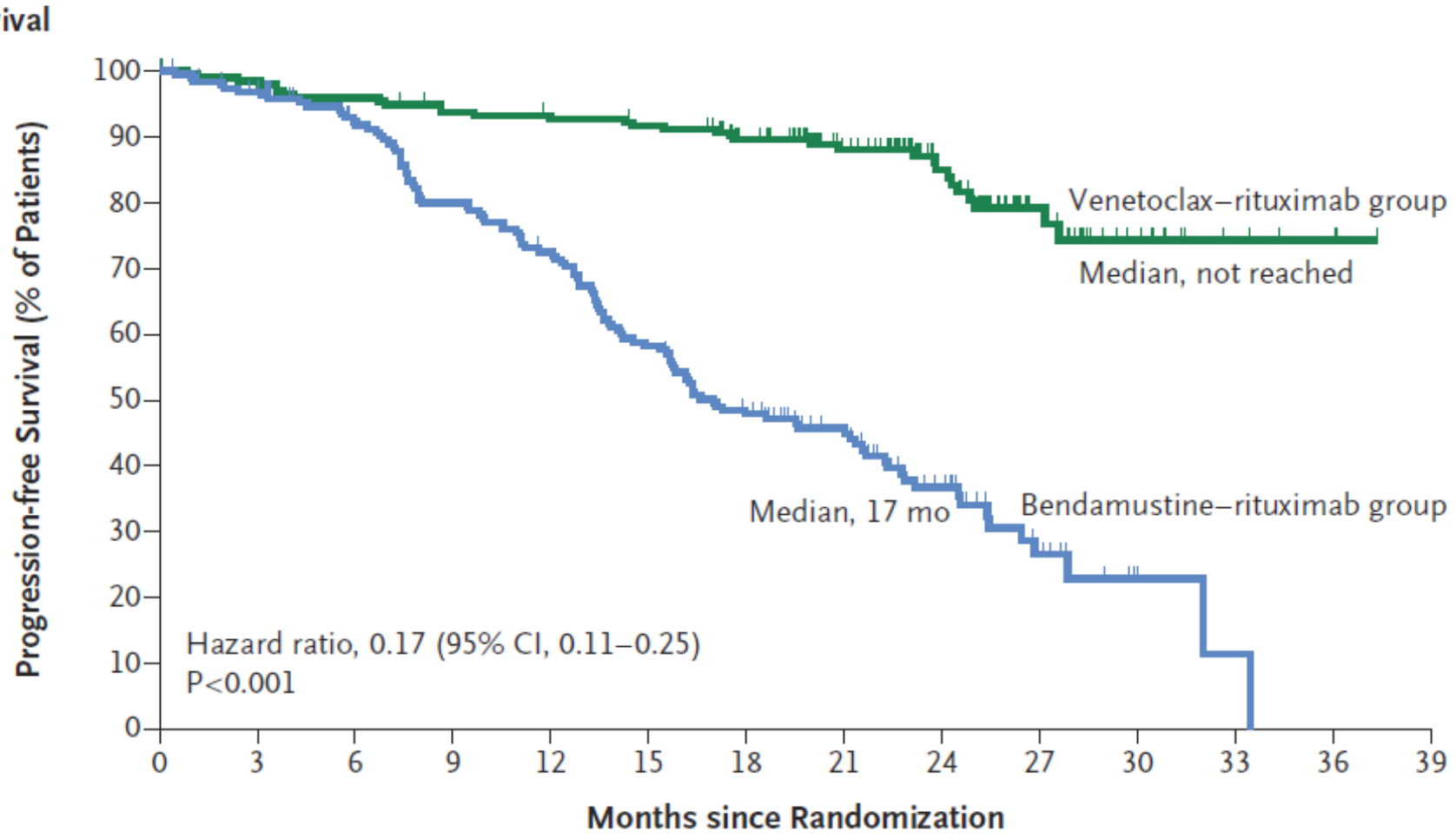
Baseline characteristics in MURANO trial (2)

Characteristic	VEN+R (n=194)	BR (n=195)
Stratification factor: risk status (derived), n (%)		
N	194	195
High	109 (56.2)	118 (60.5)
Low	84 (43.3)	75 (38.5)
Number of prior CLL therapies, n (%)		
N	194	195
1	111 (57.2)	117 (60.0)
2	57 (29.4)	43 (22.1)
3	22 (11.3)	34 (17.4)
>3	4 (2.1)	1 (0.5)
Type of prior CLL therapies, n (%)		
Alkylating agent	182 (93.3)	185 (95.4)
Purine analogue	157 (80.5)	158 (81.4)
Anti-CD20 antibody	153 (78.5)	148 (76.3)
B-cell receptor inhibitor	3 (1.5)	5 (2.6)

Progression free survival (investigator assessed)

PFS
VEN+R: the median was not reached.
BR: 17 months
HR= 0.17 (95% CI 0.11 to 0.25)
p<0.0001



No. at Risk

Venetoclax–rituximab group	194	190	185	179	176	173	157	115	76	33	14	5	3
Bendamustine–rituximab group	195	177	163	141	127	102	81	57	35	12	3	1	

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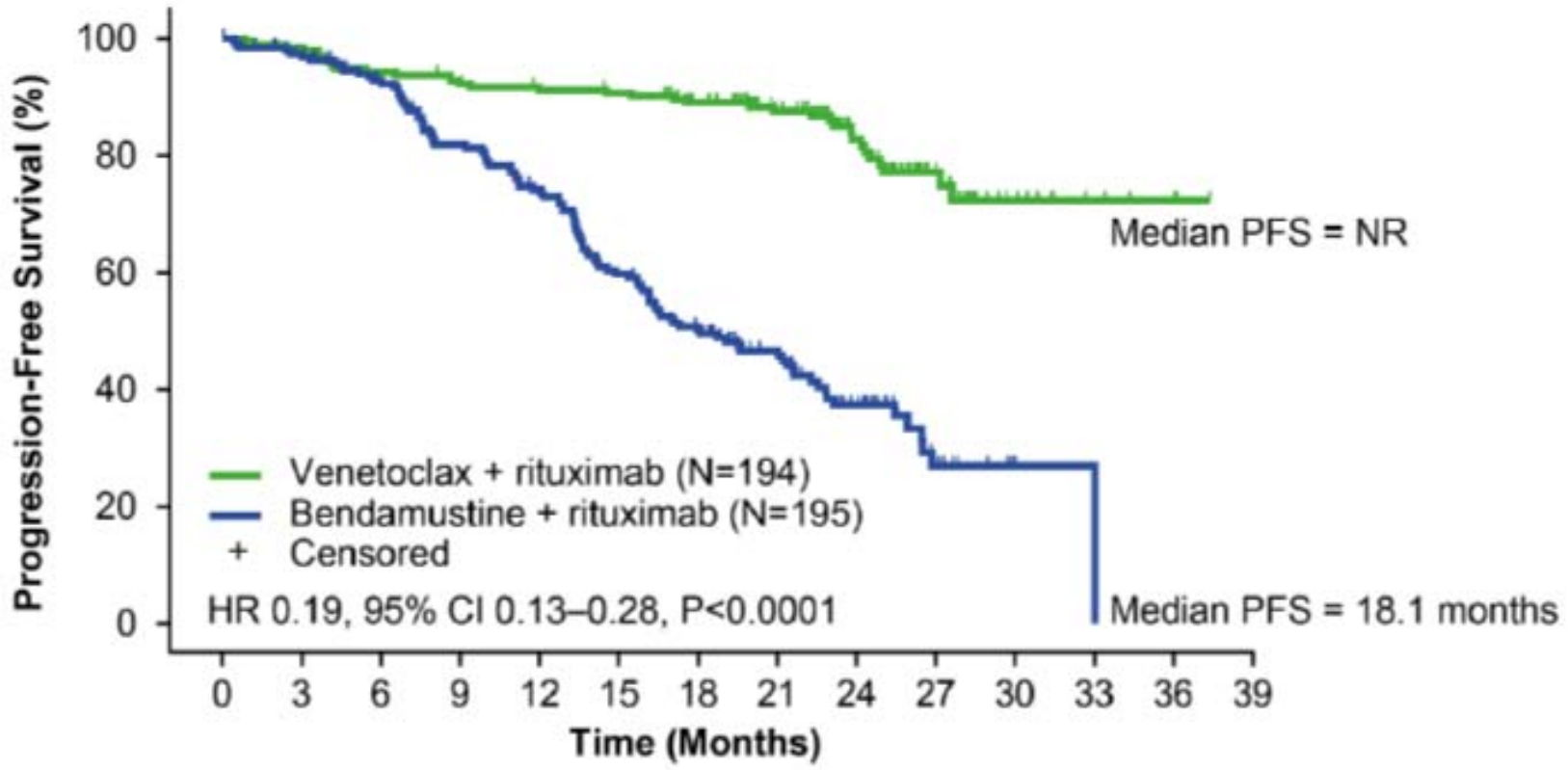
Progression free survival (Independent review committee assessed)

PFS
VEN+R: the median was not reached
BR: 18.1 months
HR= 0.19 (95% CI 0.13 to 0.28)
p<0.0001



No. of patients at risk

Venetoclax + rituximab	194	190	182	177	173	171	157	116	75	34	14	5	3
Bendamustine + rituximab	195	178	162	138	124	100	82	56	34	11	2	1	

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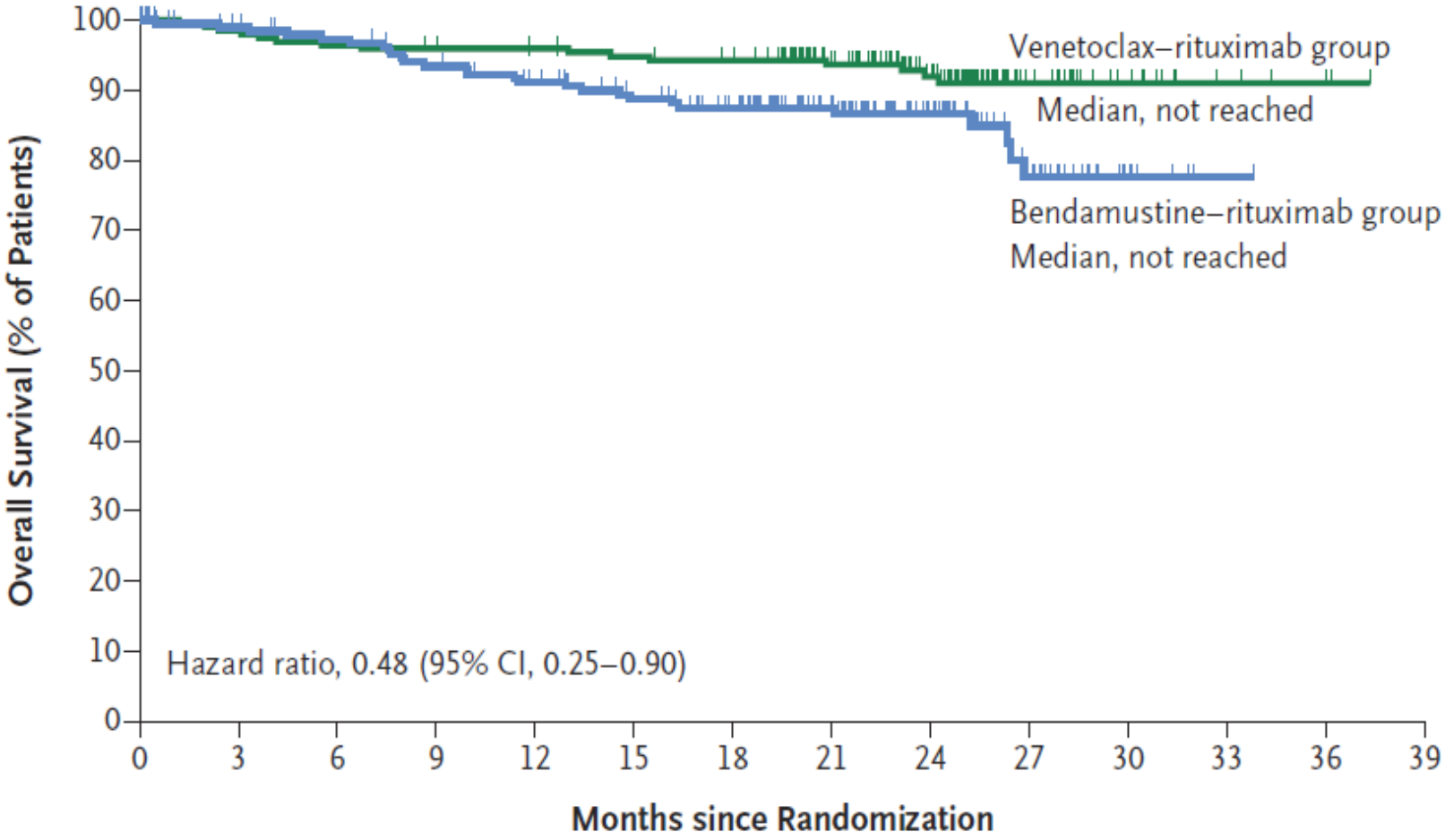
Overall survival

OS
VEN+R: the median was not reached
BR: the median was not reached
HR= 0.48 (95% CI 0.25 to 0.90)



No. at Risk

Venetoclax–rituximab group	194	190	185	183	181	178	175	142	102	36	15	5	3
Bendamustine–rituximab group	195	181	175	166	158	146	134	102	66	29	8	2	

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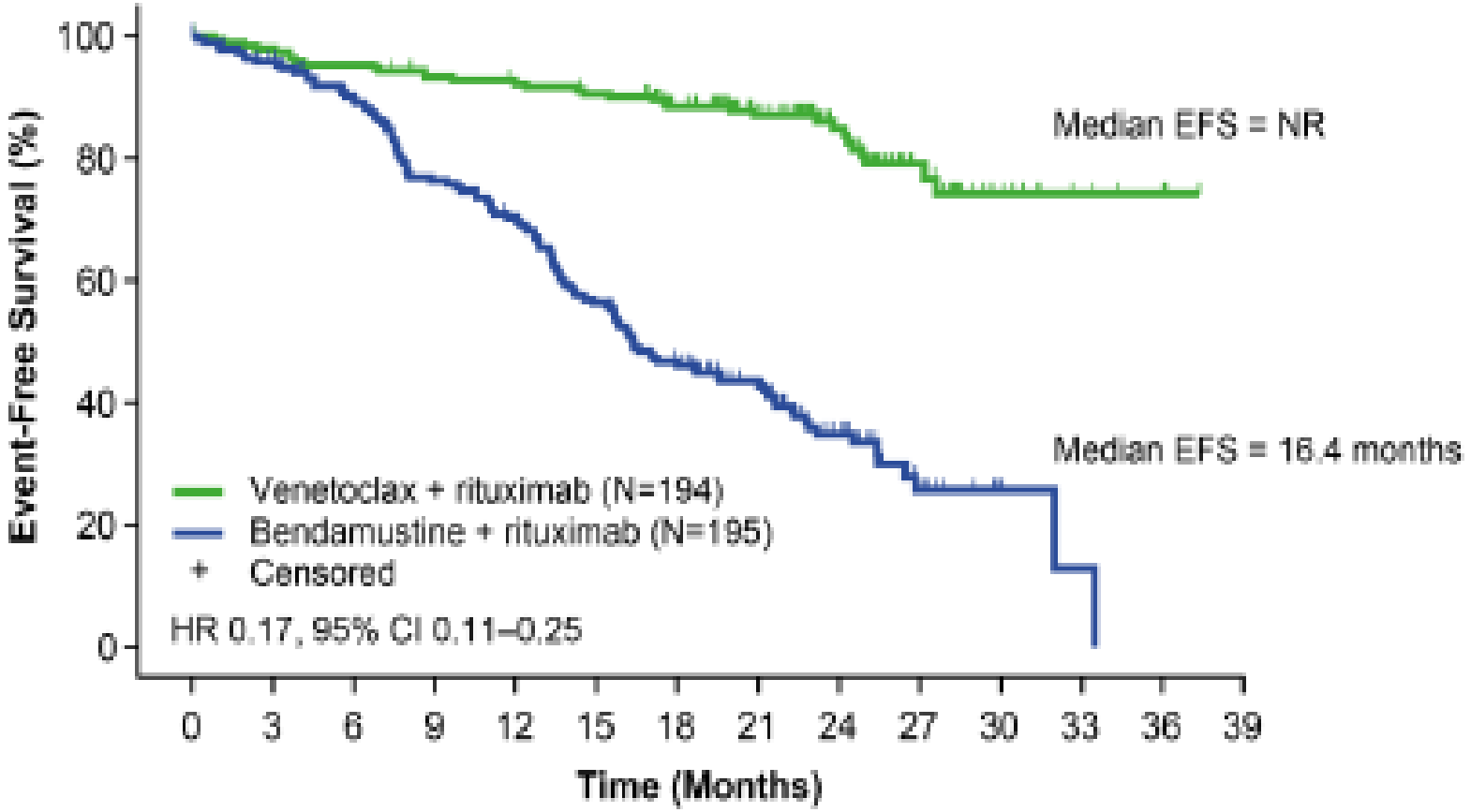
Event-free survival

EFS
VEN+R: the median was not reached
BR: 16.4 months
Is VEN+R
HR= 0.17 (95% CI 0.11 to 0.25)



No. of patients at risk													
Venetoclax + rituximab	194	189	184	178	175	171	155	113	75	33	14	5	3
Bendamustine + rituximab	195	177	162	138	126	101	80	56	34	11	3	1	

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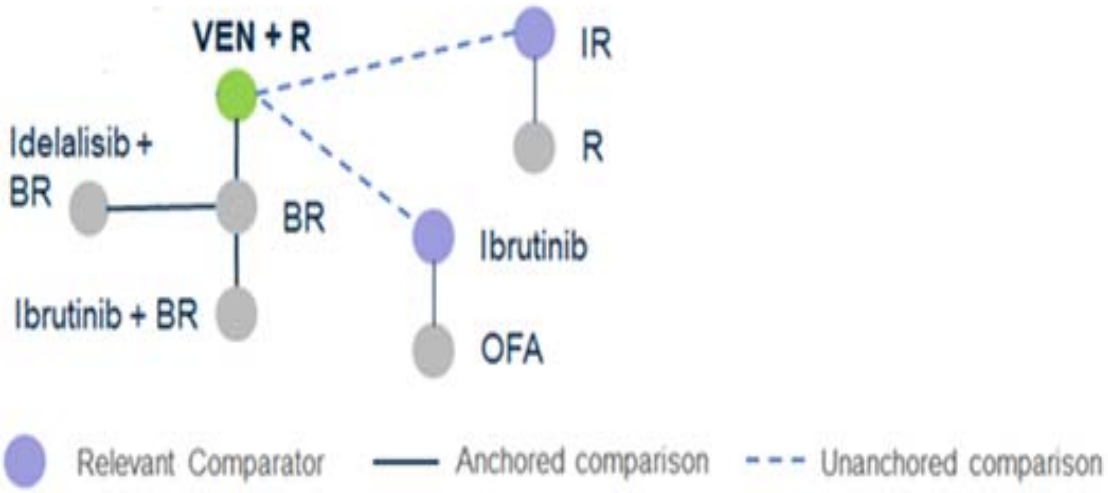
Company's indirect treatment comparison (1)

- Since there was no common comparator connecting all the treatments in the MURANO trial (VEN+R, ibrutinib, IDELA+R), the company performed an unanchored mixed adjusted indirect comparison (MAIC) analysis using data from MURANO for VEN+R, RESONATE for ibrutinib and Study 116 for Ideal+R
- The company also performed an anchored MAIC which was conducted only for Ibrutinib+BR, assuming that the relative efficacy of VEN+R vs. ibrutinib+BR can be extended to VEN+R vs. ibrutinib monotherapy. Data was used from MURANO for VEN+R and HELIOS for ibrutinib+BR



Treatment	Trial	ITT (N)
VEN +R	MURANO	VEN+R: 194 BR: 195
Ibrutinib	RESONATE	Ibrutinib:195 OFA:196
Idela +R	Study 116	Idela+R:110 Rituximab:110
Ibrutinib	HELIOS	Ibrutinib+R:289 BR:289

ERG's comments on indirect treatment comparison trial baseline characteristics

Characteristics	Before matching		After matching	
	VEN+R MURANO (N=169)[a]	Ibrutinib RESONATE (N=195)	VEN+R MURANO (N=62)[b]	Ibrutinib RESONATE (N=195)
Age ≥65	50.89%	60.51%	60.51%	60.51%
Rai stage III-IV	27.22%	55.90%	55.90%	55.90%
Bulky disease ≥5cm	43.79%	63.59%	63.59%	63.59%
Prior therapy >1	43.79%	82.05%	82.05%	82.05%
ECOG=1	45.56%	59.49%	59.49%	59.49%
β2-microglobulin>3.5 mg/L	64.50%	83.71%	83.71%	83.71%

[a] 25 patients with prior B-cell receptor inhibitor therapy, ECOG>1, and no central lab measurement for assessing del(17p) status were excluded from the VEN+R IPD population (N = 194) before matching. [b] About two-thirds of the VEN+R IPD population were unmatched to the ibrutinib arm of RESONATE.

- The ERG is concerned about the differences in the matched sample characteristics such as age, Rai stage, bulky disease status, prior therapy status, ECOG score, and Beta-2 microglobulin concentration.
- The population in the RESONATE trial seemed healthier at the offset than population in the MURANO trial.

Company's indirect treatment comparisons (2)

Anchored			
VEN+R vs.	HR PFS (95% CI)	HR OS (95% CI)	Sample Size
Ibrutinib +BR (Unadjusted)	[redacted]	0.703 (0.270 – 1.829)	[redacted]
Ibrutinib +BR (Adjusted)	[redacted]	[redacted]	VEN+R= 71.5 [redacted]

Unanchored (Adjusted Comparison)			
	HR PFS (95% CI)	HR OS (95% CI)	Sample Size
VEN+R vs. Ibrutinib	[redacted]	[redacted]	[redacted]
Unadjusted Comparison			
VEN+R vs. Ibrutinib	[redacted]	[redacted]	[redacted]

- The company also conducted a scenario analysis using HRs from the anchored MAIC where they assumed that [redacted]. The ERG explored impact of using this assumption in the cost effectiveness analysis (slide 42 and 43)

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ERG's comments on results from the company's MAIC analyses

- The ERG believes that the company MAIC produced implausible OS HRs estimates, since there is usually a correlation between PFS and OS. Within the company submission results are opposite, PFS showed higher HR than OS. Nothing in the mechanism of action of VEN+R could explain such results.

Comparison of PFS and OS outcomes in patients with R/R CLL				
Study	Treatment 1	Treatment 2	PFS HR $_{1 \text{ vs } 2}$	OS HR $_{1 \text{ vs } 2}$
HELIOS	Ibrutinib+BR	BR	0.20	0.63
MURANO	VEN+R	BR	0.19	0.48
RESONATE	Ibrutinib	Ofatumumab	0.22	0.43
Company's MAIC	VEN+R	Ibrutinib	XXXX	XXXX

- Therefore the ERG conducted a network-meta analysis to produce alternative OS and PFS estimates for ibrutinib and VEN+R.

ERG's network–meta analysis

- The ERG agrees that there is not sufficient evidence to indirectly compare ibrutinib with VEN+R using results from RCTs. However they identified an abstract by Hillmen et al. that compared single-agent ibrutinib to BR and they used it as a common comparator.
- The ERG believes that results from the NMA are more consistent because the benefit observed on PFS is associated with a lower benefit on OS.

Comparison of PFS and OS outcomes in R/R CLL using the MAIC or the ERG's exploratory NMA				
Study	Treatment 1	Treatment 2	PFS HR $_{1 \text{ vs } 2}$	OS HR $_{1 \text{ vs } 2}$
Company's MAIC	VEN+R	Ibrutinib	[redacted]	[redacted]
ERG's NMA			1.43 (0.78-2.61)	1.08 (0.42-2.73)

- It is the ERG preference to model the OS and PFS of ibrutinib using HR from exploratory network meta-analysis undertaken by ERG rather than the company's MAIC .

Summary of AEs and SAEs

Event	VEN+R (n=194)	BR (n = 188)	ERG-calculated p-values
Grade 3 or 4 AE — with at least 2% difference in incidence between groups — no. of patients (%)	159 (82.0)	132 (70.2)	0.01
Total no. of events	335	255	
Discontinuations due to AEs	24	11	0.03
Grade 3 or 4 AEs with at least 2% difference in incidence between groups — no. of patients (%)	130 (67.0)	104 (55.3)	0.02
SAEs — with at least 2% incidence in either group- no. of patients (%)	90 (46.4)	81 (43.1)	0.52

Overall, there were more AEs in the VEN+R arm (n = 335) than in the BR arm (n = 255). However, it is not specified in the company submission or the CSR if AEs were treatment-related.

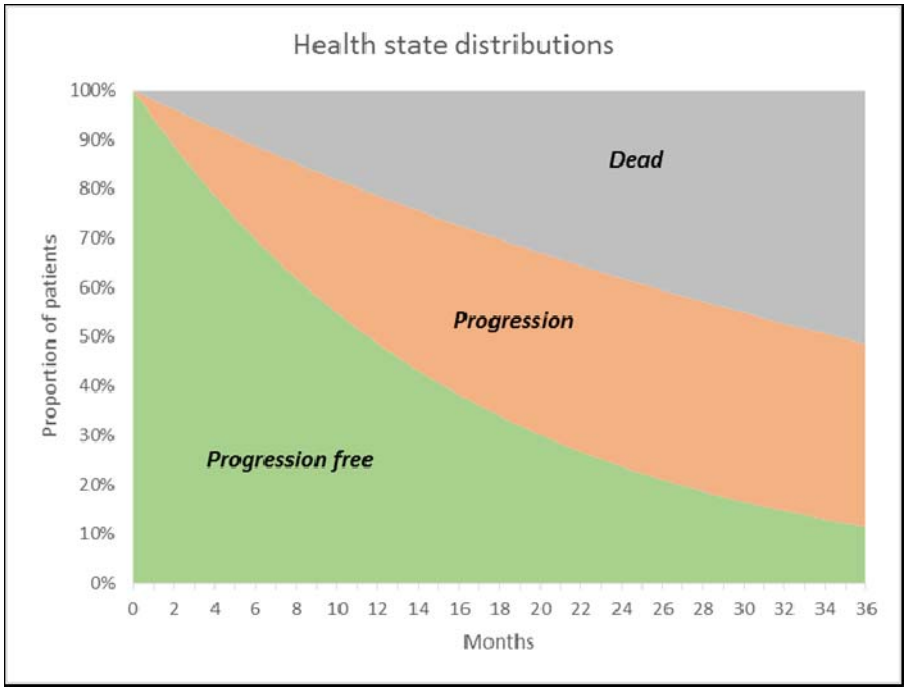
Cost effectiveness

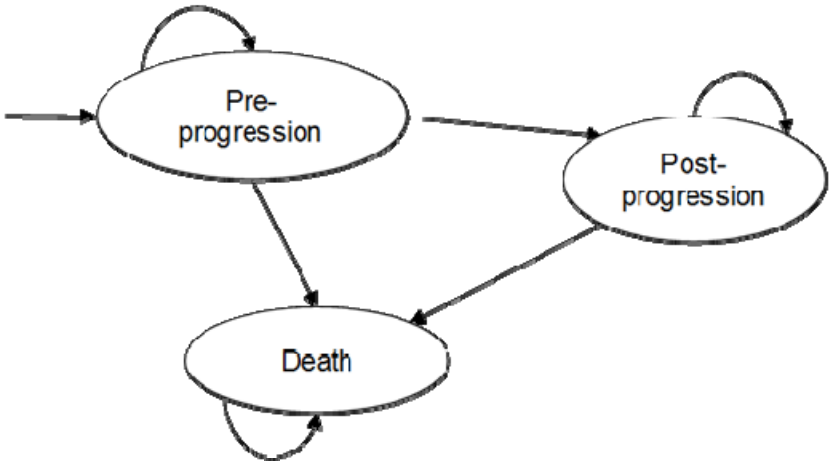
Key issues- cost

- Which method of estimating the relative benefit of VEN+R compared with ibrutinib is more appropriate – the company's (MAIC estimates) or ERG's (NMA estimates)?
- Is the extrapolation valid based on immature OS data?
- What's the most appropriate survival extrapolation for VEN+R and comparators?
- Is a two year stopping rule for VEN+R appropriate?
- What is the most plausible ICER for decision making?

Company's economic model

- De novo partitioned survival model
- Based on data from Murano trial
- Discount rate of 3.5% per annum was applied
- Lifetime horizon – estimated 30 years





Company's model: Summary

Input	Source/assumption
Population	Full population include refractory and relapsed (R/R) CLL patients. The company provided subgroup analysis for R/R CLL population: •Patients WITH a deletion of chromosome 17p (del(17p) and/or TP53 mutation) •Patients WITHOUT a deletion of chromosome 17p (non-del(17p) and/or TP53 mutation)
Intervention/ comparator	Venetoclax with rituximab is compared with ibrutinib or idelalisib with rituximab
Treatment effectiveness	Clinical outcomes included were response (CR/PR), PFS, RFS and OS, minimal residual disease negative rate, HRQoL, adverse events of treatment, del(17p)/TP53 status.
	The company modelled PFS and OS jointly across both arms, assuming proportionality and the same parametric form between OS and PFS.
	OS and PFS endpoints based on the investigator assessment and IRC assessment, clinical cut off data May 2017.
Adverse Events	Grade 3 and 4 treatment related events that occurred in at least 5% of patients in any of the three main trials (MURANO, RESONATE and Study 116) were included.
HRQoL	EQ-5D-3L data were collected in MURANO trial. However, the health state utility values used in the economic model are taken from literature sources that were used in TA487 (venetoclax monotherapy) and TA359 (idela+R).

Overall survival for VEN+R

The Company base case model selection for the extrapolation of VEN+R PFS and OS is the Weibull.

Progression-free survival for VEN+R

The base case model selection for the extrapolation of VEN+R PFS and OS is the Weibull.

ERG's Overall survival for VEN+R - jointly fitted parametric models

Company's and ERG's method of fitting comparator survival curves

- In order to estimate the comparator survival curves, estimates of relative treatment efficacy (PFS and OS hazard ratios) obtained through the MAIC were combined with the VEN+ R parametric survival curves.
- The KM data from the MAIC was taken and separate models were parameterised using the Weibull distribution.
- The graph shows company's and ERG's OS predictions of ibrutinib in MURANO population alongside observed effect of ibrutinib on OS from RESONATE.

ERG's comments on jointly fitted curves (1)

- The ERG preferred curve is Gamma for both OS and PFS rather than Weibull as it provides greater difference in the estimates between the pre- and post- progression life years. It also provides better estimates in comparison to other models, it falls within the range of estimates from the clinical experts and has a lower AIC than the Log-logistic.
- To fit a curve for ibrutinib the company used HR obtained from the MAIC to the parametric curves fitted to the VEN+R arm of the MURANO. It is the preference of the ERG to model the OS and PFS of ibrutinib using HR from the ERG's NMA as it results in a plausible balance of PFS and PPS life years for ibrutinib.
- There was no comparisons of IDELA+R to BR to generate alternative HRs. The ERG maintained the HRs estimated by the company, but applied them to the Gamma PFS and OS curves.

Undiscounted LY estimates for VEN+R

	PFS	OS	PFS LY (% of total LY)	PPS LY (% of total LY)	Total LY
Company base-case	Weibull	Weibull	[redacted]	[redacted]	[redacted]
ERG preferred assumptions	Gamma	Gamma	[redacted]	[redacted]	[redacted]
ERG scenario	Log-logistic	Log-logistic	[redacted]	[redacted]	[redacted]

ERG's comments on jointly fitted curves (2)

Undiscounted Life Year (LY) estimates of ibrutinib					
	PFS and OS Curves and HR	HR Source	PFS LY (% of total LY)	PPS LY (% of total LY)	Total LY
Company base-case	Weibull [redacted]	Company MAIC	[redacted]	[redacted]	[redacted]
ERG preferred assumptions	Weibull [redacted]	ERG NMA	[redacted]	[redacted]	[redacted]
ERG scenario	Gamma [redacted]	ERG NMA	[redacted]	[redacted]	[redacted]
Undiscounted LY estimates of IDELA+R					
Company base-case	Weibull	MAIC (IDELA+R)	[redacted]	[redacted]	[redacted]
ERG preferred assumptions	Gamma	MAIC (IDELA +R)	[redacted]	[redacted]	[redacted]
ERG scenario	Gamma	MAIC (IDELA +BR, adjusted)	[redacted]	[redacted]	[redacted]

Company's model: Health-related quality of life

- Health-state utility values derived from the MURANO trial were not used in the economic model as they were heavily skewed and lacked face validity compared with general UK adult population utility norms.
- The company used utility values from the literature source used in previous NICE technology appraisals including venetoclax monotherapy (TA487) and IDELA+R (TA359).
- The company included disutility associated with adverse events in the model and adjusted for age-related utility deterioration.

State	Utility value: mean (standard error)	95% CI (assuming SE=10% of the mean)	Literature Source
Pre-progression	0.748	0.589-0.879	Data from study 116
Post-progression	0.600	0.480-0.714	An ERG report by Dretzke et al. on the cost effectiveness of rituximab

ERG comments:

- Source and approach to choosing utility values by the company is appropriate and consistent with the previous estimates of health utility in R/R CLL patients.
- Patient population in the current appraisal of VEN+R is likely to be similar to the populations considered in TA487 and TA359.
- The company disutility values and approach to adjusting for age-related utility deterioration is appropriate.

Costs and resource use

- Model includes following costs:
  - Intervention and comparators' costs and resource use **(**active treatment costs: venetoclax, rituximab, ibrutinib, drug acquisition costs, drug administration costs (accounting for overheads, qualifications, and salary on costs, hospital-based scientific and professional staff, pharmacist time) no drug wastage costs were included in the model)
  - A two-year stopping rule was applied when calculating intervention costs for VEN+R, whereas treatment with ibrutinib and IDELA+R continued until disease progression
  - Treatment specific monitoring (the costs of Tumour Lysis Syndrome prophylaxis)
  - Health-state unit costs and resource use (routine care and monitoring unit costs: Full blood count, LDH, Chest X-ray, Bone marrow exam, Haematologist visit, Inpatient non-surgical/medical visit, Full blood transfusion)
  - Adverse reaction unit costs and resource use (anaemia, autoimmune haemolytic anaemia, neutropenia, pneumonia, thrombocytopenia)
  - Terminal Care costs (these are applied to all patients who transition to the death health state as a one-off cost)
  - Other healthcare costs (other adverse events, 'routine care and monitoring' including hospital visits, investigations and procedures undertaken during a CLL patient's treatment pathway)

ERG comment:
Uncertainty exists around the sources used to estimate adverse event costs in the economic model. The ERG have performed scenario analyses using estimates for adverse events from other sources identified in the literature.

NICE

Company's base-case results

The Company analysis used:

- PFS and OS hazard ratios from the unanchored MAIC,
- 2-year maximum treatment duration applied to the VEN+R when estimating treatment costs
- Health-state utility values of 0.748 and 0.600 used for the pre-progression and post-progression health states respectively.

Technologies	Total Costs, £	Total QALYs	Inc. Costs, £	Inc QALYs	ICER vs baseline (£/QALY)	Pairwise ICER vs. VEN+R (£/QALY)
With CAA for VEN+R						
IDELA+R	xxxxxxx	2.307	-	-	-	£2,625
VEN+R	xxxxxxx	5.666	-£8,816	-3.358	£2,625	-
Ibrutinib	xxxxxxxx	3.067	-£147,377	-0.759	£194,048	VEN+R dominates ibrutinib

ERG comment: In the company base-case, the PFS is restricted to being equal or lower than OS, resulting in zero post-progression period for ibrutinib.

- The company also conducted the total of 51 scenario analyses for R/R CLL using both list and net prices.
- The company found the model predictions were generally robust with VEN+R continuing to dominate ibrutinib in the majority of the scenario analyses undertaken.

Company's corrected base case model:

corrections to the dosing regimen and treatment costs for VEN+R

- During the clarification stage, the ERG highlighted that the dosing regimen for rituximab needed correcting since it is given in cycles 2 to 7 and not 1 to 6 as it was in the original company model. The company corrected the error and provided updated base-case results generated from the corrected model for the R/R CLL population.

Company base–case corrected model: Company base-case discounted results after ERG applied the corrections to the dosing regimen and treatment costs for VEN+R for R/R CLL population					
Technologies	Total Costs, £	Total QALYs	Inc. Costs, £	Inc. QALYs	ICER vs. VEN+R (£/QALY)
With CAA for VEN+R					
VEN+R	[redacted]	5.666	-	-	
Ibrutinib	[redacted]	3.067	-£135,650	2.599	VEN+R dominates ibrutinib
IDELA+R	[redacted]	2.307	£11,726	3.358	£3,492

ERG scenario analysis (1)

corrected model and using population data from RESONATE and Study 116

- The ERG believes that the modelled population should be taken form the comparator trial population (RESONATE and Study 116) when using the MAIC estimates and not from the MURANO trial since HRs were taken from the adjusted MAIC, for both Ibrutinib and idela+R.

Technologies	Total Costs, £	Total QALYs	Inc. Costs, £	Inc. QALYs	ICER vs. VEN+R (£/QALY)
Changed modelled population to RESONATE compared with ibrutinib (R/R CLL population)					
With CAA for VEN+R					
VEN+R	xxxxxxxx	5.55	-	-	
Ibrutinib	xxxxxxxx	3.017	-£133,765	2.533	VEN+R dominates ibrutinib
Changed modelled population to Study 116 cohorts compared with IDELA+R (R/R CLL population)					
With CAA for VEN+R					
VEN+R	xxxxxxxx	5.24	£102,033	-	
IDELA+R	xxxxxxxx	2.156	£13,815	3.084	£4,480

Minimal impact on the cost-effectiveness estimates

ERG scenario analysis (2)

corrected model and change to OS HR compared with ibrutinib

- The anchored MAIC analyses was conducted by the company assuming that relative efficacy of VEN+R vs. ibrutinib+BR could be extended to VEN+R vs. ibrutinib single-agent.
- Based on that assumption the ERG estimated scenario applying the mean, lower and higher 95% CI estimates of the OS HR in comparison with ibrutinib in R/R CLL population.

Technologies	Total Costs, £	Total QALYs	Inc. Costs, £	Inc. QALYs	Pairwise ICER (£/QALY)
Mean OS HR from company's anchored MAIC (adjusted) analysis					
With CAA for VEN+R					
Ibrutinib	XXXXXXXX	4.191			
VEN + R	XXXXXXXX	5.666	-£149,447	1.475	VEN+R dominates ibrutinib
Lower 95%CI estimate of the OS HR (0.201) from anchored MAIC (adjusted) analysis					
With CAA for VEN+R					
Ibrutinib	XXXXXXXX	2.397			
VEN + R	XXXXXXXX	5.666	-£84,647	3.269	VEN+R dominates ibrutinib
Minimal impact on the cost-effectiveness estimates					
Upper 95% CI estimate of the OS HR (1.534) from anchored MAIC (adjusted) analysis					
With CAA for VEN+R					
Ibrutinib	XXXXXXXX	6.546			
VEN + R	XXXXXXXX	5.666	-£172,056	-0.88	£195,564 (SW quadrant)
This suggests that VEN+R is cheaper but also generated fewer QALYs than ibrutinib					

ERG scenario analysis (3)

corrected model and change to OS HR compared with IDELA+R

- The company provided HRs for OS and PFS for VEN+R vs IDELA+BR based on adjusted anchored MAIC analysis but there is no published evidence to suggest IDELA+R and IDELA+BR have similar efficacy.
- In the absence of reliable comparative evidence, the ERG conducted a sensitivity analyses assuming similar effect for VEN+R and IDELA+R.

Assumed an OS HR of 1 for VEN+R vs. IDELA+R (R/R CLL population)					
Technologies	Total Costs, £	Total QALYs	Inc. Costs, £	Inc. QALYs	Pairwise ICER (£/QALY)
With CAA for VEN+R					
IDELA+R	xxxxxxxx	5.154			
VEN + R	xxxxxxxx	5.666	-£14,944	0.512	VEN+R dominates IDELA+R

Under this assumption, VEN+R was cheaper and generated more QALYs than IDELA+R

ERG scenario analysis (4)

alternative method of estimating hazard ratio for VEN+R vs. ibrutinib

- The ERG conducted an alternative indirect comparison using a fixed-effect NMA to compare survival outcomes for VEN+R vs. ibrutinib as they found OS HRs from adjusted unanchored MAIC analysis highly uncertain.
- ERG applied HRs from the indirect comparison to corrected base-case model.

Corrected model: used central estimate of PFS and OS HR for VEN+R vs. ibrutinib from ERG's NMA (R/R CLL population)					
Technologies	Total Costs, £	Total QALYs	Inc. Costs, £	Inc. QALYs	Pairwise ICER (£/QALY)
With CAA for VEN+R					
Ibrutinib	[redacted]	6.019			
VEN + R	[redacted]	5.666	-£279,766	-0.354	£790,988 (SW quadrant)

VEN+R was cheaper but also generated fewer QALYs compared with ibrutinib

Summary of ERG's scenario analysis

Assumptions	VEN+R ICER
Changed modelled population to the RESONATE compared with ibrutinib (R/R CLL population)	Dominant
Changed modelled population to Study 116 cohorts compared with IDELA+R (R/R CLL population	£4,480
Mean OS HR from company's anchored MAIC (adjusted) analysis (R/R CLL population)	Dominant
Lower 95%CI estimate of the OS HR from anchored MAIC (adjusted) analysis (R/R CLL population)	Dominant
Upper 95% CI estimate of the OS HR from anchored MAIC (adjusted) analysis (R/R CLL population)	£195,564 (SW quadrant)
Assumed an OS HR of 1 for VEN+R vs. IDELA+R (R/R CLL population)	Dominant
*Corrected model: used central estimate of PFS and OS HR for VEN+R vs. ibrutinib from ERG's indirect comparison analysis (R/R CLL population)	£790,988 (SW quadrant)

* This is the only assumption used in the ERG preferred base case

Further exploratory analyses undertaken by ERG

The ERG conducted a series of exploratory analysis based on:

- the corrected model to investigate the impact of assuming alternative parametric modelling of PFS and OS and
- use of higher estimates of routine care costs and TLS prophylaxis costs based on the figures in TA487 and adverse events costs based on figures reported in TA439.

*Changed PFS and OS parametric curves from joint-Weibull to joint-Gamma: VEN+R vs ibrutinib (R/R CLL population)					
Technologies	Total Costs, £	Total QALYs	Inc. Costs, £	Inc. QALYs	ICER vs. VEN+R (£/QALY)
With CAA for VEN+R					
VEN+R	[redacted]	6.04	-	-	
Ibrutinib	[redacted]	3.157	-£142,716	2.884	VEN+R dominates ibrutinib
IDELA+R	[redacted]	2.351	£10,711	3.69	£2,903
Corrected model: changed TLS prophylaxis, adverse events costs and routine care costs (R/R CLL population)					
With CAA for VEN+R					
VEN+R	[redacted]	5.666	-	-	
Ibrutinib	[redacted]	3.157	-£142,716	2.884	VEN+R dominates ibrutinib
IDELA+R	[redacted]	2.307	£19,123	3.358	£5,694

Implementing all these changes together had minimal impact on the ICER

* This is the only assumption used in the ERG preferred base case

ERG's preferred base-case model for the ibrutinib comparison

- The ERG's preferred base-case model for the ibrutinib comparison involves making the following assumptions and changes to the company corrected base-case model:
  - Changing the parametric survival curves from joint-Weibull to joint-Gamma for both PFS and OS (slide 20)
  - Changing the unanchored MAIC PFS and OS HRs to ERGs indirect comparison using estimates of PFS and OS for ibrutinib vs BR reported in Hillmen (2015) and for VEN+R vs BR based on the MURANO data (slide 18)

Technologies	Total Costs, £	Total QALYs	Inc. Costs, £	Inc. QALYs	ICER vs. VEN+R (£/QALY)
Using Gamma curves and data from ERGs NMA					
With CAA for VEN+R					
VEN+R	xxxxxxxx	6.04	-	-	
Ibrutinib	xxxxxxxx	6.431	-£322,979	-0.39	£827,252 (SW quadrant)

VEN+R was cheaper but also generated on average fewer QALYs compared with ibrutinib
The ERG preferred base-case corrected model produced similar estimate of incremental costs as the company's base-case corrected model but differed in the direction of incremental QALYs generated

*ICER including the ibrutinib PAS will be shown in Part 2 slides

Company's Subgroup analysis

The company explained that del(17p) and TP53 mutation are known to negatively affect a patient's prognosis, thus patients with this mutation would generally have a lower survival than the whole R/R CLL population and those patients who do not have this deletion or mutation.

Technologies	Total Costs, £	Total QALYs	Inc Costs, £	Inc QALYs	ICER vs. baseline (£/QALY)	Pairwise ICER VS. VEN+R (£/QALY)
Company's base-case results for subgroup of patients with del(17p)/TP53 mutation						
With CAA for VEN+R						
IDELA+R	xxxxxxxx	2.045	-	-	-	£6,013
VEN + R	xxxxxxxx	5.132	-£18,558	-3.087	£6,013	-
Ibrutinib	xxxxxxxxx	2.726	-£127,669	-0.681	£187,556	VEN+R dominates ibrutinib
Company's base-case results for subgroup of patients without del(17p)/TP53 mutation						
With CAA for VEN+R						
IDELA+R	xxxxxxxx	2.411	-	-	-	£1,333
VEN + R	xxxxxxxxx	5.869	-£4,608	-3.458	£1,333	-
Ibrutinib	xxxxxxxxx	3.193	-£152,538	-0.782	£194,985	VEN+R dominates ibrutinib

ERG's preferred base-case analysis including subgroup of patients with and without del(17p)/TP53 mutation for the ibrutinib comparison

ERG preferred base–case corrected model (del(17p)/TP53 mutation) compared with ibrutinib					
Technologies	Total Costs, £	Total QALYs	Inc. Costs, £	Inc. QALYs	ICER vs. VEN+R (£/QALY)
With CAA for VEN+R					
VEN+R	[redacted]	5.494	-	-	
Ibrutinib	[redacted]	5.87	-£269,728	-0.376	£718,043 (SW quadrant)
ERG preferred base–case corrected model (nondel(17p)/TP53 mutation)) compared with ibrutinib					
With CAA for VEN+R					
VEN+R	[redacted]	6.245	-	-	
Ibrutinib	[redacted]	6.638	-£343,718	-0.393	£873,858 (SW quadrant)

The results of these analyses were similar to the ERGs preferred base-case results with VEN+R being cheaper but also generating fewer QALYs compared with ibrutinib in both list and net prices comparison

ERG's preferred base-case model for the IDELA+R comparison

- The ERG was unable to conduct a preferred base-case model for the comparison with IDELA+R because no robust estimates of relative efficacy between VEN+R vs. IDELA+R was available.

End of life considerations

End of life criteria:

- the treatment is indicated for patients with a short life expectancy, normally less than 24 months and
- there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment.

In addition, the Appraisal Committees will need to be satisfied that:

- the estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review) and
- the assumptions used in the reference case economic modelling are plausible, objective and robust.

The company and ERG agree that this intervention does not meet the end of life criteria because the patient life expectancy is more than 24 months (4.64 years).

Innovation and equality

- The venetoclax plus rituximab treatment is a breakthrough therapy offering a step change for patients with relapsed CLL who have received at least one prior therapy.
- This treatment offers patients a good chance of achieving an enduring remission and MRD negative status without the associated risks of repeated lines of chemotherapy or other agents that do not offer a chance of MRD negativity.
- The current standard treatments have failed or caused severe side effects, there is a need for a more innovative treatment with less significant side effects like venetoclax plus rituximab.
- Chemoimmunotherapy is unsuitable in most cases in an elderly population or those with 17p or TP53 mutation. Chemoimmunotherapy is associated with a higher risk of febrile neutropenia , lower overall response rates and shorter progression free survival than venetoclax plus rituximab.

- No issues equality issues raised during scoping or company submission/ patient professional statements.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID 1097]

Document B

Company evidence submission

June 2018

File name	Version	Contains confidential information	Date
2. ID 1097 [REDACTED]_VenR_CLL_NICE Document B_Updated CI_17-08-2018	**1**	**NO**	**17/08/2018**

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TABLES AND FIGURES

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List of Abbreviations

Acronym	Definition
1L	First-line
2L	Second-line
3L	Third-line
AE	Adverse event
Adj	Adjusted
AdViSHE	Assessment of the Validation Status of Health-Economic decision models
AHA	American Hematology Association
AIC	Akaike Information Criterion
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASO-PCR	Allele-specific oligonucleotide polymerase chain reaction
ASH	American Society of Hematology
AUC	Area under the curve
AWMSG	All Wales Medicines Strategy Group
BCL-2	B-cell lymphoma 2
BCR	B-cell receptor
BCRi	B-cell receptor inhibitor
BCRi-F	B-cell receptor inhibitor failure
BCRP	Breast cancer resistance protein
BCSH	British Committee for Standards in Haematology
BEN	Bendamustine
BIC	Bayesian information criterion
BIM	Budget impact model
BNF	British National Formulary
BR	Bendamustine plus rituximab
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CAP	Cyclophosphamide, Adriamycin and Cisplatin
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CEM	Cost- effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisolone
CI	Confidence interval
CIC	Commercial in confidence
CLL	Chronic lymphocytic leukaemia
CR	Complete response rate
CRCL	Creatinine clearance

CRI	Incomplete hematopoietic recovery
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVP	Cyclophosphamide, vincristine, prednisolone
DEL(17p)	chromosome 17p deletion
DSU	Decision support unit
DOR	Duration of response
EAMS	Early Access To Medicines Scheme
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EHA	European Hematology Association
EMA	European Medicines Agency
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Version 3.0
EPAR	European public assessment reports
EQ-5D	EuroQoL Five-Dimension
ER	Emergency room
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EU	European Union
FCR	Fludarabine, cyclophosphamide, rituximab
FDA	US Food and Drug Administration
FISH	Fluorescence in situ hybridization
FTD	Fixed Treatment Duration
G-CSF	Granulocyte-colony stimulating factor
GI	Gastrointestinal
GP	General practitioner
HBV	Hepatitis B vaccine
HCHS	Hospital and Community Health Services
HCV	Hepatitis C vaccine
HDMP	High-dose methylprednisolone
HIV	Human immunodeficiency virus
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HTS	High-throughput sequencing
ICER	Incremental cost-effectiveness ratio
IDELA+R	Idelalisib + rituximab
IGHV	Immunoglobulin heavy-chain variable
IPD	Individual patient data

IRC	Independent review committee
ISPOR	International Society of Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
iwCLL	International Workshop on Chronic Lymphocytic Leukaemia
KM	Kaplan-Meier
LDH	Lactate Dehydrogenase
LRF	Leukaemia Research Fund
LYG	Life years gained
MAA	Marketing Authorisation Application
MAIC	Matching adjusted indirect comparison
MDASI	MD Anderson Symptom Inventory
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
MID	Minimal important difference
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MUGA	Multiple gated acquisition scan
NA	Not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-CWG	National Cancer Institute-Working Group
NCPE	National Centre for Pharmacoeconomic
nCR	Non-complete response
NHL	Non-Hodgkin lymphoma
NHS	National Health Service
NHS-EED	National Health Service Economic Evaluations Database
NICE	National Institute for Health and Care Excellence
NMB	Net Monetary Benefit
NO.	Number
NR	Not reached
OBI	Obinituzumab
OD	Once daily
OFA	Ofatumumab
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PartSA	Partitioned survival analysis
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PICOS	Population Intervention, Comparator, Outcome, Study type

PIM	Promising Innovative Medicine
PPS	Post-progression survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcomes
PR+L	Partial response with Lymphocytosis
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
PT	Prothrombin time
PVC/PE/PCTFE	Polyvinyl chloride/polyethylene/polychlorotrifluoroethylene
QALY	Quality-adjusted life year
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-CLL16	Quality of Life Questionnaire–Chronic Lymphocytic Leukemia 16
R	Rituximab
RCT	Randomised controlled trial
RPTD	Recommended phase 2 dose
R/R	Relapsed or refractory
SACT	Systemic anti-cancer therapy
SAE	Serious adverse event
SCT	Stem cell transplantation
SD	Stable disease
SE	Standard error
SLL	Small lymphocytic lymphoma
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
STA	Single technology assessment
TA	Technology Appraisal
TEAE	Treatment-emergent adverse event
TLS	Tumour lysis syndrome
ToT	Time on Treatment
TSD	Technical support document
TTF	Time to treatment failure
TTNT	Time to next treatment
TTP	Time-to-progression
TTR	Time to first response
ULN	Upper limit of normal
UK	United Kingdom
VAS	Visual analogue scale
VAT	Value-added tax
VEN+R	Venetoclax in combination with rituximab

V-mono	Venetoclax monotherapy
WTP	Willingness to pay

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's anticipated marketing authorisation (MA) for this indication: venetoclax in combination with rituximab (VEN+R) is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy. More specifically, the submission is in-line with the anticipated positioning within the United Kingdom (UK) National Health Service (NHS) treatment pathway:

- Post Chemo-immunotherapy (CIT)

(NB- the cost-effectiveness model includes all relapsed or refractory (R/R) CLL patients who have had at least one therapy in order to make use of the full Phase III trial data set. The majority (58.6%) of patients in the MURANO trial (1) *had one prior therapy while 25.7% had two prior therapies. The remaining patients had more than three prior therapies. Therefore, evidence from the MURANO trial supports the positioning of VEN+R in the setting addressed in the submission)*

The submission is consistent with the NICE final scope and the NICE reference case apart from the comparator of best supportive care (BSC) where AbbVie has provided clear rationale for the differentiation 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	Adults with R/R CLL who have had at least one therapy.	As per Final scope, but more specifically: Adults with R/R CLL in the following population: • Post CIT	The anticipated label wording positions VEN+R for adult CLL patients who have received at least one prior therapy. This is a broad label that includes many lines of therapy. However, the consensus among five UK clinical experts (CLL Forum members) consulted at a UK CLL advisory board was that in clinical practice, VEN+R is likely to be used as depicted in Figure 1. Therefore, the submission is in line with the anticipated UK NHS position of VEN+R.
Intervention	VEN+R	As per Final scope	-
Comparator(s)	• Ibrutinib • Idelalisib in combination with rituximab (idela+R) • BSC (including but not limited to regular monitoring, blood transfusions, infection control, corticosteroids with or without rituximab and psychological support).	• Ibrutinib • Idela+R (*NB: Although idela+R is included in the economic model to satisfy the requirements of the final scope, Idela+R is not considered an appropriate comparator by clinicians since it's use has been superseeded by ibrutinib as the BCRi of choice due to the toxicity profile and lesser effectiveness of idela+R relative to ibrutinib)*	BSC is not an appropriate comparator for this appraisal: • The anticipated position of VEN+R is post CIT in R/R CLL (see • Figure 1) • Patients in this line of therapy have treatment options for which efficacy has been demonstrated and are being used in UK NHS clinical practice such as ibrutinib. Therefore, these patients would not receive BSC in UK NHS clinical practice. • BSC is reserved for later lines of therapy after all treatment options (including ibrutinib) have been exhausted.

Outcomes	The outcome measures to be considered include: • Progression-free survival (PFS) • Overall survival (OS) • Response rates • Minimal residual disease (MRD) negative rate • Adverse effects (AE) of treatment • Health-related quality of life (HRQoL)	As per Final scope	-
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). 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 a NHS and Personal Social Services (PSS) perspective. The availability of any patient access schemes for the comparator technologies will be taken into account. The availability and cost of biosimilar products should be taken into account.	As per Final scope: Economic evaluation was conducted in line with the reference case requirements. The model uses a partitioned survival approach with parametric survival curves fitted onto Kaplan-Meier (KM) plots from the MURANO trial (NCT02005471) to estimate PFS and OS beyond the trial period. (1) The model includes drug administration costs, AE costs, tumour lysis syndrome (TLS) prophylaxis costs, routine care and monitoring costs and terminal care costs. The model analyses include a deterministic base case, a one-way sensitivity analysis, probabilistic sensitivity analyses and a set of scenario analyses. Results are presented discounted, and over a 30-year time horizon (life-long as <1% of R/R CLL patients in the model analyses is alive after 30 years). Cost-effectiveness of treatments is expressed as incremental cost per QALY.	-
Subgroups to be considered	If the evidence allows the following subgroups will be considered:	The following subgroups will be presented in the cost effectiveness section: • Patients with a del(17p) and/or	

	• People with a 17p deletion and/or TP 53 mutation* Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	TP53 mutation* • Patients without a del(17p) and/or TP53 mutation*	
Special considerations including issues related to equity or equality	No equality issues are presented by venetoclax.	As per Final scope.	

Key: AE, adverse event; BSC, Best supportive care; CEM, Cost-Effectiveness Model, CLL, chronic lymphocytic leukaemia; Del(17p), deletion of 17p; HRQoL, health-related quality of life; Idela+R, Idelalisib in combination with rituximab; KM, Kaplan-Meier; MRD, minimal residual disease; NHS, National Health Services; PFS, progression free survival; PSS, Personal Social Services; OS, overall survival; QALY, quality-adjusted life year; R/R, relapsed/refractory; VEN+R, venetoclax in combination with rituximab

*Subgroups will be hereafter called “del(17p)/TP53” and “non-del(17p)/TP53” throughout Document A and Document B for clarity and consistency.

B.1.2 Description of the technology being appraised

The draft Summary of Product Characteristics (SmPC) and the European Public Assessment Report (EPAR) are presented in **Error! Reference source not found.**. Table 2 provides a description of the technology being appraised.

Table 2 Technology being appraised

UK approved name and brand name	Venclyxto® (venetoclax)
Mechanism of action	Venetoclax is a first in class orally available, selective small molecule inhibitor of Bcl-2, an anti-apoptotic protein overexpressed in approximately 95% of CLL cases that restores apoptosis independently of the P53 protein. (2–5) As venetoclax is thought to act downstream of TP53, its mechanism of action provides a rationale for targeting Bcl-2 irrespective of 17p/TP53 status. (4)
MA/ Conformité Européenne mark status	VEN+R in combination with rituximab does not yet have a UK MA for treating CLL. The proposed label wording is: "venetoclax in combination with rituximab is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy". Regulatory submission was made in [redacted]. The anticipated date of Committee for Medicinal Products for Human Use (CHMP) opinion is [redacted] V-mono has a conditional MA in the UK for "'the treatment of chronic lymphocytic leukaemia (CLL) in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor" and for "the treatment of chronic lymphocytic leukaemia CLL in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor". (6) Rituximab intravenous (IV) has a MA in the UK for "the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia". (7)
Indications and any restriction(s) as described in the SmPC	"Venetoclax in combination with rituximab is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy".

Method of administration and dosage	The recommended dose of VEN+R is as follows: • **Titration phase** - venetoclax 20mg oral tablet once-daily for seven days, then gradual weekly increments over five weeks to 400mg once-daily, following this schedule:  • **Post-titration phase** - venetoclax 400mg oral tablets once-daily in combination with rituximab 375 mg/m^2 IV on day one of cycle (a cycle is 28 days) one followed by 500 mg/m^2 on day one of cycles two to six. Rituximab is stopped after cycle six and patients continue taking venetoclax 400mg once-daily for a maximum of 2-years from day one, cycle one of rituximab or until disease progression or unacceptable toxicity.
Additional tests or investigations	Not applicable.
List price and average cost of a course of treatment	Venetoclax: • 14 tab pack (10mg) = £59.87 (Week one, 20mg per day) • 7 tab pack (50mg) =£149.67 (Week two, 50mg per day) • 7 tab pack (100mg) = £299.34 (Week three, 100mg per day) • 14 tab pack (100mg) = £598.68 (Week four, 200mg per day) • 112 tab pack (100mg) = £4,789.47 (Week five onwards, 400mg per day for 28 days) Rituximab: • 500mg/50ml concentrate for solution for infusion vial (Truxima) = £785.84 The average cost of VEN+R for the course of 2-years when assuming 100% compliance and no progression or mortality events is £129,513.
Patient access scheme (if applicable)	Confidential Managed Access Agreement (MAA) with NHS England

Key: Bcl-2, b-cell lymphoma 2; CLL, chronic lymphocytic leukaemia; Del(17p), deletion of 17p chromosome; IV, intravenous; MAA, Managed Access Agreement; NHS, National Health Service; SmPC, Summary of Product Characteristics; UK, United Kingdom; VEN+R, venetoclax + rituximab; V-mono, venetoclax monotherapy

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview and epidemiology

CLL is the most common of the chronic leukaemias, comprising 30% of all adult leukaemia. (8) CLL is a clonal disease of unknown aetiology, characterised by the accumulation of mature B cells in blood, lymph nodes, spleen, liver, and bone marrow. The progressive accumulation of monoclonal B lymphocytes leads to leucocytosis, lymphadenopathy, hepatosplenomegaly, anaemia, thrombocytopenia, neutropenia, bone marrow failure, recurrent infections and systemic symptoms (fatigue, loss of appetite, weight loss, night sweats and shortness of breath when exercising). (9)

Recurrent genetic abnormalities (deletions or mutations) can be identified in the majority of cases of CLL. The disease is also genetically heterogeneous, and subject to clonal variation during the disease course with the emergence of treatment resistant sub-clones, especially following DNA damaging chemotherapy. Mutation of the tumour suppressor gene TP53 (via deletion of the short arm of chromosome 17 (del[17p]), which contains TP53, or mutation of the TP53 gene sequence) plays a critical role in cancer development and mediates resistance to chemotherapy. (10) TP53 dysregulation is observed in 5-10% of untreated CLL patients but is increasingly common with disease progression and is present in up to 40-50% of patients with refractory disease. (11) Treatment of patients with relapsed disease and high risk genetic subtypes (including TP53 dysregulation) is an area of unmet need with a requirement to identify effective therapies with alternative mechanisms of action and acceptable side effect profiles. (12,1)

In England, the annual European age-standardised incidence of CLL is 6.5 new cases per 100,000 with an estimated 3,252 new diagnoses in 2015. (13–15)

Survival of CLL patients is observed to be significantly shorter than that of the age-matched general population for patients aged <55-years ($p<0.001$), 55-64-years ($p<0.001$), and 65-74 years ($p<0.001$) at CLL diagnosis; and a trend of shorter survival for those ≥75-years albeit not statistically significant ($p=0.136$). (16)

B.1.3.2 Disease burden

Patients with CLL, including those with del(17p)/TP53, have reduced Health-related quality of life (HRQoL). HRQoL in patients with CLL is associated with a variety of factors, including disease stage and severity, patient age and comorbidities, treatment effects, and patient expectations. (17,18)

Disease progression and increased fatigue in CLL are often closely associated, and both have been shown to negatively impact the HRQoL of patients. (18–20) In the multinational, randomised Leukaemia Research Fund (LRF) CLL4 trial, patients were assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) over a 5-year follow-up period. Results from the 409 analysed patients showed that disease progression had a negative impact across all 15 QoL domains when

compared to remission. Across follow-up time points from baseline up to 5-years, patient-reported HRQoL was most strongly correlated with fatigue (mean r=0.72) as well as role functioning (mean r=0.74). (20) Therefore, in addition to direct impact on patient's HRQoL, as CLL progresses it can be expected to have an increasingly negative impact on people's carers. (20)

In addition to the described trial evidence, patient experts at a recent NICE appraisal committee meeting (TA429) described how the uncertainty associated with living with CLL greatly affects patients' quality of life. The committee understood that patients with CLL risk infection, and that recurrent infections are common. The patient experts described how patients become isolated from family and friends to protect themselves from infection, which stops them from living a normal life, reduces their contribution to society and can shorten life expectancy. The committee heard from clinical and patient experts that current treatment options are associated with significant adverse effects that are often life threatening, which means that not all patients can have these treatments. The clinical experts also stated that, once treatment is stopped because of disease progression, if no other treatment is available, survival is poor and so additional treatment options are very valuable. A patient expert described the fatigue and illness she had experienced with chemotherapy, and said that repeat chemotherapy had resulted in only a short period of remission. The committee understood the importance of having different treatment options available for treating CLL. (6,21)

The economic burden of CLL is substantial, leading to high lifetime costs for patients, the system and carers. As patients relapse or become refractory to first-line (1L) treatments, costs increase with each subsequent line of treatment. (22,23) Recent evidence suggests that costs associated with this disease are increasing over time. (24) Healthcare resource utilisation is also substantial for patients with CLL. A significant proportion of patients with CLL are hospitalised, even in the early stages of the disease. (25–28) R/R CLL appears to be a key driver of healthcare resource use in patients with CLL. (23) A recent retrospective database analysis found that patients with CLL had significantly increased resource use (inpatient admissions, inpatient days, emergency room (ER) visits, and outpatient visits) during the period after the disease relapsed or became refractory compared to the period preceding progression to R/R CLL. (29)

B.1.3.3 Minimal Residual Disease (MRD)

MRD describes the presence of a very small number of leukaemic cells remaining in the blood or marrow following treatment. Presence of undetectable MRD (also called "MRD negativity") indicates the depth of remission. MRD can be measured in blood and bone marrow by highly sensitive molecular based assays or immunophenotyping. Currently, techniques for assessing MRD have become well standardised, with the six-colour flow cytometry (MRD flow), allele-specific oligonucleotide Polymerase Chain Reaction (ASO-PCR), and high-throughput sequencing (HTS) using the ClonoSEQ assay being reliably sensitive down to a level below one CLL cell per 10,000 leukocytes (10^{-4} CLL cells per leukocyte). Patients will be defined as having undetectable MRD remission if they have blood or marrow with less than one CLL cell per 10,000 leukocytes. The blood generally can be used for making this assessment although it is less sensitive than testing marrow, in particular in cases where therapies preferentially clear the blood but not the marrow (such as monoclonal antibodies). Therefore, it may be important to

confirm that the marrow aspirate also is MRD negative when the blood is found to be MRD negative. (30)

Multiple studies have demonstrated that achieving MRD below 10^{-4} CLL cells per leukocyte in the blood and/or bone marrow (i.e. undetectable MRD or MRD negativity) corresponds to longer PFS. (31)

In December 2015, the European Medicines Agency (EMA) has included undetectable MRD as an intermediate endpoint in a revision document to appendix 4 to the guideline on the evaluation of anticancer medicinal products in man. EMA states that *"undetectable MRD in patients with CLL in clinical complete remission (= MRD response rate) after induction therapy may be used as an intermediate endpoint for licensure in randomised well controlled studies designed to show superiority in terms of PFS"*. (32) In addition, based on studies reporting longer remission, improved OS and PFS for patients with undetectable MRD, the CLL guidelines of the British Society for Haematology (BSH) present MRD as a factor which affects prognosis. (33) The importance of MRD in CLL is furthermore underscored by the publication of the updated International Workshop on CLL (iwCLL) guidelines in March 2018: According to the iwCLL update "*Prospective clinical trials have provided substantial evidence that therapies that are able to eradicate MRD usually result in an improved clinical outcome*". (30)

(NB- Please note that the cost-effectiveness model in this submission does not include MRD and response status of patients as comparators data is not available.)

B.1.3.4 NICE CLL guidelines/guidance

Table 3 below outlines NICE guidelines and guidance related to this appraisal. (34)

Table 3 NICE guidelines and recommended technologies in CLL

NICE guideline or Technology Appraisal (TA)	Line of treatment: Summarised population according to NICE TA recommendations
Improving outcomes in haematological cancer (2016). NICE guidance 47. Review date TBC. (35)	Applicable to all lines of treatment and treatment settings
Haematological cancers (2017). NICE quality standard [QS150]. (36)	Applicable to all lines of treatment and treatment settings
Venetoclax for CLL. NICE TA487. (6)	1L: CLL with del(17p)/TP53 if B-cell receptor inhibitor (BCRi) is unsuitable 2L: R/R CLL post BCRi 3L: R/R CLL post BCRi 4L: R/R CLL post BCRi
Ibrutinib for previously treated CLL and untreated CLL with 17p deletion or TP53 mutation (2017). NICE TA429. (21)	1L: CLL with del(17p)/TP53 if CIT is unsuitable 2L: R/R CLL 3L: R/R CLL
Idelalisib (in combination with rituximab) for treating CLL (2015). NICE TA359. (37)	1L: CLL with del(17p)/TP53 2L: R/R CLL 3L: R/R CLL (NB: In 2016, the Pharmacovigilance Risk Assessment Committee of the EMA published safety concerns for idelalisib. (38) Furthermore, it is less effective than Ibrutinib. Therefore Idela+R is no longer routinely used in clinical practice)
Obintuzumab in combination with chlorambucil for untreated chronic lymphocytic leukemia (2015). NICE TA343. (39)	1L: CLL; only if full-dose fludarabine, and BEN unsuitable
OFA (ofatumumab) in combination with chlorambucil or BEN for untreated CLL (2015). NICE TA344. (40)	1L: CLL; only if full-dose fludarabine, and BEN unsuitable
BEN for the first-line treatment of chronic lymphocytic leukemia (2011). (41)	1L: CLL (Binet stage B or C), if fludarabine combination chemotherapy is unsuitable
Rituximab for the first-line treatment of CLL (2009). NICE TA174. (42)	1L: CLL; in combination with fludarabine and cyclophosphamide (FCR)
Rituximab for the treatment of R/R CLL (2010). NICE TA193. (7)	2L: R/R CLL; in combination with fludarabine and cyclophosphamide (FCR)
Fludarabine for B-cell CLL (2001). NICE TA29. (43)	2L: CLL

Key: 1L, first-line; 2L, second-line; 3L, third-line; 4L, fourth-line; BCRi, B-cell receptor signalling inhibitor; BEN, bendamustine; CLL: chronic lymphocytic leukemia; del(17p), deletion of 17p chromosome; EMA, European Medicines Agency; FCR, fludarabine + cyclophophamide + rituximab; NICE: National Institute for Care and Health Excellence; OFA, ofatumumab; R/R, relapsed/refractory; TA, Techonology Appraisal

B.1.3.4.1 Current UK CLL clinical pathway of care

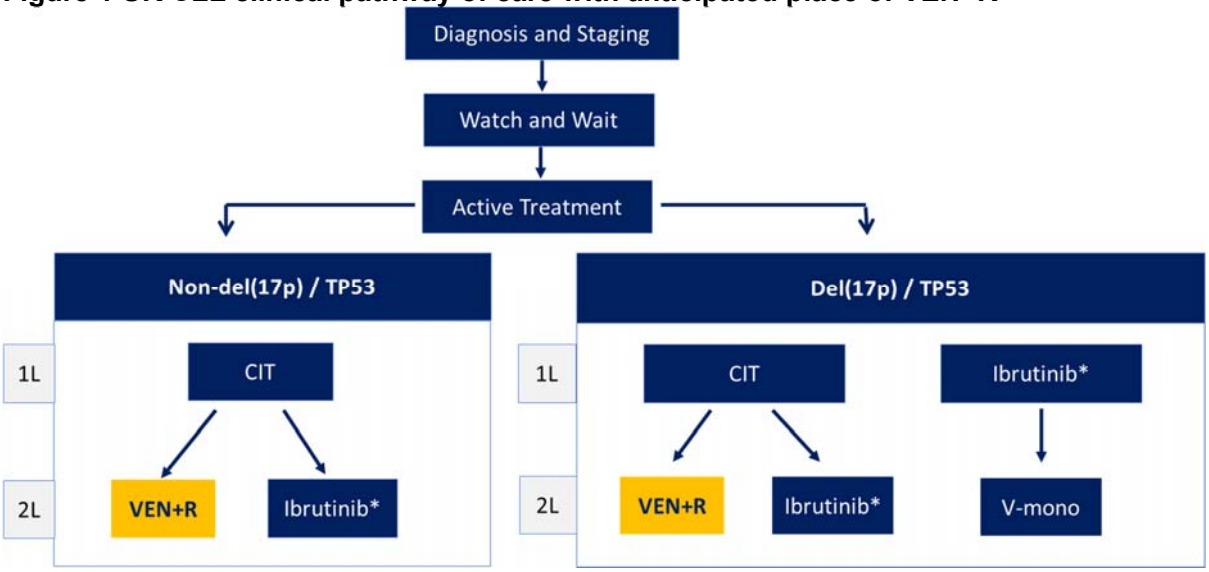
CLL is diagnosed based on the combination of lymphocyte morphology, the detection of >5x10^9/L circulating clonal B cells persisting for greater than three months and a characteristic immunophenotype. (44) Additional investigations including cross sectional imaging and bone marrow biopsy and cytogenetic analysis by fluorescent in-situ hybridisation (FISH). Assessment of additional genetic biomarkers such as immunoglobulin heavy chain (IGHV) sequence, may be undertaken to assess the stage of disease and to provide prognostic information. (45) Disease is staged using the Binet system (common in Europe) or Rai system (common in the US and Japan) (33,46) and with the increasing use of routine blood tests over time, the majority of patients are currently diagnosed with early stage asymptomatic disease. (47)

In line with NICE guidance (NG47) and quality standards for haematological cancers (QS150), adults with CLL should have an integrated report produced by a specialist integrated haematological malignancy diagnostic service (SIHMDS) that is shared with the haemato-oncology multidisciplinary team (MDT). The MDT is responsible for initial treatment and long-term support for adults with CLL. (35,36)

There are several pharmaceutical treatments available for CLL, although none is considered curative. Early intervention with chemotherapy does not improve the natural history of the disease and may drive clonal evolution and later treatment resistance and hence, therapy is only recommended for patients with rapidly progressive or symptomatic disease. (48,49) The time from diagnosis to treatment is variable according to the biological characteristics of the disease (for example the type of chromosomal deletions present or the presence of mutated IGHV sequence although it is often greater than 5-years especially for patients with early stage disease. (50) The aims of treatment are to achieve good quality remissions, leading to durable periods of PFS and to extend long-term OS whilst minimising side effects and toxicities from treatment. (33) Given the prognostic significance of achieving undetectable MRD and its relationship with longer periods of remission and survival, (51)undetectable MRD is now a key treatment goal for patients and clinicians.

Figure 1 presents a simplified version of the clinical pathway of care for adult patients with CLL which takes into account NICE guidance and guidelines published by the British Committee for Standards in Haematology (BCSH). (33,34) This simplified clinical pathway was validated by five UK clinical experts (all members of the UK CLL Forum) in a 2018 CLL advisory board.

Figure 1 UK CLL clinical pathway of care with anticipated place of VEN+R



Key: 1L, first-line; 2L, second-line; CIT, chemoimmunotherapy; Del(17p)/TP53, patients with deletion of 17p chromosome and/or TP53 mutation; Non-del(17p)/TP53, patients without deletion of 17p chromosome and/or TP53 mutation; V-mono, venetoclax monotherapy; VEN+R, venetoclax + rituximab
* Ibrutinib is depicted in this figure as it is the preferred BCRi therapy because of its effectiveness and because of the AE associated with idelalisib with rituximab (idela+R) as per clinical experts' opinion as stated in NICE TA429.

B.1.3.4.2 Current UK 1L treatment for CLL (non-del(17p)/TP53)

The mainstay of treatment in the 1L CLL setting is chemotherapy, typically administered in combination with anti-CD20 monoclonal antibody therapy (chemoimmunotherapy [CIT]). NICE TA174 recommends **FCR**. (42) Patients who are not fit enough to tolerate fludarabine-based therapy have the option of chlorambucil-based therapy or bendamustine (BEN). NICE TA343 recommends **obinutuzumab in combination with chlorambucil** and NICE TA344 recommends **ofatumumab (OFA) in combination with chlorambucil**. (39,40) NICE TA216 recommends **BEN** as an option for 1L CLL (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate. (41)

B.1.3.4.3 Current UK 2L treatment for CLL (non-del(17p)/TP53)

NICE TA429 recommends **ibrutinib** as an option for treating non-del(17p)/TP53 CLL in adults who have had at least one prior therapy. (21) The phase III RESONATE trial comparing ibrutinib with OFA for patients with R/R CLL demonstrated that after a median of 16 months, the median PFS had not been reached with ibrutinib; while for patients randomised to the control arm OFA the median PFS was 8.1 months (hazard ratio (HR) 0.106, 95% confidence interval (CI) 0.073 to 0.153, p <0.0001). (52)

Another BCRi, **idelalisib** in combination with rituximab is also recommended by NICE TA359 for R/R CLL. (37) However, treatment with ibrutinib is preferred because of its effectiveness and because of the adverse effects associated with idelalisib. The EMA has also published safety concerns. (38)

NICE TA193 recommends **FCR** as an option for patients with R/R CLL unless their disease is refractory to fludarabine or has been previously treated with rituximab. (7) However, since the vast majority of CIT eligible patients would have had FCR (or another rituximab containing CIT regimen) 1L, this option is typically not available or appropriate in 2L. (21) BEN in combination with rituximab (BR) is no longer available through the Cancer Drugs Fund (CDF) for R/R CLL and according to the NICE appraisal committee for TA429 (21), it is not available in NHS practice except for a small number of individual funding requests.

In summary, BCRis have changed the treatment landscape for R/R CLL in recent years; reducing the reliance on CIT, which increases the burden of genomic instability and clonal evolution. However, treatment options besides BCRi therapy are limited. There is thus a high unmet need for effective treatments with manageable toxicities. Moreover, treatments with a different mechanism of action to the BCRis are required to broaden the therapeutic armamentarium for R/R CLL.

B.1.3.4.4 Current UK 1L treatment for CLL (del[17p]/TP53)

CIT is not widely used as a treatment option for 1L therapy in patients with del(17p)/TP53 due to the advent of the BCRis, which have considerably improved outcomes for this sub-group of patients with a poor prognosis. The simplified clinical pathway of care as presented in Figure 1 includes ibrutinib as a 1L treatment option in-line with clinical experts' opinion as stated in NICE TA429 "*The clinical experts stated that both ibrutinib and idelalisib have been available on the CDF and, wherever possible, treatment with ibrutinib is preferred because of its effectiveness and because of the adverse effects associated with idelalisib*". (21,37) However, a small number of patients receive CIT as 1L treatment.

NICE TA429 recommends ibrutinib as 1L treatment option for adults with CLL with del(17p)/TP53 and for whom CIT is unsuitable. (21) For R/R patients, in extended follow-up of the RESONATE trial, there was no statistically significant difference in the HR for PFS between the two treatment arms for patients with del(17p)/TP53 (HR 1.421, 95% CI 0.771-2.620 *p*=0.2575). (53)

NICE TA359 recommends idela+R for adults with CLL with del(17p)/TP53. (37) In R/R patients, the second interim analysis of the GS-US-312-0116 trial reported median PFS not reached (NR) for 95 patients with del(17p)/TP53 treated with idela+R compared to four months for patients treated in the placebo arm (HR 0.16, 95% CI 0.07-0.37). (54) In previously untreated patients, published data are sparse but in a trial of 64 older patients with previously untreated disease (NCT01203930), the overall response rate (ORR) following treatment with idela+R for nine patients with del(17p)/TP53 was 100% with no disease progression reported at 36 months follow up. However, 45% of the total patient cohort had to discontinue treatment prematurely due to treatment toxicity. (55)

B.1.3.4.5 Current UK 2L treatment for CLL (del(17p)/TP53)

NICE TA487 recommends V-mono for CLL patients with del(17p)/TP53 whose disease has progressed after treatment with a BCRi. (6) In study M13-982 (open-label, single-arm, pivotal

phase two trial) adults with R/R CLL with del(17p) were included. Median PFS was 27.2 months and median OS was not reached with 71.6% patients being alive at 24 months. (56)

For the small number of patients with del(17p)/TP53 mutation who receive CIT 1L, NICE TA429 recommends ibrutinib as 2L treatment option for adults with CLL who have had at least 1 prior therapy.

B.1.3.5 Anticipated place of VEN+R in clinical practice

As depicted in the pathway in Figure 1, the anticipated place of VEN+R is:

- Post CIT

The anticipated MA covers "patients with CLL (CLL) who have received at least one prior therapy" without specifying specific subpopulations. This is a broad label that includes many lines of therapy. However, the consensus among five UK clinical experts (CLL Forum members) consulted at a UK CLL advisory board was that in clinical practice, VEN+R is likely to be used as described above. Therefore, the submission is in line with the anticipated positioning of VEN+R within the UK NHS treatment pathway.

Based on the anticipated place of VEN+R in clinical practice, the appropriate comparator for this appraisal is ibrutinib. Although idela+R has been included in the economic model to satisfy the requirements of the final scope, Idela+R is not considered an appropriate comparator by clinicians since it's use has been superseeded by ibrutinib as the BCRi of choice due to the toxicity profile and lesser effectiveness of idela+R relative to ibrutinib. BSC is not an appropriate comparator as it is reserved for later lines of therapy after all treatment options (including ibrutinib) have been exhausted.

As described above, patients with R/R CLL still have limited treatment options post CIT, with even fewer options for del(17p)/TP53 compared to non-del(17p)/TP53. BCRis provide an alternative option to 2L treatment with CIT in CLL non-del(17p)/TP53 patients, but idelalisib is used infrequently due to toxicity concerns, leaving just ibrutinib. BCRi therapies are highly effective, but are associated with an indefinite treatment period and do not result in high rates of undetectable MRD. There is a high unmet need for therapies demonstrating improved PFS and OS, that are effective in both del(17p)/TP53 and non-del(17p)/TP53 subpopulations and that demonstrate potential to achieve undetectable MRD. There are also benefits to patients, clinicians and the NHS if these can be achieved with a fixed treatment duration of therapy.

MURANO was a randomised, open label phase 3 trial, which demonstrated that VEN+R has the potential to meet this high unmet need in R/R CLL: offering a highly effective treatment of fixed duration with manageable toxicity, improvement in PFS and high rates of undetectable MRD. After a median follow-up period of 23.8 months, the rate of investigator-assessed PFS was significantly higher in the VEN+R group (32 events of progression or death in 194 patients) than in the BR group (114 events in 195 patients); the 2-year rates of PFS were 84.9% and 36.3%, respectively (HR for progression or death, 0.17; 95% CI 0.11 to 0.25; P<0.001 by the stratified log-rank test). Furthermore, the benefit was maintained across all clinical and biologic subgroups, including the subgroup of del(17p) patients; the 2-year rate of PFS among del(17p) patients was 81.5% in the VEN+R group versus 27.8% in the BR group (HR 0.13; 95% CI, 0.05 to 0.29), and the 2-year rate among non-del(17p) patients was 85.9% versus 41.0% (HR 0.19;

95% CI, 0.12 to 0.32). The benefit of VEN+R over BR was confirmed by an independent review committee (IRC) assessment of PFS and other secondary efficacy end points. (1)

In conclusion, the MURANO trial provides evidence that VEN+R can increase the range of effective treatment options available to treat R/R CLL in both patients with and without del(17p)/TP53 mutation, providing a valuable alternative to BCRis.

B.1.4 Equality considerations

No equality issues are presented by venetoclax.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify clinical evidence for VEN+R and its relevant comparators from randomised and non-randomised studies. In the following sections the review methodology is described.

B.2.1.1 Search strategy

The search strategy was developed and tested as part of the *a priori* protocol to identify relevant studies. The search algorithms used were generated using the PICOS (Population, Intervention, Comparators, Outcomes, Study design) framework and were in-line with the objective to identify clinical evidence for VEN+R and its relevant comparators from randomised and non-randomised studies.

Across all the electronic database searches, articles with published, unpublished or on-going status were permitted. The sources that were searched are provided in Table 4. Additionally, to retrieve further studies not identified through the electronic database search, reference lists of included articles and systematic reviews were screened. Furthermore, the proceedings of conferences held in 2014-2018 were additionally searched. All searches were conducted on 21 July, 2017 with an update of the SLR performed on 30 April, 2018, respectively. Full details of the review methodology are provided in Table 4.

Table 4 Search sources clinical SLR

Type of database	Name of database	Search strategy
Electronic databases	• Medline (via ProQuest) (link) • Embase (via ProQuest) (link)	See **Error! Reference source not found.**
	• The Cochrane Library, incorporating: o Cochrane Database of Systematic Reviews (CDSR) (link) o Cochrane Central Register of Controlled Trials (CENTRAL) (link) o Database of Abstracts of Reviews of Effects (DARE) (link):	See **Error! Reference source not found.** - **Error! Reference source not found.**
Conferences proceedings	• American Society of Haematology (ASH) (link) • British Society for Haematology (BSH) (link) • European Society for Medical Oncology (ESMO) (link) • American Society of Clinical Oncology (ASCO) (link) • International Society For Pharmacoeconomics and Outcomes Research (ISPOR) (link) • International Workshop on Chronic Lymphocytic Leukaemia (iwCLL) (link) • European Hematology Association (EHA) (link)	See **Error! Reference source not found.** - **Error! Reference source not found.**

Key: ASCO, American Society of Clinical Oncology; ASH, American Society of Haematology; BSH, British Society for Haematology; CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Database of Abstracts of Reviews of Effects; EHA, European

Hematology Association; ESMA, European Society for Medical Oncology; iwCLL, International Workshop on Chronic Lymphocytic Leukaemia

B.2.1.1.1 Limits applied to the search strategy

A few limits were applied to the search strategy to ensure that all relevant articles were identified, while minimising the amount of irrelevant results. The limits applied to the search strategy were as follows:

- The search for articles and reports was conducted using English language search terms.
- Except for the searches in Embase, Medline and Cochrane, the publication date for all conference proceedings was set from 21 July, 2014. The approach is justified based on the assumption that all research before 21 July, 2014 are published as full-text journal publications and would be captured through the search in Embase, Medline and Cochrane.
- Publication limits which exclude letters, notes, erratums and editorials were applied. Review articles were included, but were not extracted: instead, these reviews were reported in a separate tab of the selection spreadsheet and were checked for relevant references that may have been missed during the literature review.

B.2.1.2 Study selection of relevant studies

Eligibility criteria for selection

The articles identified underwent a selection process based on pre-specified criteria for inclusion and exclusion. The pre-specified eligibility criteria were based on the PICOS framework which reached beyond the criteria of the NICE final scope[1] (Table 1) and are provided in Table 5.

Table 5 Inclusion and exclusion criteria

PICOS	Inclusion criteria	Exclusion criteria
Population	• Adult patients (≥18 years)[a] • Human • Established R/R CLL • Established R/R CLL including del(17p) R/R CLL	• Patients without established R/R CLL • Paediatric patients (<18 years) • Animal studies • In vitro studies
Intervention	• Ibrutinib • Idela + R • V-mono • Rituximab • VEN+R • High dose methylprednisolone (HDMP) • HDMP + rituximab • Lenalidomide • Oxaliplatin • Acalabrutinib • Fludarabine • Cytarabine	Any interventions not specified under inclusion criteria

[1]During the conduct of the review as the NICE scope was not yet available, thereby the list of comparators was more comprehensive, but the NICE final scope is reflected in the eligibility criteria.

PICOS	Inclusion criteria	Exclusion criteria
	• OFA • Allogenic stem cell transplantation • Alemtuzumab • Flavopiridol • FCR • Chlorambucil • Chlorambucil + rituximab • Obinutuzumab • Obinutuzumab + chlorambucil • BEN • BEN + rituximab • BEN + ibrutinib • BEN + idelalisib	
Comparator	• Any comparator • No treatment • Placebo	NA
Outcomes	• Efficacy Parameter o Time to treatment failure (TTF) o Time to progression (TTP) o PFS o OS o Duration of response (DOR) o Time on treatment (ToT) o Discontinuation rates o Reason for discontinuation o Discontinuation due to AEs o Cumulative events (death, progressions) • Response o ORR o Complete response rates (CR) o Non-complete response (nCR) o Partial complete response (pCR) o Partial response (PR) o Partial response with lymphocytosis (PR+L) o Incomplete hematopoietic recovery (CRi) o Stable disease o Progressive disease (PD) o Change in measured size of lymph nodes from baseline o Change in Absolute lymphocyte count (ALC) o Undetectable MRD o AEs: (Frequency, any Grade, Grade ≥3/4) o Haematological AE o Non-haematological AE o Tolerability	Any outcome not specified under inclusion criteria
Study Design	• Clinical trials • Observational studies	Any study design not described under inclusion criteria

PICOS	Inclusion criteria	Exclusion criteria
Publication Type	• Conference proceedings from July 2014 onwards • Full-text articles • Conference proceedings	• Conference proceedings published before July 2014[b] • Review articles[c] • Notes • Erratum • Comments • Editorials
Language	Publications in English	Others

Key: AE, adverse event; ALC, absolute lymphocyte count; CLL, chronic lymphocytic leukemia; CR, complete response rates; CRi. incomplete hematopoietic recovery; Del(17p), chromosome 17p deletion; DOR, duration of response; FCR, fludarabine + cyclophophamide + rituximab; HDMP, high dose methylprednisolone; idela +R, idelalsib + rituximab; MRD, minimal residual disease; NA, not applicable; nCR, non-complete response; ORR, overall response rate; pCR, partial complete response; PD, progressive disease; PFS, progression-free survival; PR, partial response; PR+L, partial response lymphocytosis; R/R, relapsed/refractory; SD, stable disease; ToT, time on treatment; TTF, time to treatment failure; TTP, time to progression; VEN+R, venetoclax + rituximab; V-mono, venetoclax monotherapy

[a] Studies which reported patient populations both above and below 18 years were included; provided stratified results for the ≥18 population were reported.

[b] This was applicable to the searches in clinical trial databases and conferences proceedings. This approach is justified based on the assumption that all research before July 2014 would have been published as full-text journal publications and would be captured via the search in Embase, Medline and Cochrane.

[c] Review articles were included, but were not extracted: instead, these reviews were reported on a separate tab of the selection spreadsheet and were checked for relevant references that may have been missed during the literature review.

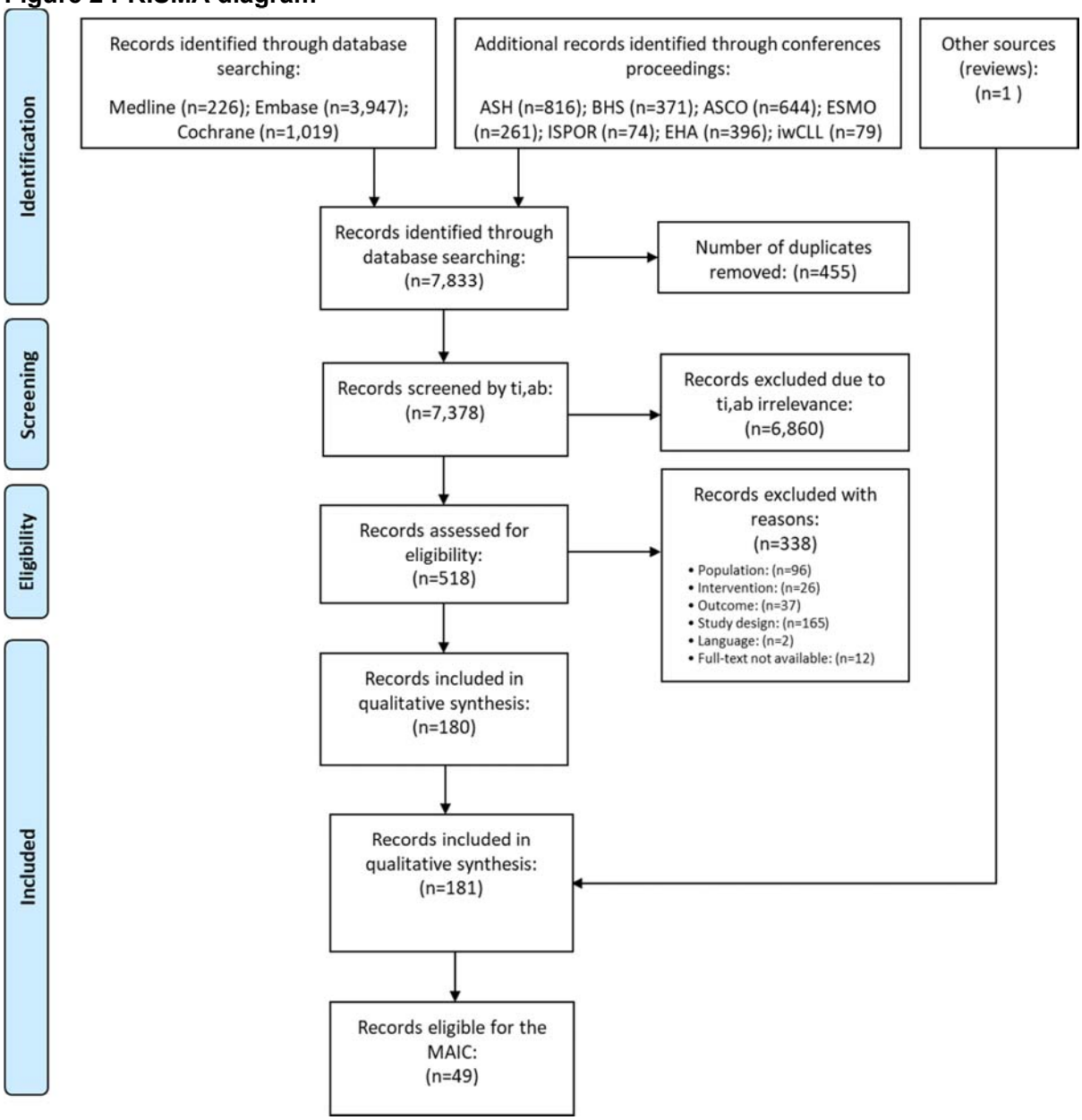
B.2.1.2.1 Study selection process

After the initial removal of duplicate citations, a two-stage screening process (title/abstract and full-text, respectively) by two reviewers working independently in parallel was completed. The identified studies were initially assessed based on title and abstract, followed by a full-text assessment of those articles deemed eligible during the title and abstract screening phase. Any discrepancies were resolved through the involvement of a third reviewer or through a team discussion until a consensus was reached.

B.2.1.2.2 Clinical PRISMA flow diagram

The combined 21 July, 2017 and 30 April, 2018 searches resulted in the identification of 7,833 articles, of which 455 were identified as duplicates and thus excluded. This resulted in a total of 7,378 articles, of which 6,860 publications were excluded based on the review of title and abstract screening, making 518 records eligible for full-text screening. Of these 518 records, 338 were excluded based on the review eligibility criteria (see Table 5). In the end, 181 publications met the inclusion criteria including one more additional source identified by published literature reviews. Of these 181 included publications, 49 publications reported on relevant comparators in-line with the NICE scope and were eligible for the methods of analysis of studies included in the indirect or mixed treatment comparison (ITC) feasibility assessment (see Section B.2.9) (see Figure 2). From these 49 studies, none was identified for the treatment under assessment (i.e. VEN+R).

Figure 2 PRISMA diagram



B.2.2 List of relevant clinical effectiveness evidence

The MURANO trial investigated the VEN+R treatment regimen in R/R CLL and provides evidence on the efficacy and safety for VEN+R treatment in R/R CLL. (1).

Table 6 provides an overview of the MURANO trial.

Table 6 Overview of the MURANO trial

Study	MURANO
Study design	Randomised, open-label, phase III trial

Study	MURANO				
Population	Patients with R/R CLL				
Intervention(s)	VEN+R				
Comparator(s)	BR[a]				
Indicate if trial supports application for marketing authorisation	Yes	x	Indicate if trial used in the economic model	Yes	x
	No			No	
Rationale for use/non-use in the model	The MURANO trial is the only randomised study containing the VEN+R treatment regimen in R/R CLL and is therefore, the most relevant source of efficacy and safety data. A phase I trial was also conducted. (57) The primary outcome of this phase I trial was to assess the safety of VEN+R and to establish the recommended dose of the venetoclax treatment when given in combination with rituximab. Therefore, due to the large difference in trial design, the data was not deemed applicable for the decision problem and was not meta-analysed.				
Reported outcomes specified in the decision problem	Primary endpoint: **Investigator-assessed PFS[b]**				
All other reported outcomes	Secondary endpoints: • **IRC-assessed PFS[b]** • **Investigator-assessed and IRC–assessed PFS among del(17p) patients[b]** • **AEs[b]** • **OS[b]** • Rates of clearance of MRD • Investigator-assessed and IRC–assessed ORR and CR • DOR • EFS (event-free survival) • Time to the next treatment (TTNT) for CLL • HRQoL				

Source: Seymour et al. (1)

Key: AE, adverse event; BR, bendamustine + rituximab; CLL, chronic lymphocytic leukaemia; CR, complete response, DOR, duration of response; Del(17p), chromosome 17p deletion; EFS, event free survival; HRQoL, health-related quality of life; IRC, independent review committee; MRD, minimal residual disease; NA, not applicable; OS, overall survival; ORR, overall response rate; FCR, fludarabine + cyclophophamide + rituximab; PFS, progression-free survival; R/R, relapsed/refractory; TTNT, time to the next treatment; VEN+R, venetoclax + rituximab

[a] BR was selected as the comparator arm for the MURANO trial as it was considered the most effective regimen for relapsed CLL when the study was initiated. (58) Furthermore, BR was considered a reasonable option per the National Comprehensive Cancer Network and ESMO guidelines. Other available recommended and/or approved therapies in the R/R CLL setting were either associated with high toxicity (e.g. FCR, allogeneic stem cell transplantation, high-dose steroid combinations, and alemtuzumab) or had limited effectiveness (e.g., OFA, rituximab, or chlorambucil). (58) Furthermore, BR was recommended as a second-line therapy for fit or elderly patients experiencing short durations of initial treatment response. Although response rate to BR in relapsed CLL with the del(17p) is low, more effective alternatives were not universally available at the time of study initiation in 2014.

[b] Bold reported outcomes were incorporated into the economic model.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

The MURANO trial was an international, randomised, open-label, phase III trial which compared VEN+R with a standard chemoimmunotherapy BR in patients with R/R CLL. The full detail of the trial methodology is provided in Table 7. (1)

Table 7 Summary of MURANO trial methodology

Trial number (acronym)	GO28667 (MURANO) (1)
Location	International, multi-centre trial conducted in 20 countries: Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Italy, Korea, Netherlands, New Zealand, Poland, Russia, Spain, Sweden, Taiwan, UK and USA.
Trial design	• Design: phase III, parallel-arm RCT • Masking: open-label • Duration: median follow-up at recent data cut: 23.8 months
Inclusion criteria	• Patients were eligible for the trial if they were≥ 18 years. • Patients with CLL with R/R disease. (NB: Relapsed: a patient who previously achieved a CR or PR but after a period of 6 months or more demonstrated evidence of progression; Refractory: treatment failure or disease progression within 6 months after the last anti-leukaemia therapy) • Patients treated with at least one but not more than three lines of therapy. • Patients previously treated with BEN only if their DOR was ≥ 2-years. • Patient required treatment in the opinion of the investigator. • Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1 (on a give-point scale, with higher numbers indicating greater disability). • Absolute neutrophil count (ANC) of ≥1000cells/µl. • Platelet count of ≥30,000 cells/µl. • Adequate bone marrow, renal, and hepatic function.
Exclusion criteria	• Patients receiving warfarin or strong CYP3A4/5 inhibitors. • Patients with transformation of CLL to aggressive or central nervous system involvement by CLL. • Patients with previous allogeneic or autologous stem-cell transplant. • Patients with major organ dysfunction, active infection, other active malignancy, current pregnancy or breastfeeding. • Patients receiving warfarin (during venetoclax dose titration) or strong CYP3A4/5 inhibitors.
Settings and locations where the data were collected	Data were collected within a secondary care or hospital settings at 109 sites in 20 countries: Australia (n=12), Austria (n=4), Belgium (n=6), Canada (n=4), Czech Republic (n=6), Denmark (n=5), France (n=13), Germany (n=3), Hungary (n=5), Italy (n=8),

	Korea (n=4), Netherlands (n=7), New Zealand (n=3), Poland (n=6), Russia (n=5), Spain (n=6), Sweden (n=2), Taiwan (n=1), UK (n=4) and USA (n=5).
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) (n=[x]) and comparator(s) (n=[x])	Patients were randomised in a 1:1 ratio to receive VEN+R and BR: • VEN+R (n=194): venetoclax was administered according to a five-week schedule of a gradual increase in the dose titration from 20 mg per day to 400 mg per day. After completion of the dose titration period for venetoclax, IV administration of rituximab (375 mg per square meter of body-surface area for the first dose (day one of cycle one) and 500 mg per square meter thereafter (day one of cycles two through six) was initiated in 28-day treatment cycles, while daily administration of venetoclax was continued. Administration of venetoclax at a dose of 400 mg per day was continued for 2-years (which was calculated from day one of cycle one) unless disease progression or unacceptable toxic effects occurred sooner. • BR (n=195): BEN at a standard dose of 70 mg per square meter was administered IV on days one and two of each 28-day cycle for six cycles in combination with rituximab according to the aforementioned dosing schedule.
Permitted concomitant medication	• Any medication used by a patient from 28-days prior to the initiation of study treatment through to the end of treatment. • Supportive measures for optimal medical care, including the use of growth factors. • Anti-emetic therapy if clinically indicated.
Disallowed concomitant medication	• Any therapies intended for the treatment of leukaemia (outside of study). • Anti-retroviral medications. • Hormone therapy (other than contraceptives, hormone replacement therapy, or megestrol acetate). • Systemic steroid therapy either during or within 7-days prior to the first dose of study treatment with the exception of inhaled corticosteroids for the treatment of asthma or chronic obstructive pulmonary disease, single infusions of hydrocortisone prior to rituximab infusions, topical steroids, or replacement corticosteroid therapy for an inherited or acquired deficiency. • CYP1A2 inhibitors and inducers.
Primary outcomes (including scoring methods and timings of assessments)	• **Investigator-assessed PFS** (pre-specified)[b]

Other outcomes used in the economic model/specified in the scope	• **IRC-assessed PFS**[b] • **Investigator-assessed and IRC–assessed PFS among del(17p) patients**[b] • **AEs**[b] • **OS**[b] • Rates of clearance of MRD[b] • Investigator-assessed and IRC–assessed ORR and CR • DOR • EFS • TTNT for CLL • HRQoL
PRO Outcomes	• HRQoL
Pre-planned subgroups and pre-planned subgroup stratification	Pre-planned subgroups: • Age (<65 vs. ≥65 years). • CLL risk status (low vs. high). High risk: defined as harbouring del(17p) or no response to front-line chemotherapy-containing regimen or relapsed within 12 months after chemotherapy or within 24 months after chemoimmunotherapy. Low risk: defined as relapse more than 12 months after chemotherapy or 24 months after chemoimmunotherapy. • Geographical region (US and Canada, Australia and New Zealand, Western Europe, Central and Eastern Europe, Asia). • Number of prior treatment lines (1,2, ≥3). • Effect of most recent therapy (refractory, relapse). • Del(17p) status (absent, present). • TP53 (unmutated, mutated). • Baseline IGHV mutation status (unmutated, mutated). Pre-planned subgroup Stratification. o 1:1 (VEN+R and BR). o Treatment group randomisation was stratified according to: ▪ The presence or absence of del(17p). ▪ Risk status: high risk vs. low risk. ▪ Geographic region.

Key: AE, adverse event; ANC, Absolute neutrophil count; BEN, bendamustine; BR, bendamustine + rituximab; CLL, chronic lymphocytic leukaemia; CR, complete response; DOR, duration of response; del(17p), chromosome 17p deletion; HRQoL, health-related quality of life; IRC, independent review committee; MRD, minimal residual disease; NA, not applicable; Non-del(17p), non deletion of 17p chromosome; OS, overall survival; ORR, overall response rate; FCR, fludarabine + cyclophophamide + rituximab; IGHV, immunoglobulin heavy-chain variable; IV, intravenous; PFS, progression-free survival; RCT, randomised controlled trial; R/R, relapsed/refractory; V-mono, venetoclax monotherapy; VEN+R, venetoclax + rituximab

[b] Bold reported outcomes were incorporated into the economic model.

B.2.3.1 Endpoints

All patients had baseline tumour assessments and were assessed for response to treatment by the investigator using standard clinical and laboratory examinations and computerised tomography (CT) scans according to iwCLL guidelines. (45)

B.2.3.1.1 Primary endpoint

The primary endpoint is investigator-assessed PFS defined as the time from randomisation to the first occurrence of progression or relapse using iwCLL guidelines (30) or death from any cause; whichever occurs first. All patients who discontinued due to AEs or any reasons other than progression were followed until they withdrew their consent or died and were included in the primary PFS analysis. All patients are followed for OS regardless of progression status. Disease status was evaluated by CT scans of target lesions, blood counts and physical examinations of indicator lesions in up to six of the largest dominant nodes or tumour masses as well as in six extra-nodal lesions. A similar procedure was conducted for non target lesions.

B.2.3.1.2 Secondary Endpoints

Secondary endpoints included: IRC-assessed PFS, investigator- and IRC–assessed PFS in patients with del(17p), protocol-defined investigator and IRC–assessed ORR, MRD, Duration of response (DOR), OS, event-free survival (EFS) and time to next anti-CLL treatment. Further details on the endpoints are discussed below:

- IRC-assessed PFS was assessed by an IRC review using the 2008 criteria of the iwCLL on CLL (30). PFS in patients with del(17p) was assessed by both IRC and investigators in patients with del(17p) identified by FISH-testing.
- Undetectable MRD was defined as blood or marrow samples containing less than one CLL cell per 10,000 leukocytes (10^{-4}). MRD was assessed in all patients in peripheral blood by iwCLL recommended methods, ASO-PCR and flow cytometry, and in bone marrow by flow cytometry (due to sample limitation). For both ASO-PCR and flow cytometry, only samples that had a limit of detection below 10^{-4} were considered. Undetectable MRD rates are reported separately in blood and bone marrow.
- OS was defined as the time from the date of randomisation to the date of death from any cause.
- EFS was defined as the time between the date of randomisation and the date of progressive disease (PD), relapse, death, or the start of a new anti-CLL treatment.
- Time to the next treatment (TTNT) was defined as the time from randomisation to start of new, non-protocol, anti-CLL therapy or death from any cause.
- ORR comprises of complete response (CR) and partial response (PR). The protocol criteria for response were based on the criteria from iwCLL 2008; (45) the definitions of the various levels of response are shown in Table 8 and the criteria are shown in Table 9.

Table 8 Explanation of the various levels of response

Level of response	Explanation/Criteria
CR	All of the criteria need to be met and patients have to lack disease related constitutional symptoms. Lymphoid nodules should be absent and a bone marrow aspiration is required to confirm CR.
CRi	Defined as patients who fulfil the criteria for CR (including bone marrow), but who have persistent cytopenia, and do not show any clonal infiltrate.
PR+L	The presence of lymphoid nodules.
PR	Requires two criteria from group A, if abnormal at baseline to respond plus 1 of the criteria from group B must be met (see Table 9 for group classification).
PD	At least one of the above criteria from group A or B are met or development of transformation to a more aggressive histology (see Table 9 for group classification).
SD	The absence of PD and the failure to achieve a CR, CRi, nPR, PR, or PR with lymphocytosis.

Key: CR, complete response; CRi, incomplete hematopoietic recovery; PD, progressive disease; PR, partial response; PR+L, partial response with lymphocytosis; SD, stable disease

The protocol criteria for response were based on the criteria from the iwCLL 2008 (45) and are provided in Table 9.

Table 9 Protocol criteria for response based on the (iwCLL) 2008 response definitions

Parameter	CR[a]	PR[b]	PD[c]
Group A (tumour load)			
Lymphadenopathy[d]	None >1.5 cm	Decrease ≥50%	Increase ≥50%
Hepatomegaly	None	Decrease ≥50%	Increase ≥50%
Splenomegaly	None	Decrease ≥50%	Increase ≥50%
Blood lymphocytes	<4,000/μL	Decrease ≥50% over baseline	Increase ≥50% over baseline
Marrow	Normocellular, <30% lymphocytes, no B-lymphoid nodules. Hypocellular marrow defines CR with incomplete marrow recovery	50% reduction in marrow infiltrate or B-lymphoid nodules	NA
Group B (function of hematopoietic system, or marrow)			
Platelet count	>100,000/μL	>100,000/μL or increase ≥50% over baseline	Decrease ≥50% over baseline secondary to CLL
Haemoglobin	>11.0 g/dL	>11.0 g/dL or increase ≥50% over baseline	Decrease >2 g/dL over baseline secondary to CLL
Neutrophils[e]	>1500/μL	>1500/μL or ≥50% improvement over baseline	NA

Source: Hallek et al. (45)
Key: CLL, chronic lymphocytic leukemia; CR, complete response; iwCLL, international Workshop on Chronic Lymphocytic Leukaemia; NA, not applicable; PD, progressive disease; PR, partial response
[a] All of the criteria have to be met, and patients have to lack disease-related constitutional symptoms.

[b] At least two of the criteria of Group A plus one of the criteria of Group B have to be met; SD is absence of PD and failure to achieve at least a PR.
[c] At least one of the above criteria of Group A or Group B has to be met.
[d] Sum of the products of multiple lymph nodes (as evaluated by CT scans in clinical trials, or by physical examination in general practice).
[e] These parameters are irrelevant for some response categories.

B.2.3.2 Reliability and validity of endpoints

The reliability, validity and current use of each outcome reported in the MURANO trial (1) in clinical practice is provided in Table 10.

Table 10 Reliability/validity/current use in clinical practice

Outcome	Reliability/validity/current use in clinical practice
Primary endpoint	
PFS	PFS is used in clinical practice and is an important measure of disease control. However, PFS is affected by the timing of assessments and can be prone to investigator bias unless strict criteria for response evaluation are used, as were implemented in the MURANO trial. (1)
Secondary endpoints	
OS	OS is the gold standard endpoint for studies in cancer. Death is definitive, is easily compared across disease sites and is not subject to investigator bias.
Response rate	Response rate provides an indication of the patients who will benefit from treatment. Not all patients who respond to treatment will benefit from treatment, but patients must have an initial response in order to demonstrate benefit from treatment.
MRD	MRD testing is a sensitive methodology for the detection of very small numbers of cancer cells and represents a more robust measure of assessing quality of response to treatment.
TTNT	TTNT is defined as the time from randomisation to start of new non-protocol anti-CLL therapy or death from any cause, it is easily compared across disease sites and can provide an endpoint meaningful to patients given the incurable nature of R/R CLL.
HRQoL	HRQoL is an important measure given the incurable nature of R/R CLL.

Key: HRQoL, health related quality of life; MRD, minimal residual disease; OS, overall survival; PFS: progression-free survival; TTNT, time to next treatment

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The statistical analysis and the definition of the study groups in the MURANO trial are presented in Table 11.

Table 11 Overview of primary hypothesis in the MURANO trial

Primary hypothesis objective	The primary hypothesis of the study is to test the equality of investigator-assessed PFS distributions in the VEN+R and in BR groups.
Calculation of study sample size	The primary endpoint of PFS was used to determine the sample size for the study. Estimates of the number of events required to demonstrate efficacy with regard to PFS are based on the following assumptions: • Two-sided log-rank test at the 0.05 level of significance. • 80% power to detect a HR for VEN+R vs. BR of 0.66, corresponding to an approximate median improvement of 15.2 months to 23 months (34% reduction in risk of a PFS event). • Exponential distribution of PFS. • An annual dropout rate of 5%. • One interim analysis for efficacy.
Primary analysis	The treatment comparison has been performed using a two-sided stratified log-rank test (at the 0.05 significance level, appropriately adjusted for an interim analysis), stratified according to the presence or absence of del(17p), risk status (high or low risk) and geographic region. Sensitivity analysis of the primary endpoint was conducted for PFS by investigator and IRC assessments censoring for: non-protocol therapy prior to disease progression in the ITT population and missing PFS assessments.
ITT population	The ITT population included all randomised patients; data were analysed according to the treatment to which patients were randomised (VEN+R [n=194] BR [n=195]). The ITT population was used for analysis of all efficacy endpoints and baseline characteristics. A per-protocol analysis was not carried out. The safety population was defined as all randomised patients who received at least one dose of study drug and patients were analysed according to the actual treatment received (VEN+R [n=194] BR [n=188]).

Key: BR, bendamustine + rituximab; Del(17p), chromosome 17p deletion; HR, hazard ratio; IRC, independent review committee; ITT, intention to treat; PFS, progression-free survival; VEN+R, venetoclax + rituximab

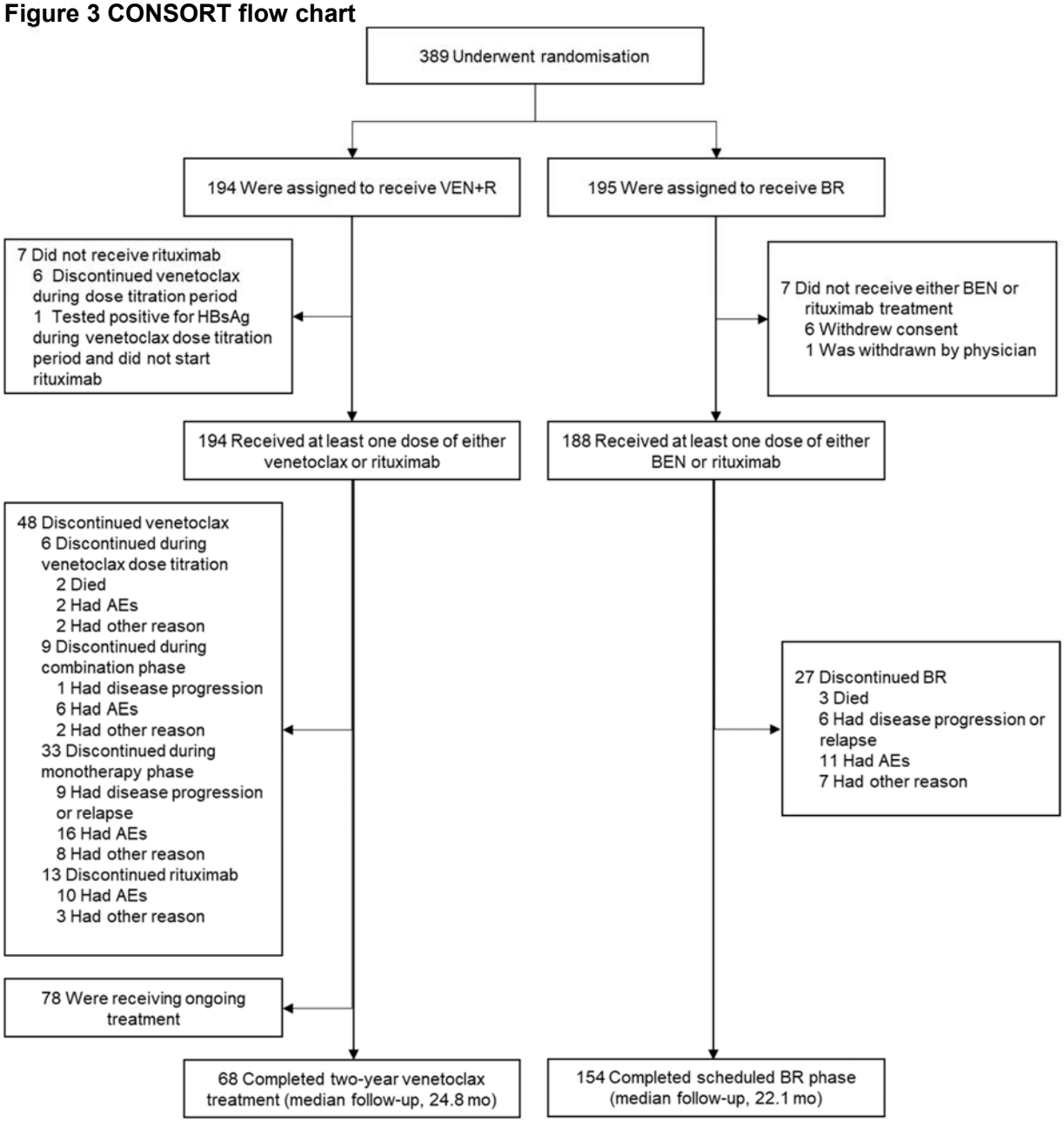
Crossover to treatment with VEN+R after PD was not permitted and therapy after the occurrence of PD was at the investigators' discretion.

B.2.4.1 Participant flow in the relevant randomised controlled trials (RCT)

In the MURANO trial, from March 31, 2014, to September 23, 2015, a total of 389 patients were enrolled at 109 sites in 20 countries and were randomly assigned to receive VEN+R (n=194 patients) or BR (n=195 patients). Of the 194 patients randomised to receive VEN+R, seven patients did not receive rituximab (six patients discontinued venetoclax during dose titration period and one patient tested positive on the HBsAg test during venetoclax dose titration period and did not start rituximab). Of the 195 patients randomised to receive BR; seven patients did not receive any trial treatment (six patients withdrew consent and one patient was withdrawn by physician) (see Figure 3).

In total, 74 patients (19.0%) discontinued from the study at clinical cut-off date. The main reason for study discontinuation was death (15 patients [7.7%] in the VEN+R treatment group and 26 patients [13.3%] in the BR group). Three patients (0.8%) were withdrawn due to physician decision (one VEN+R, two BR) and one patient (0.3%) in the BR group was lost to follow-up. The remaining 25 patients who discontinued the study (seven patients [3.6%] in the VEN+R group, 18 patients [9.2%] in the BR group) withdrew consent. However, the meaningfulness of a comparison of the discontinuation rates between the two treatment groups may be questioned, e.g. due to differences in duration of therapy. Patients in the BR treatment group received 6 x 28-day cycles of treatment whereas patients in the VEN+R treatment group received four to five weeks of venetoclax dose titration followed by six cycles of VEN+R and then continued to receive venetoclax treatment up until 2-years from initiation of combination therapy.

Figure 3 CONSORT flow chart



Source: Seymour et al. (1)
Key: AE, adverse event; BEN, bendamustine; BR, bendamustine + rituximab; VEN+R, venetoclax + rituximab

B.2.4.2 Patient characteristics

Across the two treatment groups, the median age was 65 years (range, 22 to 85), and a majority of the patients (73.8%) were men. In total, 92 of 342 patients (26.9%) who were assessed for del(17p) status had del(17p), 99 of 376 patients (26.3%) who were tested for TP53 mutation status had TP53 mutations, and 246 of 360 patients (68.3%) who were tested for IGHV mutational status had unmutated IGHV. In the MURANO trial, patient characteristics at baseline were well balanced between the two treatment groups (see Table 12).

Table 12 Patient characteristics at baseline

Characteristic	VEN+R (n=194)	BR (n=195)
Sex, n (%)		
Male	136 (70.1)	151 (77.4)
Female	58 (29.9)	44 (22.6)
Age, years		
Median	64.5	66.0
Min–Max	28–83	22–85
ECOG score, n (%)		
N	194	194
0	111 (57.2)	108 (55.7)
1	82 (42.3)	84 (43.3)
2	1 (0.5)	2 (1.0)
Rai staging at diagnosis, n (%)[a]		
N	130	140
Stage 0–II	88 (67.7)	103 (73.6)
Stage III–IV	30 (23.1)	18 (12.9)
Fludarabine refractory, n (%)[b]		
N	191	194
Yes	27 (14.1)	30 (15.5)
No	164 (85.9)	164 (84.5)
Creatinine clearance, n (%)[c]		
N	194	195
<50 mL/min	6 (3.1)	10 (5.1)
≥50 mL/min	188 (96.9)	185 (94.9)
Baseline Tumour lysis syndrome (TLS) risk, n (%)		
N	194	195
High	54 (27.8)	55 (28.2)
Medium	106 (54.6)	104 (53.3)
Low	34 (17.5)	36 (18.5)
ALC, × 10^9/L		
<25	65 (33.5)	61 (31.3)
Platelets, × 10^9/L		
Median (min–max)	113.0 (13.0–419.0)	123.5 (11.0–457.0)

<100 × 10^9/L, %	42.8	33.5
Haemoglobin, g/dL		
Median (min–max)	11.4 (5.5–16.7)	12.0 (6.8–16.1)
<10 g/dL, %	31.4	19. 1
Del(17p) status, n (%)		
N	173	169
Present	46 (26.6)	46 (27.2)
Absent	127 (73.4)	123 (72.8)
TP53 mutation status, n (%)		
N	192	184
Mutated	48 (25.0)	51 (27.7)
Unmutated	144 (75.0)	133 (72.3)
Del(17p) vs. TP53 mutation status, n/N (%)	171	158
Only del(17p)	24 (14.0)	18 (11.4)
TP53 mutation only	19 (11.1)	23 (14.6)
Del(17p) and TP53 mutated	22 (12.9)	22 (13.9)
Del(17p) and TP53 mutated	53 (27.8)	50 (26.6)[d]
Non-del(17p) andTP53 mutated[d]	141 (72.7)	138 (73.4)[d]
IGHV mutational status[e], n (%)[d]		
N	180	180
Mutated	53 (29.4)	51 (28.3)
Unmutated	123 (68.3)	123 (68.3)
Stratification factor: risk status (derived), n (%)		
N	194	195
High	109 (56.2)	118 (60.5)
Low	84 (43.3)	75 (38.5)
Number of prior CLL therapies, n (%)		
N	194	195
1	111 (57.2)	117 (60.0)
2	57 (29.4)	43 (22.1)
3	22 (11.3)	34 (17.4)
>3	4 (2.1)	1 (0.5)
Type of prior CLL therapies, n (%)		
Alkylating agent	182 (93.3)	185 (95.4)
Purine analogue	157 (80.5)	158 (81.4)
Anti-CD20 antibody	153 (78.5)	148 (76.3)
BCRi	3 (1.5)	5 (2.6)

Source: Seymour et al. (1)

Key: ALC, absolute lymphocyte count; BR, bendamustine + rituximab; BCRi, B-cell receptor inhibitors; CLL, chronic lymphocytic leukaemia; Del(17p), chromosome 17p deletion; ECOG, eastern cooperative

oncology group; IGHV, immunoglobulin heavy-chain variable; TLS, tumour lysis syndrome; VEN+R, venetoclax + rituximab

[a] Unknown Rai stage at diagnosis: 12 (9.2%) patients in the VEN+R group and 19 (13.6%) patients in the BR group.

[b] Per investigator assessment. indicating not fludarabine refractory did not mean patients were exposed to fludarabine.

[c] Based on Cockcroft–Gault formula.

[d] Outcomes based on n=188.

[e] Unknown IGHV mutational status: 4 (2.2%) patients in the VEN+R group and 6 (3.3%) patients in the BR group.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The quality assessment for the MURANO trial is provided in Table 13.

Table 13 RCT quality assessment of the MURANO trial

Parameter	Comment
Was randomisation carried out appropriately?	Yes, the randomisation method was appropriate. Randomisation was performed by an interactive voice-/web-based system. Patients were assigned in 1:1 ratio to one of the two treatment groups through a block stratified randomisation procedure according to the presence or absence of del(17p), risk status (high or low risk) and geographic region.
Was the concealment of treatment allocation adequate?	The MURANO trial was open label, using two different methods of administration (oral or IV).
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, the characteristics of the patients were well balanced between the two groups, hence there were no significant differences.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Given that the study was open-label in design and given that the treatment was administered using two different methods (oral or IV); neither the subjects nor the investigators were blinded to treatment. However, the IRC was blinded throughout the study to treatment assignment and relevant clinical data such as response and progression/non-progression.
Were there any unexpected imbalances in drop-outs between groups?	No, in both groups seven patients did not receive full trial treatments but were included in the efficacy analyses since they met the criteria for inclusion in the ITT population: • In the VEN+R group, seven patients did not receive rituximab: six patients discontinued venetoclax during dose titration period and one patient tested positive for HBsAg during venetoclax dose titration period and did not start rituximab. • In the BR group, seven patients did not receive any trial treatment. Sensitivity analysis of the primary endpoint was conducted for PFS by investigator and IRC assessments censoring for: non-protocol therapy prior to PD in the ITT population, missing PFS assessments and stratified log-rank test (as treated).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	None.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, the ITT population included all randomised patients and the data were analysed according to the treatment to which patients were randomised. The ITT population was used for analysis of all efficacy endpoints and baseline characteristics. Yes, appropriate measures were taken to account for missing data, please see Table 11 for summary of censoring methods.

Also consider whether the authors of the study publication declared any conflicts of interest.	Yes, the authors have declared all conflicts of interest. (1)
Consider how closely the trials reflects routine clinical practice in England	The MURANO trial compares VEN+R to BR. At the time of study initiation BR was the most effective treatment in R/R CLL patients with del(17p) in England.

Key: ALC, absolute lymphocyte count; BR, bendamustine + rituximab; Del(17p), chromosome 17p deletion; IRC, independent review committee; ITT, intention to treat; IV, intravenous; PD, progressive disease; PFS, progression-free survival; VEN+R, venetoclax + rituximab

B.2.6 Clinical effectiveness results of the relevant trials

- Treatment with VEN+R resulted in statistically significant and clinically meaningful higher rates of investigator-assessed PFS than BR. The benefit was maintained across all clinical and biologic subgroups and confirmed by the independent assessment of PFS.
- Pre-specified secondary efficacy measures including the CR, ORR and OS showed consistent patterns of clinically meaningful benefit with VEN+R compared to BR.
- VEN+R achieved substantial rates of clearance of MRD.

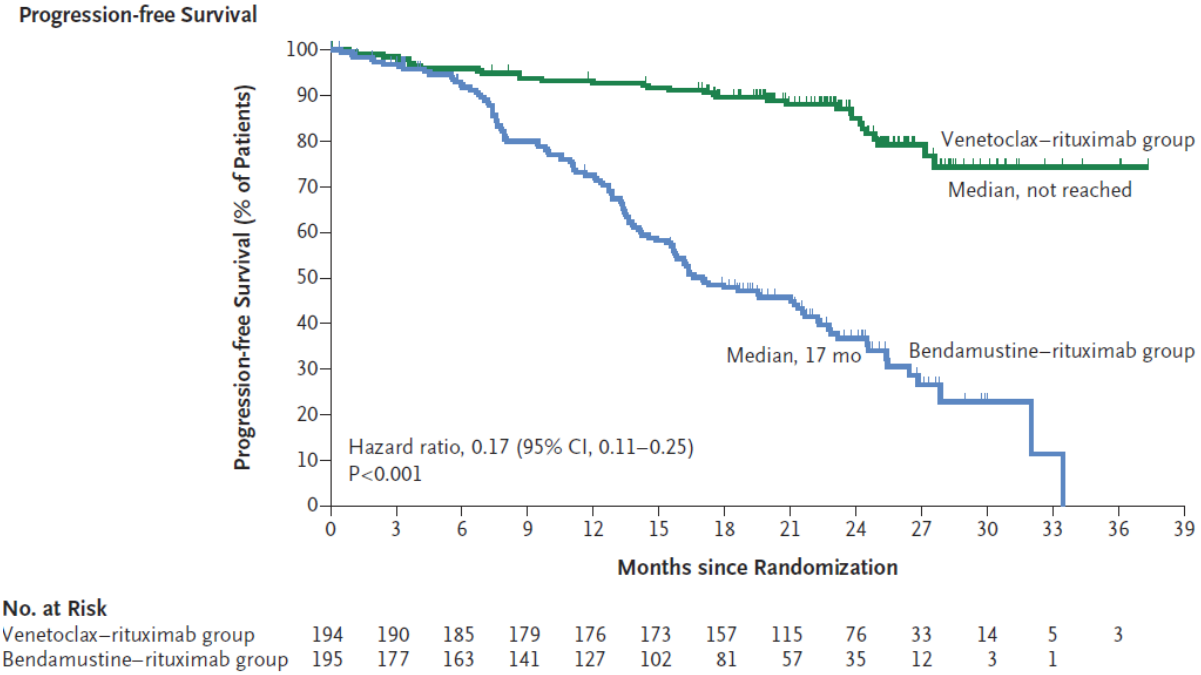
B.2.6.1 Primary endpoint: Investigator-assessed PFS

After a median follow-up period of 23.8 months (range: 0.0 to 37.4), the median investigator-assessed PFS was significantly longer in the VEN+R treatment group than in the BR treatment group. The median PFS was not reached in the VEN+R treatment group (32 events of progression or death in 194 patients; 16.5%) and was 17 months in the BR group (114 events in 195 patients; 58.5%), with 40% of patients in the VEN+R group still receiving venetoclax at the time of the published analysis. The risk of having a PFS event was notably reduced by 83% (stratified HR=0.17; 95% CI: 0.11, 0.25; p<0.0001, stratified log-rank test) for patients in the VEN+R group. The results of the unstratified analysis of PFS were similar to those for the stratified analysis (see Figure 4). (1)

Furthermore, progression-free estimates at 1-year were 93% in the VEN+R group and 73% in the BR group, with the 2-year rate of investigator-assessed PFS being 84.9% (95% CI, 79.1 to 90.6) in the VEN+R treatment group and 36.3% (95% CI, 28.5 to 44.0) in the BR treatment group.

Notably, this PFS benefit was maintained across all clinical and biologic subgroups including patients with del(17p) as well as non-del(17p) patients (please refer to section B.2.7). These results demonstrate that VEN+R has a statistically significant and clinically meaningful improvement in PFS, making VEN+R an important addition to the currently limited range of available treatment options for R/R CLL patients who have received at least one prior therapy.

Figure 4 KM estimates of investigator-assessed PFS for VEN+R compared with BR



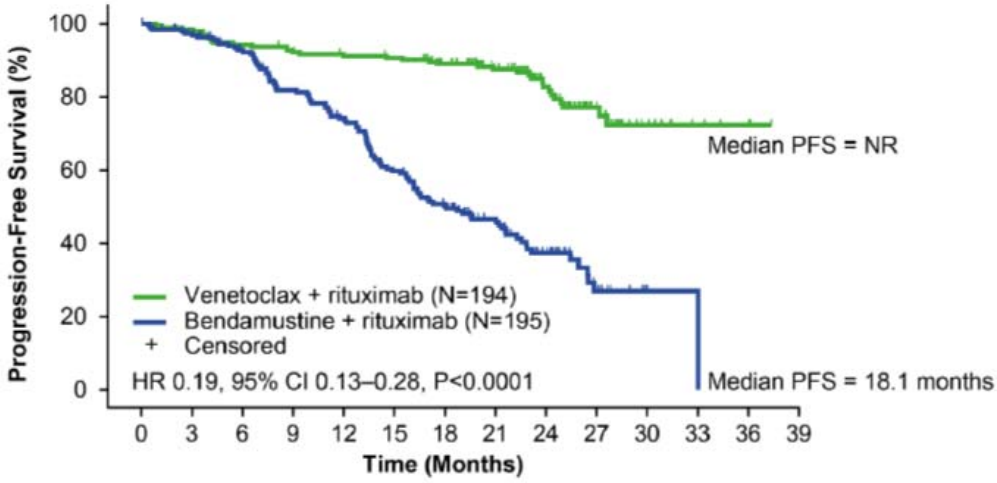
Source: Seymour et al. (1)
Key: BR; bendamustine + rituximab; PFS, progression-free survival; VEN+R, venetoclax + rituximab

B.2.6.2 Secondary endpoints

B.2.6.2.1 IRC-assessed PFS

The results of the primary IRC PFS analysis showing the benefit of VEN+R over BR were consistent with the primary PFS analysis based on the investigator's assessment, confirming that results were not biased due to the open label design of the study (see Figure 5). After a median follow-up of 23.8 months, the median PFS in the VEN+R treatment group was not reached whereas the median duration of PFS was 18.1 months in the BR treatment group. The 2-year rate of IRC-assessed PFS was 82.8% (95% CI, 76.6 to 88.9) in the VEN+R treatment group and 37.4% (95% CI: 29.4 to 45.4) in the BR treatment group. The risk of having a PFS event was significantly reduced by 81% (stratified HR=0.19; 95% CI: 0.13, 0.28; p <0.0001, log rank test).

Figure 5 KM estimates of IRC-assessed PFS for VEN+R compared with BR



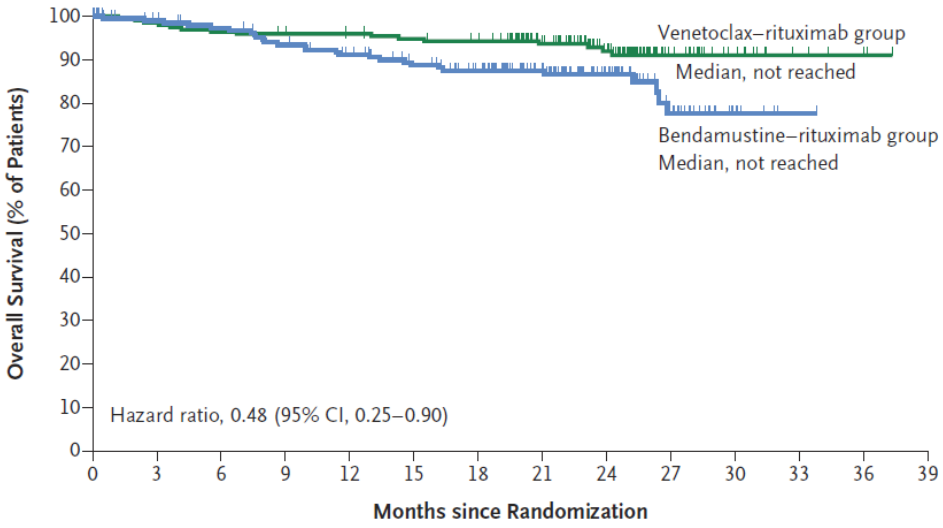
No. of patients at risk													
Venetoclax + rituximab	194	190	182	177	173	171	157	116	75	34	14	5	3
Bendamustine + rituximab	195	178	162	138	124	100	82	56	34	11	2	1	

Source: Seymour et al. (1)
Key: BR; bendamustine + rituximab; PFS, progression-free survival; VEN+R, venetoclax + rituximab

B.2.6.2.2 OS

The rate of OS was higher in the VEN+R group than in the BR group with 2-year rates of 91.9% and 86.6%, respectively (HR=0.48; 95% CI, 0.25 to 0.90) with an estimated risk of death of 52% for patients treated with VEN+R. The survival benefit presented in Figure 6 shows a separation of the curves in favour of treatment with VEN+R compared to BR after approximately eight months, which was maintained until the data cut-off for the primary analysis (8 May, 2017).

Figure 6 KM curve of OS for VEN+R compared with BR



No. at Risk													
Venetoclax–rituximab group	194	190	185	183	181	178	175	142	102	36	15	5	3
Bendamustine–rituximab group	195	181	175	166	158	146	134	102	66	29	8	2	

Source: Seymour et al. (1)
Key: BR; bendamustine + rituximab; PFS, progression-free survival; VEN+R, venetoclax + rituximab

B.2.6.2.3 Investigator-assessed and IRC-assessed CR/CRi

Both investigator-assessed and IRC-assessed CR or CRi was higher in the VEN+R treatment group compared to the BR treatment group (see Figure 7).

- The rate of investigator-assessed CR or CRi was 26.8% in the VEN+R treatment group as compared with 8.2% in the BR treatment group (descriptive p< 0.0001, Cochran-Mantel-Haenszel test).
- The rate of IRC-assessed CR or CRi was 8.2% in the VEN+R treatment group as compared with 3.6% in the BR treatment group (descriptive p=0.0814, Cochran-Mantel-Haenszel test).

Reasons for the difference in investigator-assessed CR or CRi can be explained by the fact that of the 68 investigator-assessed patients across both treatment groups who had a CR or CRi; 50 patients were classified as having a PR and one patient was classified as having stable disease (SD) according to assessment by the IRC. The main reason for the discordance in the rates of investigator-assessed and IRC-assessed CR or CRi was the divergence in the interpretation of residual adenopathy on CT, specifically with respect to lesions measuring 30mm or smaller, despite bone marrow clearance. While achieving CR arguably leads to longer response duration and OS than PR, (59,60) more recent evidence suggests that patients with a PR and undetectable MRD have shown better survival outcomes compared to those patients with a CR and detectable MRD (61) (please refer to Table 14).

Table 14 Lower IRC-CR/CRi rate relative to investigator-assessed CR/CRi rate

Reason for lower IRC-CR/CRi rate relative to investigator-assessed CR/CRi rate	VEN+R (n=42)	BR (n=9)
CT scan (all reasons)	33	7
Lesions 16–20mm	18	3
Lesions 21–30	10	2
Lesions >30mm	1	2
Anatomy missing	3	0
Spleen enlarged	1	0
Bone marrow, elements missing	4	2
Growth factor use	2	0
Spleen size/ALC fluctuation	2	0
AE- secondary malignancy[a]	1	0

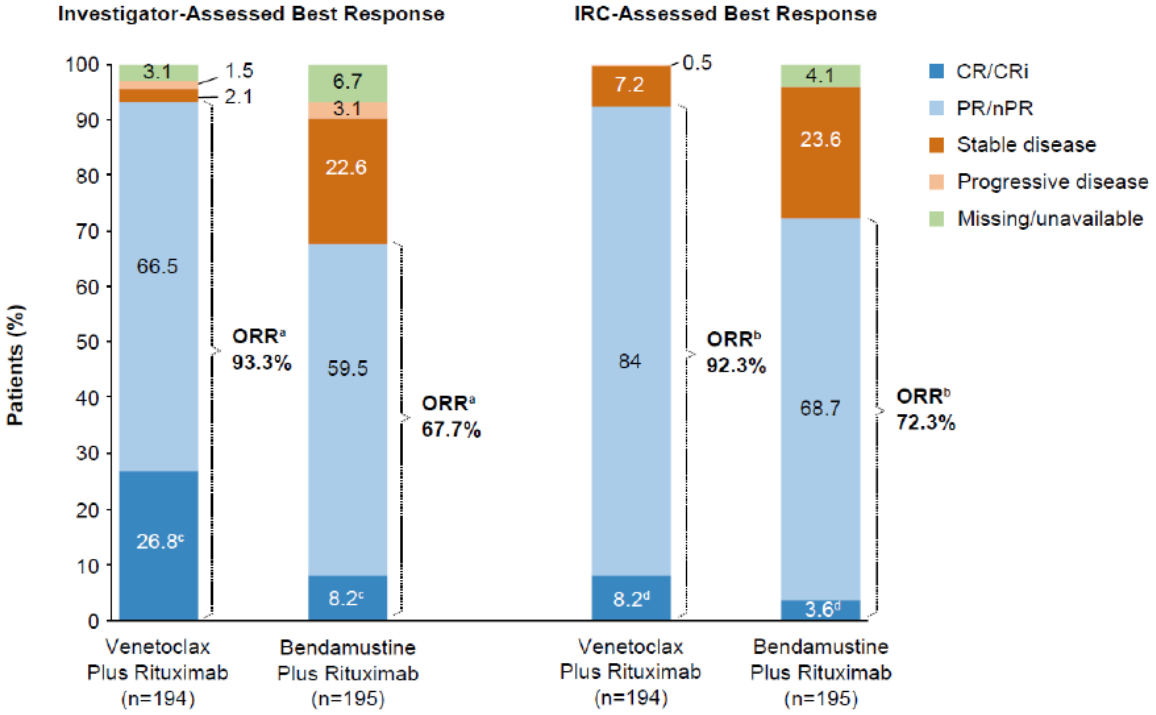
Source: Seymour et al. (1)
Key: AE, adverse event; ALC, absolute lymphocyte count; BR, bendamustine + rituximab; CT, computerised tomography; VEN+R, venetoclax + rituximab
[a] Omental peritoneal nodules likely related to metastatic lung cancer rather than CLL. No biopsy available.

B.2.6.2.4 ORR

ORR was consistently higher in the VEN+R treatment group compared to the BR treatment group, regardless of whether ORR was investigator-assessed or IRC-assessed (see Figure 7).

- The investigator-assessed ORR was 93.3% (95% CI, 88.8 to 96.4) in the VEN+R treatment group and 67.7% (95% CI, 60.6 to 74.2) in the BR treatment group (descriptive p-value<0.0001; Cochran-Mantel-Haenszel test). Difference between VEN+R vs. BR treatment groups was 25.6% (95% CI, 17.9 to 33.3).
- The IRC assessed ORR was 92.3% (95% CI, 87.6 to 95.6) in the VEN+R treatment group and 72.3% (95% CI, 65.5 to 78.5) (descriptive p-value<0.0001; Cochran-Mantel-Haenszel test). Difference between VEN+R vs. BR treatment groups was 20.0% (95% CI, 12.4 to 27.6).

Figure 7 Best response rates (ITT population)



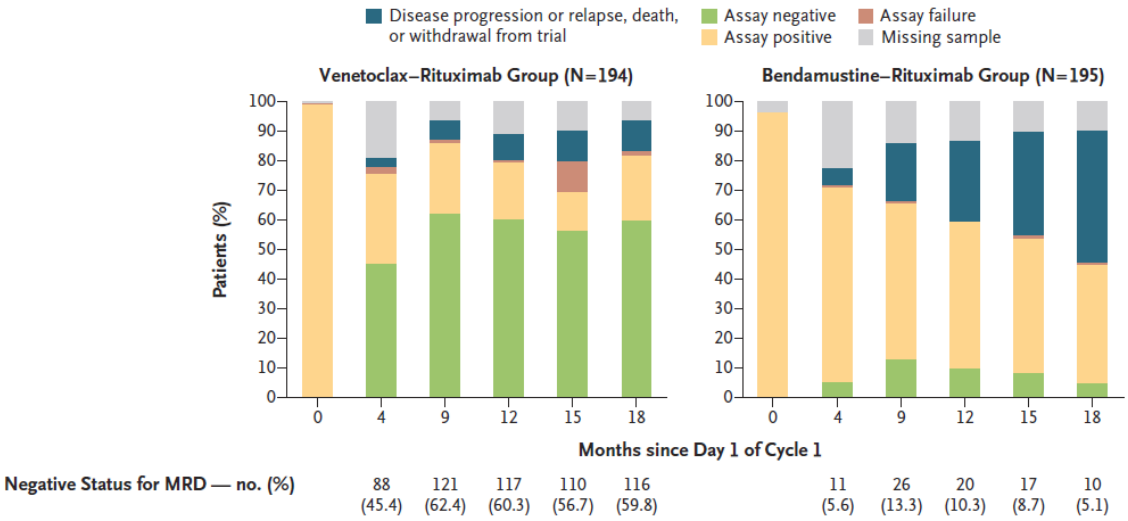
Source: Seymour et al. (1)
Key: CR, complete response; CRi, complete response with incomplete haematological recovery; ORR, overall response rate; nPR, nodular partial response; PR, partial response.
[a] Difference (95% CI) between groups. 25.6% (17.9 to 33.3).
[b] Difference (95% CI) between groups, 20.0% (12.4 to 27.6).
[c] Difference (95% CI) between groups, 18.6%.
[d] Difference (95% CI) between groups, 4.7% (-0.3 to 9.6); P=0.0814.

B.2.6.2.5 Clearance rates of MRD

Assessments of MRD were available for 366 patients (94.1%) on the basis of peripheral-blood samples and from 115 patients (29.6%) on the basis of bone marrow aspirate.

On the basis of peripheral-blood samples, at the 9-month time point, the rate of clearance of MRD was higher in the VEN+R treatment group vs. the BR treatment group (121 of 194 patients [62.4%] vs. 26 of 195 patients [13.3%]). The rate was also higher in the VEN+R treatment group than in the BR treatment group at any time during the trial (162 of 194 patients [83.5%] vs. 45 of 195 patients [23.1%]). The absolute difference between the treatment groups in the rate of clearance of MRD was 49.0% (95% CI, 40.4 to 57.6) at the time of the 9-month combination-treatment response assessment visit and 60.4% (95% CI, 52.3 to 68.6) at any time during the trial (see Table 15). Notably, the higher rate of clearance of MRD on the basis of peripheral-blood samples in the VEN+R treatment group was also maintained over time (see Figure 8).

Figure 8 Rate of clearance of MRD over time



Source: Seymour et al. (1)

Table 15 MRD status determined on the basis of peripheral-blood samples in the MURANO trial

MRD Status	At 9-months Combination-Treatment Response Assessment Visit		At Any time during Trial	
	VEN+R (n=194)	BR (n=195)	VEN+R (n=194)	BR (n=195)
Number of patients (percent)				
Negative[a]	121 (62.4)	26 (13.3)	162 (83.5)	45 (23.1)
Non-negative	73 (37.6)	169 (86.7)	32 (16.5)	150 (76.9)
Assay positive	46 (23.7)	102 (52.3)	24 (12.4)	134 (68.7)
Assay failure	2 (1.0)	2 (1.0)	1 (0.5)	0
Withdrew from study due to reasons other than death	4 (2.1)	15 (7.7)	NA	NA
Missing sample	12 (6.2)	27 (13.8)	7 (3.6)	16 (8.2)

Source: Seymour et al. (1)
Key: BR, bendamustine + rituximab; MRD, minimal residual disease; NA, not applicable; VEN+R, venetoclax + rituximab
[a] The threshold for MRD was one tumour cell per 10^4 leukocytes. Results below this threshold were considered negative.

In the assessment of bone marrow aspirate, higher rates of clearance of MRD in the VEN+R treatment group were also seen (53 of 194 patients [27.3%] in the VEN+R treatment group vs. 3 of 195 patients [1.5%] in the BR treatment group) at any timepoint (please refer to Table 16).

Table 16 MRD response rate in bone marrow

	Best MRD negativity rate on study	
ITT population	**VEN+R (n=194)**	**BR (n=195)**
MRD in bone marrow[a] Negative, n (%)	53 (27.3)	3 (1.5)
Non-negative, n (%)	141 (73)	192 (99)
Assay positive	17 (9)	36 (19)
Assay failure	4 (2)	2 (1)
PD/death/withdrew	NA	NA
Sample missing	120 (62)	154 (79)
Difference of MRD negativity (95% CI)	25.8% (19.0, 32.6)	
P-value[b]	<0.0001	

Source: Seymour et al. (1)
Key: BR, bendamustine + rituximab; MRD, minimal residual disease; NA, not applicable; PD, progressive disease; VEN+R, venetoclax + rituximab
[a] Combining (ASO-PCR) and flow cytometry.
[b] Descriptive P-values.

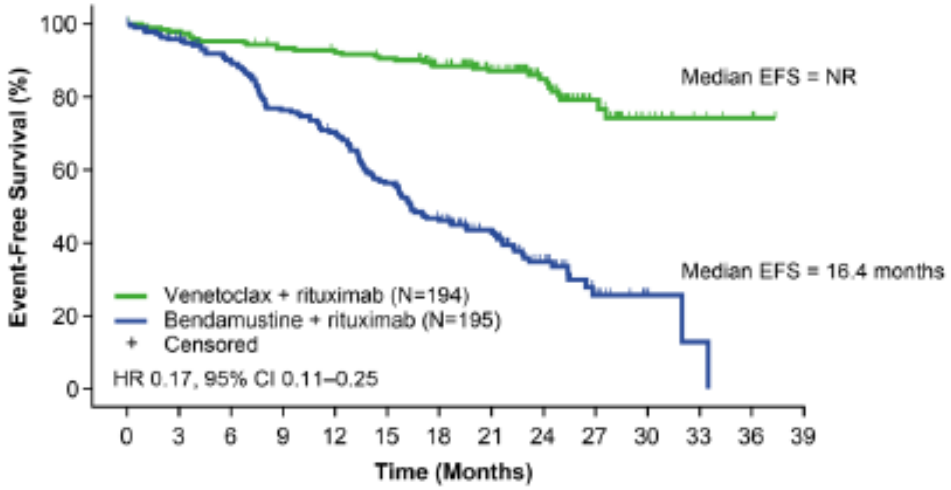
Concordance between MRD status in peripheral blood and bone marrow was 84.3% based on 108 pairs of post baseline samples across both treatment groups, 82.5% for the VEN+R treatment group and 85.3% for the BR treatment group; 48 of 60 (80%) patients with peripheral blood MRD negativity also measured MRD negative in bone marrow samples, while 48 out of 53 (91%) patients that measured MRD negative in bone marrow also measured MRD negative in blood. These findings suggest that peripheral blood MRD negativity data may be a good surrogate for bone marrow MRD negativity in this study.

In conclusion, significant higher peripheral blood and bone marrow MRD-negativity rates were maintained over time in the VEN+R treatment group vs. the BR treatment group. At the end of combination-treatment response assessment visit, MRD status was predictive of PFS indicating a potential survival benefit with VEN+R.

B.2.6.2.6 Duration of EFS

A clinically meaningful improvement in duration of EFS was observed in the VEN+R treatment group compared to the BR treatment group. At 2-years, 84.9% of the patients in the VEN+R treatment group and 34.8% in the BR treatment group were event-free (HR for disease progression, death, 0.17; 95% CI, 0.11 to 0.25) (see Figure 9). These data confirm the survival benefit as demonstrated with PFS and OS data.

Figure 9 EFS for VEN+R compared with BR



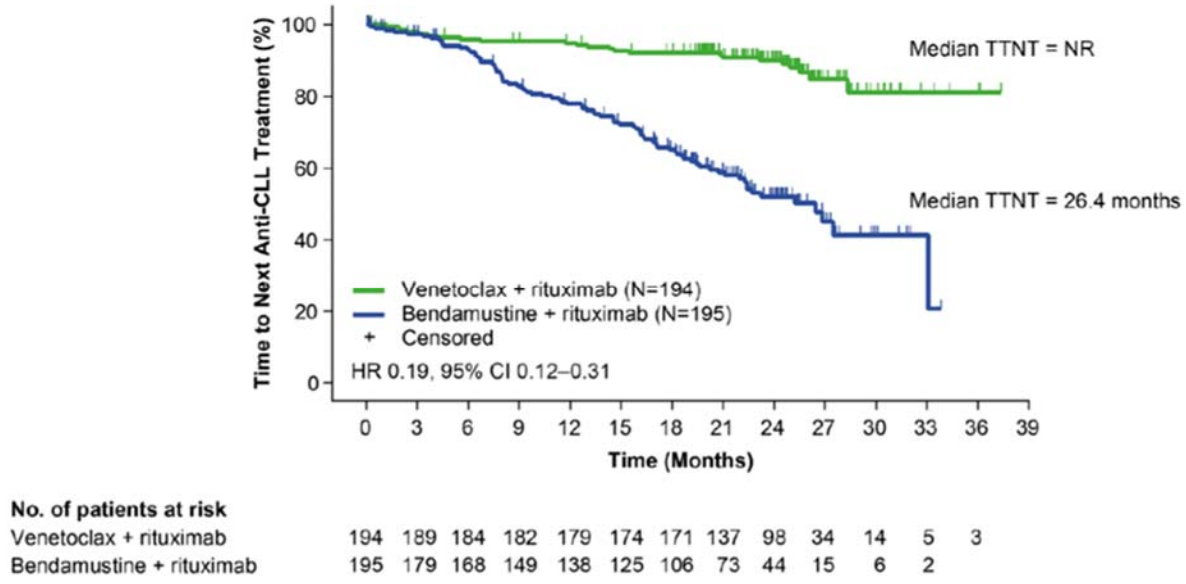
No. of patients at risk													
Venetoclax + rituximab	194	189	184	178	175	171	155	113	75	33	14	5	3
Bendamustine + rituximab	195	177	162	138	126	101	80	56	34	11	3	1	

Source: Seymour et al. (1)
Key: BR; bendamustine + rituximab; EFS, event-free survival, VEN+R, venetoclax + rituximab

B.2.6.2.7 TTNT

Treatment with VEN+R significantly extended the duration of TTNT compared to treatment with BR. At 2-years, 90.0% and 52.1% of patients receiving VEN+R and BR had not received a next treatment for R/R CLL, respectively (HR for receipt of next treatment or death, 0.19; 95% CI, 0.12 to 0.31) (see Figure 10). A total of three patients (1.5%) in the VEN+R group and 40 (20.5%) in the BR group received targeted CLL therapies, such as BCRi and BCL2 inhibitors, after disease progression occurred.

Figure 10 Time to next anti-CLL treatment for VEN+R compared with BR



Source: Seymour et al. (1)
Key: BR; bendamustine + rituximab; EFS, event-free survival, VEN+R, venetoclax + rituximab

B.2.6.2.8 HRQoL

The MURANO trial scheduled EuroQoL Five-Dimension 3-level version (EQ-5D-3L) collection at regular intervals within a patient's pre-progression period, once at progression and once at the first assessment following progression. As of the data locked on 8 May, 2017, there were 4,197 complete EQ-5D reports from a total of 379 patients (22 reports had incomplete data and were therefore removed from the analysis dataset). In the MURANO trial, (1) only 35% of patients in the VEN+R treatment group completed baseline patient-reported outcomes (PRO). This was due to an undetected protocol error: baseline PRO data (prior to dose titration) were not collected for 65% of VEN+R patients. Therefore, the data was missing at random.

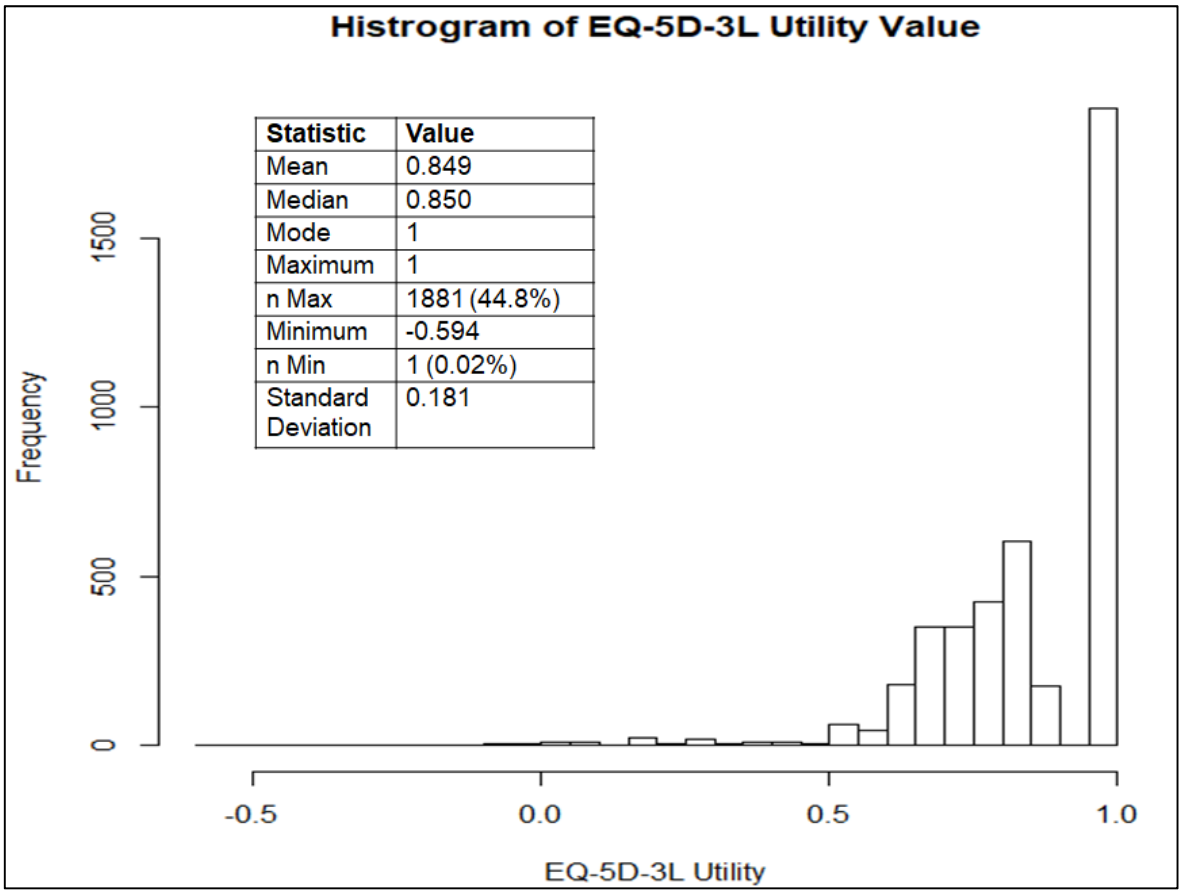
A breakdown of the reporting by dimension is provided below in Table 17. There was significant clustering at the mildest level of each dimension particular for Mobility and Self-care. A total of 1881 (44.8%) of the observations were for the mildest EQ-5D-3L profile "11111". This means that a large proportion of the observations conveyed a health state with "no problems" for all of the five domains.

Table 17: EQ-5D-3L reporting by dimension

	Dimension									
	Mobility		**Self-care**		**Usual Activities**		**Pain/Discomfort**		**Anxiety Depression**	
Level 1	3,341	79.6%	4,019	95.8%	3,005	71.6%	2782	66.3%	2,913	69.4%
Level 2	853	20.3%	172	4.1%	1133	27.0%	1372	32.7%	1231	29.3%
Level 3	3	0.1%	6	0.1%	59	1.4%	43	1.0%	53	1.3%

The Dolan value set was used to combine dimension scores into a "utility" value. (62) This represents a patient's HRQoL as defined by the five EuroQol dimensions where the scores of 1 and 0 are anchored by perfect health and death respectively. A histogram of the 4,197 utility values is given below in Figure 11. A clustering of values at 1 is observed due to the large proportion of "11111" profiles.

Figure 11 Distribution of EQ-5D-3L utility data



B.2.7 Subgroup analysis

- Across all the subgroups, a consistent treatment benefit in favour of VEN+R treatment on investigator-assessed PFS was observed over the entire follow-up period of 23.8 months.
- VEN+R provides a clinically meaningful improvement in OS and PFS in del(17p)/TP53 and non-del(17p)/tp53 adult R/R CLL patients.

Pre-specified subgroup analyses of PFS as assessed by the investigator or by IRC were performed to evaluate internal consistency of the primary efficacy analysis and to determine whether baseline clinical characteristics or molecular features had an impact on the efficacy of VEN+R (Table 18).

Table 18 Pre-planned subgroups for PFS at screening or baseline

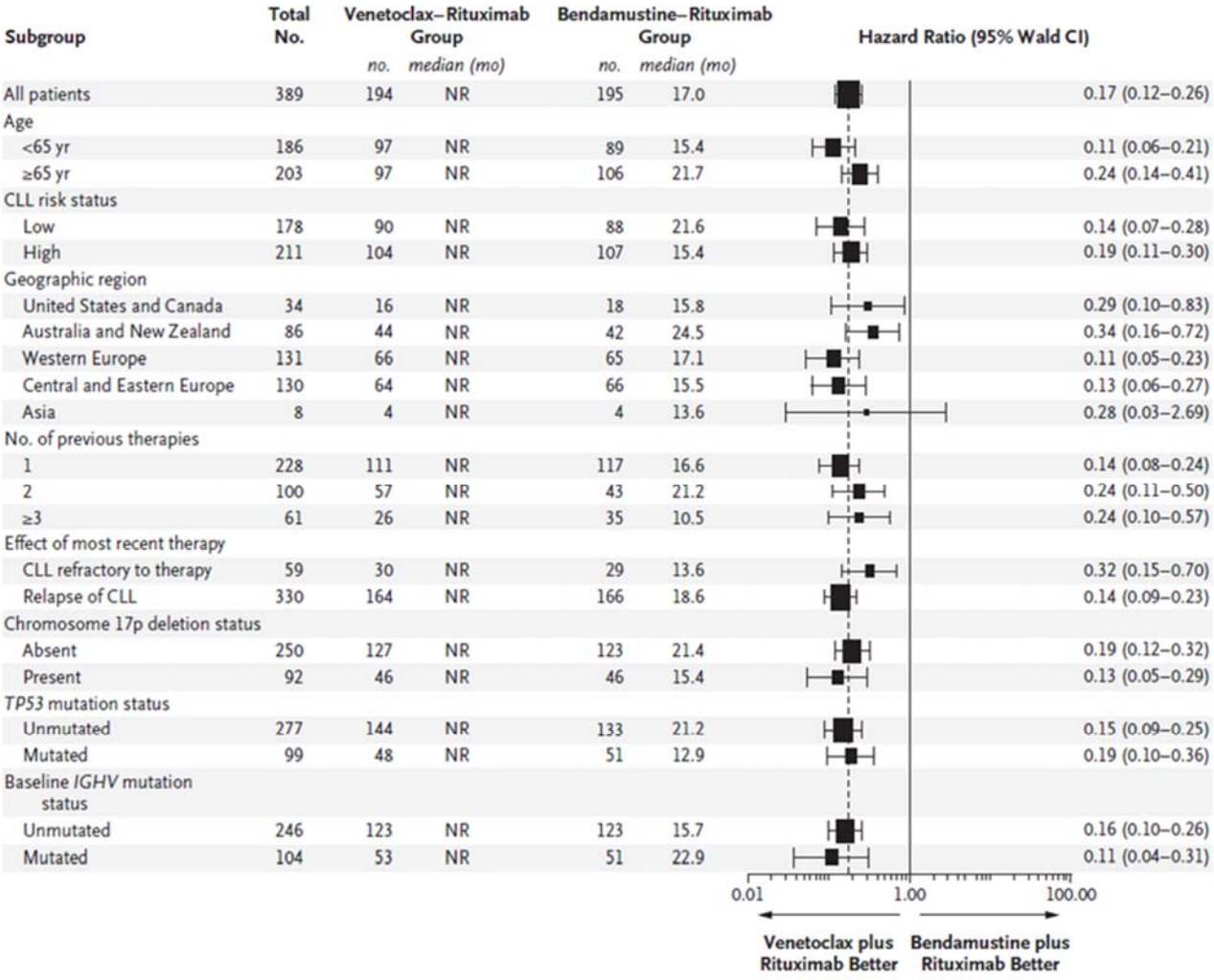
Variable	Comparison
Age	<65 vs. ≥65 years
CLL risk status	Low vs. high
Geographical region	US and Canada, Australia and New Zealand, Western Europe, Central and Eastern Europe, Asia
Number of prior treatment lines	1, 2, ≥3
Effect of most recent therapy	Refractory vs. relapse
Del(17p) status	Non-del(17p) patients vs. del(17p) patients
TP53	Unmutated vs. mutated
Baseline IGHV mutation status	Unmutated vs. mutated

Source: Seymour et al. (1)
Key: CLL, chronic lymphocytic leukaemia; Del(17p), chromosome 17p deletion; IGHV, immunoglobulin heavy-chain variable

B.2.7.1.1 Investigator-assessed PFS

Across all the subgroups, a consistent treatment benefit in favour of VEN+R treatment on investigator-assessed PFS was observed over the entire follow-up period of 23.8 months (see Figure 12).

Figure 12 Prespecified subgroup analysis of investigator-assessed PFS



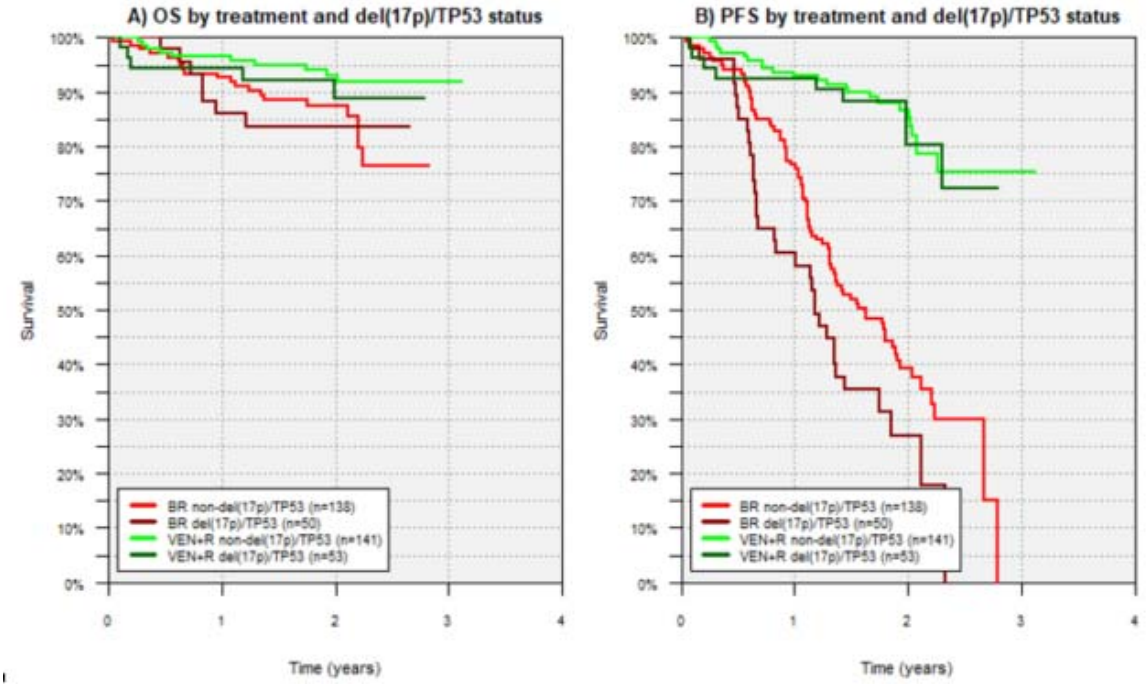
Subgroup	Total No.	Venetoclax–Rituximab Group		Bendamustine–Rituximab Group		Hazard Ratio (95% Wald CI)
		no.	*median (mo)*	*no.*	*median (mo)*	
All patients	389	194	NR	195	17.0	0.17 (0.12–0.26)
Age						
<65 yr	186	97	NR	89	15.4	0.11 (0.06–0.21)
≥65 yr	203	97	NR	106	21.7	0.24 (0.14–0.41)
CLL risk status						
Low	178	90	NR	88	21.6	0.14 (0.07–0.28)
High	211	104	NR	107	15.4	0.19 (0.11–0.30)
Geographic region						
United States and Canada	34	16	NR	18	15.8	0.29 (0.10–0.83)
Australia and New Zealand	86	44	NR	42	24.5	0.34 (0.16–0.72)
Western Europe	131	66	NR	65	17.1	0.11 (0.05–0.23)
Central and Eastern Europe	130	64	NR	66	15.5	0.13 (0.06–0.27)
Asia	8	4	NR	4	13.6	0.28 (0.03–2.69)
No. of previous therapies						
1	228	111	NR	117	16.6	0.14 (0.08–0.24)
2	100	57	NR	43	21.2	0.24 (0.11–0.50)
≥3	61	26	NR	35	10.5	0.24 (0.10–0.57)
Effect of most recent therapy						
CLL refractory to therapy	59	30	NR	29	13.6	0.32 (0.15–0.70)
Relapse of CLL	330	164	NR	166	18.6	0.14 (0.09–0.23)
Chromosome 17p deletion status						
Absent	250	127	NR	123	21.4	0.19 (0.12–0.32)
Present	92	46	NR	46	15.4	0.13 (0.05–0.29)
TP53 mutation status						
Unmutated	277	144	NR	133	21.2	0.15 (0.09–0.25)
Mutated	99	48	NR	51	12.9	0.19 (0.10–0.36)
Baseline *IGHV* mutation status						
Unmutated	246	123	NR	123	15.7	0.16 (0.10–0.26)
Mutated	104	53	NR	51	22.9	0.11 (0.04–0.31)

Source: Seymour et al. (1)

B.2.7.1.2 OS and investigator-assessed PFS by del(17p) status and/or TP53 mutation

In-line with the results of the total population, treatment with VEN+R provides a clinically meaningful improvement in OS and PFS in del(17p)/TP53 and non-del(17p)/tp53 adult R/R CLL patients (see Figure 13).

Figure 13 OS and investigator-assessed PFS by treatment and del(17p)/TP53 status



Source: MURANO trial (1); figures generated from unpublished data.
Key: BR, bendamustine + rituximab; DEL17/TP53; del(17p)/TP53, with deletion of 17p chromosome and/or TP53; Non-DEL17/TP53, without deletion of 17p chromosome and/or TP53; OS, overall survival; PFS, progression-free survival; VEN+R, venetoclax + rituximab

B.2.7.1.3 Exploratory subgroup analyses

Results from the exploratory subgroup analyses of IRC-assessed PFS and ORR as assessed by the investigator or by IRC and MRD response rates in peripheral blood by del(17p) status and number of prior regimens (1 or >1) subgroups are provided in **Error! Reference source not found.**.

B.2.8 Meta-analysis

A formal meta-analysis has not been carried out for VEN+R or its comparators. The MURANO trial (1) is the only RCT containing the VEN+R treatment regimen in R/R CLL and is therefore the most relevant source of efficacy and safety data. A phase I trial was also conducted, however, the primary outcomes of this phase I trial comprised a safety assessment,

determination of the maximum tolerated dose, and the identification of the recommended dose of venetoclax when given in combination with rituximab. (57)

B.2.9 Indirect and mixed treatment comparisons

- The evidence network for treatments for R/R CLL is disconnected meaning that there is no common comparator. Therefore, an unanchored MAIC was performed to draw relative efficacy estimates for the comparators relevant to the NICE decision problem.
- The unanchored MAIC results suggest VEN+R has improved OS (statistically significant) and similar PFS vs. ibrutinib and improved OS and PFS (statistically significant) vs. idela+R.
- There is potential for residual bias using the methodologies for unanchored comparisons due to unobserved differences in the trials.
- Evidence from the literature suggests that ibrutinib-BR has similar efficacy to Ibrutinib single agent. Therefore, further exploratory analyses (Bucher method and adjusted MAIC) using anchored comparisons vs. ibrutinib-BR were conducted, using BR as a common comparator.
- The relative efficacy estimates derived from the anchored comparisons were broadly in line with that of the unanchored comparisons.
- AbbVie acknowledges the limitations of the methodology used to synthesise the available data and there is no short- or medium-term solution for connecting the evidence network. Nevertheless, it is expected that further maturity of the MURANO trial dataset will address the current level of uncertainty boundaries surrounding the relative efficacy estimates and improve their use for decision-making.

B.2.9.1 Data

A MAIC was performed to estimate the relative efficacy of VEN+R with relevant comparators in adult patients with R/R CLL having received at least one prior therapy. The outcomes required for the economic model are PFS and OS HRs. To perform the MAIC, the clinical SLR (See section B.2.1) was leveraged to identify RCT evidence for the efficacy of ibrutinib and idela + R.

B.2.9.2 Search strategy

Details of the search strategy and eligibility criteria are reported in Section B.2.1.

B.2.9.3 Study selection

As reported in Section B.2.1, 49 studies were included in the review after applying the inclusion and exclusion criteria. Of the identified RCTs and observational studies, one study for each comparator of interest was selected for inclusion within the MAIC, subject to the following criteria:

- Study must report baseline clinical characteristics,

- Study must include a KM-PFS and OS diagram clearly displaying the survival and progression events and numbers at risk over time.
- Study must report outcomes defined similarly to the outcomes of the MURANO trial. (1)
- Follow-up duration of survival data matches closely to that of MURANO (i.e. comparator survival data is ≥ duration of the MURANO trial).

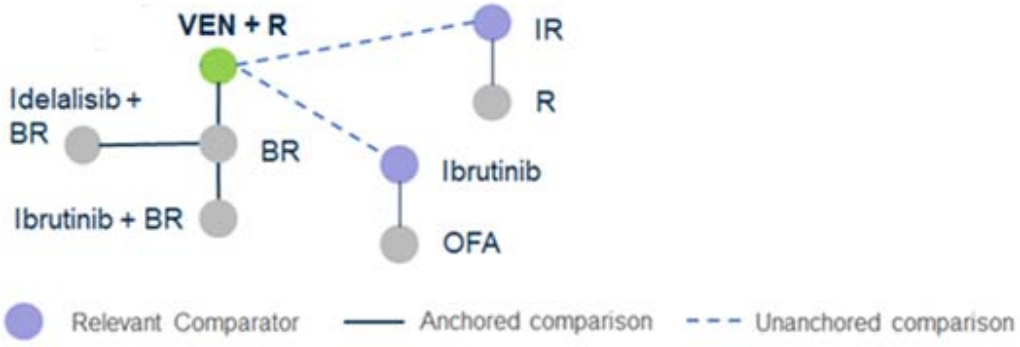
The sources of data for each treatment included in the ITC are listed below. A summary of the trials used to carry out the ITC is provided in **Error! Reference source not found.**.

- VEN+R (MURANO trial) (1)
- Ibrutinib (RESONATE study by Byrd et al. 2017) (63)
- Idela+R (STUDY 116 by Sharman et al. 2014) (54)

Network of evidence

The evidence network for the relevant comparators to VEN+R is shown in Figure 14. No connections were identified for the key comparators relevant to UK clinical practice.

Figure 14 Evidence network in R/R CLL



Key: BR, bendamustine + rituximab; IR, idelalisib + rituximab; OFA, ofatumumab; R, rituximab; VEN, venetoclax

B.2.9.4 Methods

With such limited RCT data available and the absence of a common comparator (as illustrated in Figure 14) it was not possible to perform a standard (anchored) indirect comparison for all relevant comparators. Therefore, in order to minimise the bias associated with a simple naïve comparison, we explored an unanchored MAIC instead, following the NICE guidance on "Methods for population-adjusted indirect comparisons in submissions to NICE". (64) The aim of MAIC was to try and balance any differences in treatment-effect modifying patient characteristics between MURANO and its comparator trials. In doing so, the goal is to reduce or remove any bias in relative treatment effect estimates which might be a result of differences in sample size. This process was performed according to the methodology outlined in Signorovitch et al. (65) The method is applied separately on a pairwise basis for each comparison required. Patients in the MURANO trial were assigned propensity score weights (according to how well their individual characteristics match the target trial sample). These weights are optimised so the re-weighted aggregate MURANO trial patient characteristics match that of the target trial

(across all relevant variables). Relative treatment effect estimates are then estimated using these weights (so patients who are better aligned to the target trial sample contribute more heavily to the estimates).

The full details of the unadjusted MAIC methodology are presented in **Error! Reference source not found.**. To determine which variables were most appropriate for matching, the status for each variable as prognostic and effect modifier was examined using the literature review and quantitative assessment of the MURANO trial data. (1) Effect modifiers were then validated by clinical experts. Details of this process are presented in **Error! Reference source not found.**. A matching variable was selected if it satisfied at least one of the criteria:

- Variables in MURANO that exhibited association at p≤0.25 when interacted with treatment in the prediction of PFS (investigator-assessed definition)
- Some evidence of potential effect modifying status in comparator trial publication

Based on the above, the effect modifiers that were included in all the analyses are listed in Table 19. The p value of interaction terms was less than 0.25 for all variables other than Rai Staging at baseline which is included based upon the evidence from the HELIOS study. (66)

Table 19 Variables considered to be potential effect modifiers for the purposes of the ITC

Variable	Covariate	Available observations in MURANO	HR for interaction term with treatment in MURANO	P value for interaction term with treatment in MURANO	Published study	HR for interaction term with treatment in comparator study	Decision on whether effect modifier
Age	>=65 years of age	389	2.141	0.0608	Chanan-Khan 2016 (66)	1.576	**Possibly effect modifier**
	<65 years of age		ref				
ECOG	1	388	1.834	0.1329	Chanan-Khan 2016 (66)	1.666	**Possibly effect modifier**
	0		ref				
Rai staging at baseline	Stage 3-4	389	0.878	0.578	Chanan-Khan 2016 (66)	2.263	**Possibly effect modifier**
	Stage 0-2		ref				
Bulky disease (5cm)	Nodes ≥ 5 cm	369	1.818	0.1477	-	-	**Possibly effect modifier**
	Nodes < 5 cm		ref				
ALC	< 25 × 10^9/L	389	2.023	0.0886	-	-	**Possibly effect modifier**
	≥ 25 × 10^9/L		ref				
Chromosome 11q deletion	Abnormal	342	0.526	0.1736	Chanan-Khan 2016 (66)	0.302	**Possibly effect modifier**
	Normal		ref				
Del(17p)	Abnormal	342	0.716	0.1014	Zelenetz 2017 (67)	2.137	**Possibly effect modifier**
	Normal		ref				
Baseline beta-2 microglobulin	> 3.5 mg/L	375	3.367	0.0216	Byrd 2017 RESONATE (63)	1.814	**Possibly effect modifier**

	<= 3.5 mg/L		ref				
IgVH mutation, n (%)	Unmutated	350	1.742	0.0083	Chanan-Khan 2016 (66)	0.369	**Possibly effect modifier**
	Mutated		ref				
Response duration to recent prior therapy	< 12 months	330	0.499	0.2151	-	-	**Possibly effect modifier**
	≥ 12 months		ref				
Number of prior CLL therapy	More than one therapy	389	1.631	0.226	Brown 2018 RESONATE (53)	2.659	**Possibly effect modifier**
	One therapy		ref				
Prior purine analog agent	Yes	389	0.398	0.0692	-	-	**Possibly effect modifier**
	No		ref				

Source: MURANO trial (1)

Key: ALC, absolute lymphocyte count; CLL, chronic lymphocytic leukaemia; ECOG, Eastern Cooperative Oncology Group; DEL17, with deletion of 17p chromosome; HR, hazard rate; IgHV, immunoglobulin heavy-chain variable; ITC, indirect treatment comparison

Upon implementation of the MAIC, the following analyses were performed for both PFS and OS:

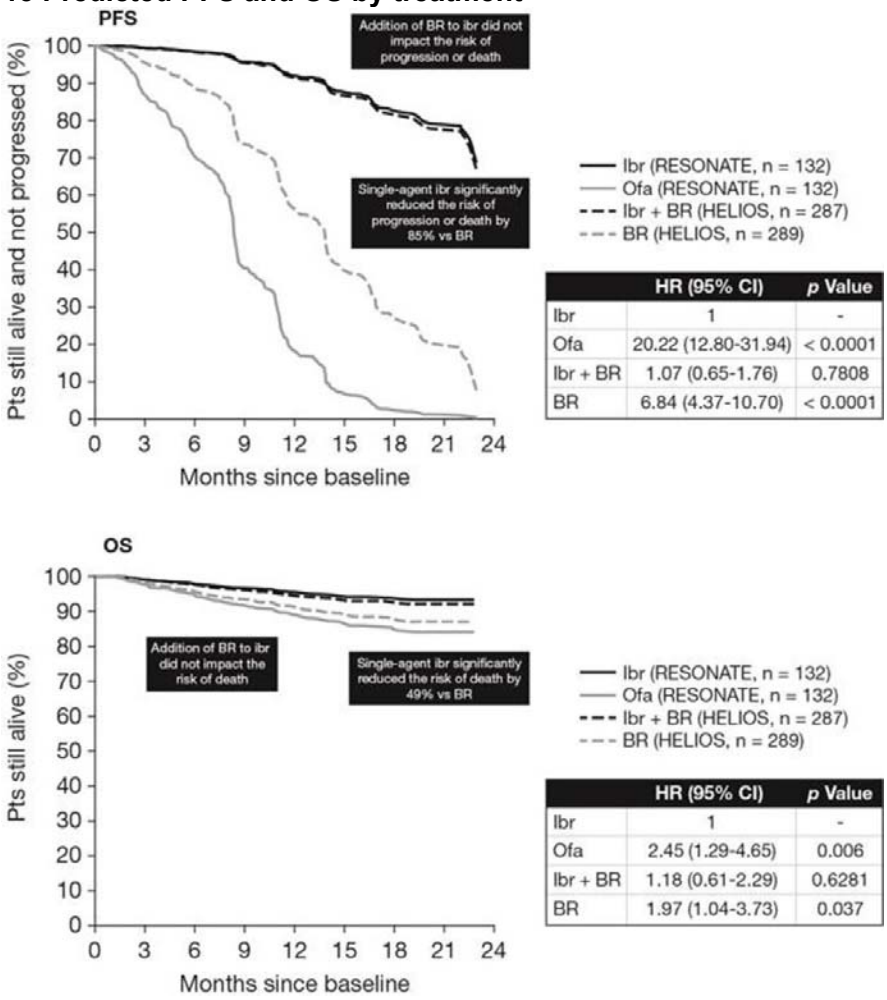
- Unanchored MAIC of VEN+R vs. ibrutinib by adjusting the MURANO patient-level data in order to match the VEN+R population to the ibrutinib population as represented by the RESONATE KM data (63) as individual patient data (IPD) was not available. To match the definition of PFS in RESONATE, the investigator-assessed PFS was utilised in MURANO. Details of the final number of patients after adjustment are presented in **Error! Reference source not found.**.
- Unanchored MAIC of VEN+R vs. idela+R by adjusting the MURANO patient-level data in order to match the VEN+R population to the idela+R population as represented by the Study 116 KM data as IPD was not available. (54) To match the definition of PFS in Study 116, the IRC-assessed PFS was utilised in MURANO. Details of the final number of patients after adjustment are presented in **Error! Reference source not found.**.

The above summarises the main analyses conducted to support the two comparisons presented in this appraisal. To further strengthen the outputs of the analyses vs. ibrutinib (which is unanchored and hence at higher risk of residual bias), two further indirect comparisons were also explored:

- A pair-wise ITC based on Bucher methodology for VEN+R vs. ibrutinib+BR using BR as a common comparator. This comparison was performed using the HELIOS trial. (66) To match the definition of PFS in HELIOS, the investigator-assessed PFS was utilised in MURANO.
- An adjusted anchored MAIC for VEN+R vs. ibrutinib+BR using BR as a common comparator. This comparison was performed using the HELIOS trial. (66) The approach combines the anchoring of the Bucher method, with the patient characteristic balancing of the MAIC. Details of the final number of patients after adjustment are presented in **Error! Reference source not found.**

The exploratory analyses were conducted as a published indirect comparison of the RESONATE and HELIOS trials concluded that the addition of BR to ibrutinib did not improve PFS or OS compared to ibrutinib single-agent. Therefore, the results of the above two exploratory analyses were used to compare VEN+R vs. ibrutinib single agent. A comparison of OS and PFS between ibrutinib+BR and ibrutinib single-agent is presented in Figure 15. The publication concluded that ibrutinib + BR and ibrutinib single-agent can be assumed to have the same efficacy with a HR of 1.07 (95% CI, 0.65 to 1.76) for PFS and a HR of 1.18 (95% CI: 0.61 to 2.29) for OS. (68)

Figure 15 Predicted PFS and OS by treatment



	HR (95% CI)	*p* Value
Ibr	1	-
Ofa	20.22 (12.80-31.94)	< 0.0001
Ibr + BR	1.07 (0.65-1.76)	0.7808
BR	6.84 (4.37-10.70)	< 0.0001

	HR (95% CI)	*p* Value
Ibr	1	-
Ofa	2.45 (1.29-4.65)	0.006
Ibr + BR	1.18 (0.61-2.29)	0.6281
BR	1.97 (1.04-3.73)	0.037

Source: Figure 1 from Hillmen et al. (68)
Key: BR, bendamustine + rituximab; CI, confidence interval; HR, hazard rate; Ibr, ibrutinib; OFA, ofatumumab; OS, overall survival; PFS, progression-free survival; Pts, patients

B.2.9.5 Results

Table 20 presents the results for the unanchored comparisons, adjusted and unadjusted, for the comparisons versus ibrutinib and idela+R.

The influence of the matching process on the HR estimates can be seen by comparing the adjusted results with the unadjusted results. The adjustment process had a reasonably small impact on the ibrutinib OS HR and the idela+R PFS HR. The ibrutinib PFS HR increased moderately after adjustment by approximately [redacted]. The idela+R OS HR decreased substantially after adjustment by approximately [redacted].

Table 20 MAIC comparisons (Unanchored)

	Adjusted Comparison			Unadjusted Comparison		
VEN+R vs.	**HR PFS (95% CI)**	**HR OS (95% CI)**	**Sample Size**	**HR PFS (95% CI)**	**HR OS (95% CI)**	**Sample Size**
VEN+R vs. Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R vs. Idela+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; CLL, chronic lymphocytic leukemia; Eff, effectiveness sample; HR, hazard ratio; Idela+R, idelalisib + rituximab; IRC; independent review committee; PFS, progression-free survival; OS, overall survival; VEN+R, venetoclax + rituximab

Considering the findings from Hillmen et al. (Figure 15, it is assumed that the relative efficacy of VEN+R vs. ibrutinib+BR can be extended to VEN+R vs. ibrutinib single agent). The results of the anchored analysis vs. ibrutinib+BR are summarised below in Table 21. [redacted]. These HRs are used for the ibrutinib comparison in the economic model scenario analysis (Table 67).

Table 21 MAIC results (Anchored)

VEN+R vs.	HR PFS (95% CI)	HR OS (95% CI)	Sample Size
Ibrutinib +BR (Unadjusted)	[redacted]	0.703 (0.270 – 1.829)	[redacted]
Ibrutinib +BR (Adjusted)	[redacted]	[redacted]	VEN+R= 71.5 [redacted]

Key: BR, bendamustine + rituximab; CI, confidence interval; HR, hazard rate; OS, overall survival; PFS, progression-free survival; VEN+R, venetoclax with rituximab

B.2.9.6 Discussion

The premise of population-based adjustment is that the treatment effect depends on the population. It is therefore not sufficient to use patient characteristics adjustment to generate an "unbiased" comparison in just any population; the methodology only achieves this purpose if it can produce a fair comparison in the target population for the decision. In general, the target population is a UK cohort relevant to the clinical decision.

Unanchored comparisons must include every effect modifier and prognostic variable – compared to the anchored case, where only effect modifiers are required. An immediate consequence of this is that an unanchored indirect comparison performed using population-adjustment will always have less precision than an anchored indirect comparison in the presence of imbalanced prognostic variables, and – more importantly – is more likely to be biased given that all prognostic variables as well as effect modifiers in imbalance must be

included in the weighting model (while some of them could be unobserved and thus impossible to include in the adjustment model). Including too many variables will reduce the effective sample size, negatively affecting the precision of the estimate; conversely, failure to include relevant variables will result in a biased estimate.

The reviewed published evidence on the effect modification status of various patient characteristics in R/R CLL does not conclusively show that variables such as prior therapies, genetic abnormalities, ECOG, RAI, beta-2 microglobulin, IGVH mutation, age, are strong modifiers of the relative efficacy of novel tyrosine kinase inhibitors compared to more traditional CIT agents. Therefore, slight imbalance between the MURANO data and comparator trial may not necessarily result in bias.

To make the determination on which variables should be adjusted for in unanchored MAIC, the status for each variable as prognostic and/or effect modifier was examined using expert opinion, literature review as well as quantitative assessment in the MURANO trial data. The main variables associated with uncertainty are described in Table 22.

Table 22 Uncertainty in the selection of matching variables

Covariate	Uncertainty and decision
RAI staging at baseline	The MURANO trial did not exhibit an association with PFS when interacted with treatment. However, based on the Chanan-Khan 2016 publication, there was some evidence that RAI staging is an effect modifier and therefore was included.
Refractory to last anti-leukaemia therapy	While this patient characteristic exhibited some evidence of effect modification, AbbVie clinicians opined that the definition for R/R disease may not be standardised across trials so it would not be good practice to consider adjusting for that covariate in case trials definitions are different. Therefore, this variable is dropped from further consideration.

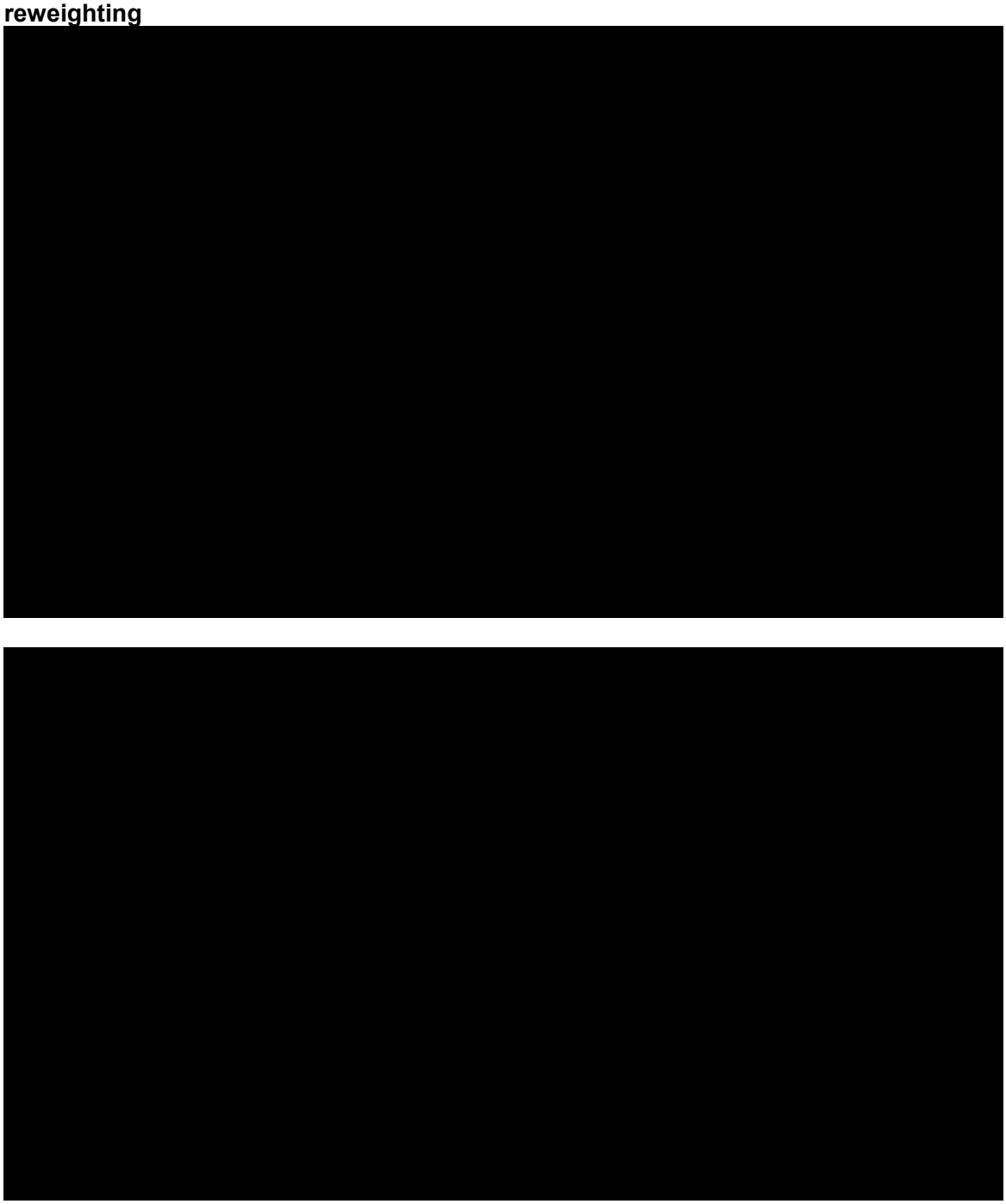
Key: BCRi, B-cell receptor inhibitor; PFS, progression-free survival

Results from unanchored analyses should be interpreted with a high degree of caution, given the possibility of unaccounted unobserved residual bias. This is a common occurrence in unanchored comparisons in oncology. (69,70) This occurs since unobserved trial differences cannot be accounted for within the MAIC framework. It is considered likely that a degree of residual bias remains in the unanchored comparisons. Although the evidence supporting this conclusion is derived from the anchored comparisons (which, if all heterogeneity was adjusted for, should show the BR anchor arms tracing each other closely), it can be considered an indicator of bias in the unanchored estimates.

Figure 16 and Figure 17 show the evidence for anchored comparisons with treatments that are not relevant to the NICE scope. HELIOS was a phase III double-blind, placebo controlled trial. Ibrutinib + BR was compared to BR + placebo in a non-del(17p) R/R CLL population. (66) Study 115 was a phase III, double blind, placebo controlled trial. (67) Idelalisib + BR was compared to BR + placebo in R/R CLL. The difference between the (adjusted) MURANO BR curves and the external trial BR curves indicate that not all of the variation has been accounted for by the matching variables. If the patient characteristics were perfectly controlled, then one would expect to see the "BR (HELIOS)" and the "BR Adj (MURANO)" KM curves follow each other more closely in each diagram.

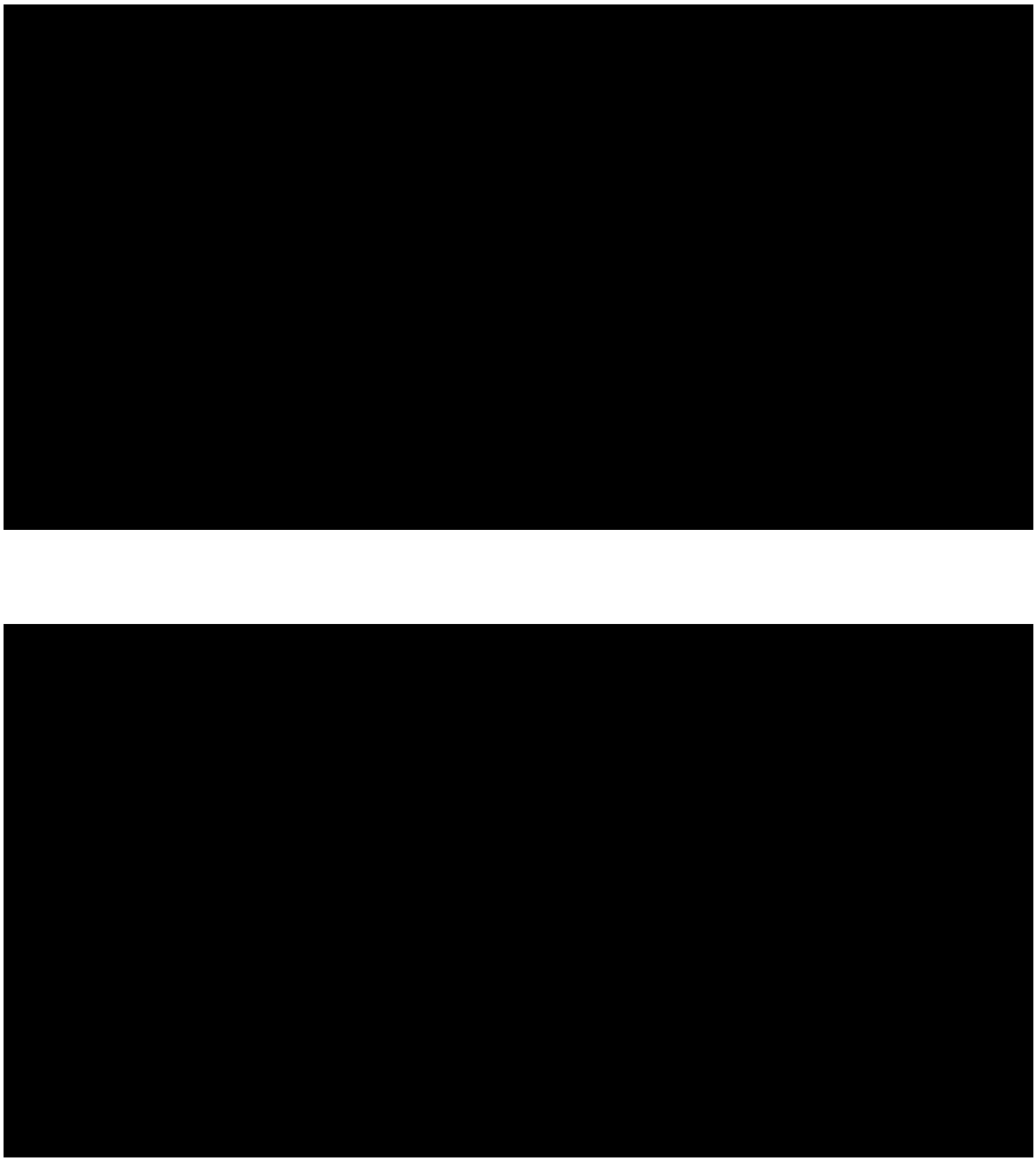
For the ibrutinib comparison, the uncertainty in the HR estimates leads to a model dynamic which holds no face validity. When the MAIC hazard ratios are applied to the parameterised VEN+R curves, ibrutinib PFS exceeds OS. The model makes a correction for any instances of this illogical outcome by restricting PFS to be equal or lower than OS. The consequence of this dynamic and subsequent modelling restriction is that post-progression survival (PPS) for ibrutinib is estimated to be zero. This maps very poorly to clinical expectations and suggests these outcomes should be interpreted with caution.

Figure 16 KM curves of VEN+R vs. ibruntinib+BR for PFS (above) and OS (below), after reweighting



Key: BR, bendamustine + rituximab; IB + BR, ibrutinib with bendamustine + rituximab; KM, Kaplan-Meier; PFS, progression-free survival; OS, overall survival; VEN+R, venetoclax with rituximab

Figure 17 KM curves of VEN+R vs. Idela+BR for PFS (above) and OS (below) after reweighting



Key: BR, bendamustine + rituximab; IDE + BR, idelalisib with bendamustine + rituximab; KM, Kaplan-Meier; PFS, progression-free survival; OS, overall survival; VEN+R, venetoclax + rituximab

In conclusion, the disconnected evidence network has required the estimation of relative treatment effects to be made through unanchored comparisons. In general, as observed in Table 21, the ITC-estimated HRs have very large CIs. There is limited survival data available for

all comparators, but the data immaturity is particularly pronounced for VEN+R in the MURANO trial, (1) which is naturally affecting the precision of all comparisons. Although the median follow-up in the MURANO trial is around 2-years, PFS and OS data maturity is also a function of how many events occur during the observed period; notably in the MURANO trial relatively few events were demonstrated in the VEN+R treatment group. This is likely a testament to the potency of VEN+R treatment, but this same effect is limiting the ability to obtain robust estimates about its relative effectiveness against relevant comparators.

The MAIC results suggest that VEN+R has a similar efficacy to ibrutinib and is more effective than idela+R. Evidence from the literature supports an equal efficacy assumption between ibrutinib and ibrutinib + BR. (68) Combining this assumption with the anchored VEN+R vs. ibrutinib + BR MAIC outcomes, it provides additional credence that VEN+R and ibrutinib perform similarly.

There are limitations of the methodology that has been used to synthesise the available data to obtain evidence on relative treatment effects. Although there is no short- or medium-term solution for connecting the evidence network (to allow anchored comparisons across the board) it is expected that further maturity of the MURANO trial dataset will address the current level of uncertainty boundaries surrounding the relative efficacy estimates and improve their use for decision-making.

B.2.10 Adverse reactions

- The safety profile of VEN+R was acceptable, predictable and generally consistent with the known safety profiles of venetoclax and rituximab as single agents.
- Higher rates of grade 3 or 4 AEs in the VEN+R group (82%) compared to the BR group (70%) were observed. The difference was mainly driven by a higher rate of grade 3 or 4 neutropenia (57.7% vs. 38.8%). Notwithstanding the higher rate of neutropenia, the rates of grade 3 infections and infestations (17.5% vs. 21.8%) and febrile neutropenia (3.6% vs. 9.6%) were lower in patients in the VEN+R treatment group compared to those in the BR treatment group.
- Neutropenia was manageable with standard of care measures including growth factor support, dose interruptions and dose reductions.
- The rate of grade 3 or 4 TLS was higher in the VEN+R treatment group compared to the BR treatment group. TLS was reported in 3.1% of patients in the VEN+R group compared with 1.1% in the BR group.
- No laboratory or clinical TLS was observed after addition of rituximab to venetoclax.

Overall, in patients with R/R CLL, including patients with del(17p), VEN+R is well tolerated by patients, with the majority of patients who had an AE able to continue study treatment. The safety profile of VEN+R was acceptable, predictable and generally consistent with the known safety profiles of venetoclax and rituximab as single agents. No new safety signals were observed. (1)

B.2.10.1 Safety

The reporting period for AEs was longer in the VEN+R group than in the BR group owing to the longer duration of treatment with venetoclax. Patients in the BR group received 6 x 28-day cycles of treatment whereas patients in the VEN+R group received four to five weeks of venetoclax dose-titration followed by six cycles of VEN+R and then continued to receive venetoclax up until 2-years from initiation of combination therapy (cycle 1, day 1).

- In the BR group, patients received a median of six cycles of rituximab (range: 1-6) and a median of six cycles of BEN (range: 0-6). The median dose intensity for BEN was 100% (range: 50%-100%).
- All patients in the VEN+R group had the potential to receive at least 18 months of venetoclax therapy. In total, 78.9% of patients received at least 18 months of venetoclax treatment in the VEN+R group. The median duration of exposure to venetoclax was 22.1 months (range: 0.1-27.9) and the median dose intensity for venetoclax was 97.0% (range: 26%-100%).

The proportion of patients experiencing AEs was similar in both treatment groups, regardless of this difference in the length of the AE reporting period. Overall, 379 patients (99.2%) had at least one AE: all 194 patients (100.0%) in the VEN+R group and 185 patients (98.4%) in the BR group. The most common AE of any grade in both treatment groups was neutropenia (VEN+R:

60.8%; BR: 44.1%). AEs of grade 3 or 4 severity were reported in 82.0% and 70.2% of patients in the VEN+R and BR groups, respectively. Neutropenia was the most common grade 3 or 4 AE, with a higher incidence in the VEN+R group than in the BR group (57.7% vs. 38.8%). Notwithstanding the higher rate of neutropenia, the incidence of grade 3 or 4 febrile neutropenia (3.6% vs. 9.6%) and of grade 3 or 4 infections or infestations (17.5% vs. 21.8%) was lower in the VEN+R group compared to the BR group. Neutropenia was manageable with standard of care measures including growth factor support, dose interruptions and dose reductions.

Table 23 provides the incidence of SAEs, which was balanced between the treatment groups (VEN+R: 46%; BR: 43%). Pneumonia was the most frequently observed SAE in both treatment groups followed by febrile neutropenia, pyrexia, anaemia, infusion related reaction, sepsis, TLS and hypotension. Richter's transformation (i.e., conversion into an aggressive lymphoma, typically diffuse large B-cell lymphoma) was confirmed in six patients in the VEN+R group and in five patients in the BR group. AEs that resulted in death were reported in 5.2% and 5.9% of patients in the VEN+R and BR groups, respectively (see Table 23).

Table 23 AEs

Event	**VEN+R (n=194)**	**BR (n = 188)**
Grade 3 or 4 AE — no. of patients (%)	159 (82.0)	132 (70.2)
Total no. of events	335	255
Grade 3 or 4 AEs with at least 2% difference in incidence between groups — no. of patients (%)	**130 (67.0)**	**104 (55.3)**
Neutropenia[a]	112 (57.7)	73 (38.8)
Infections and infestations	34 (17.5)	41 (21.8)
Anaemia	21 (10.8)	26 (13.8)
Thrombocytopenia	11 (5.7)	19 (10.1)
Febrile neutropenia	7 (3.6)	18 (9.6)
Pneumonia	10 (5.2)	15 (8.0)
Infusion-related reaction	3 (1.5)	10 (5.3)
TLS	6 (3.1)	2 (1.1)
Hypotension	0	5 (2.7)
Hyperglycaemia	4 (2.1)	0
Hypogammaglobulinemia	4 (2.1)	0
SAEs with at least 2% incidence in either group — no. of patients (%)	**90 (46.4)**	**81 (43.1)**
Pneumonia	16 (8.2)[b]	15 (8.0)
Febrile neutropenia	7 (3.6)	16 (8.5)
Pyrexia	5 (2.6)	13 (6.9)
Anaemia	3 (1.5)	5 (2.7)
Infusion-related reaction	1 (0.5)	6 (3.2)
Sepsis	1 (0.5)	4 (2.1)
TLS	4 (2.1)	1 (0.5)
Hypotension	0	5 (2.7)
Fatal AEs— no. of patients (%)	10 (5.2)[b]	11 (5.9)

Source: Seymour et al. (1)
Key: AE, adverse event; SAE, serious adverse events; TLS, tumour lysis syndrome, VEN+R, venetoclax + rituximab, BR: bendamustine + rituximab
AEs were assessed using the National Cancer Institute Common Terminology Criteria for AEs, version 4.0 (NCI CTCAE, v4.0) Grade≥3 AEs and Grade≥3 laboratory toxicities.
[a] A higher percentage of new-onset events of neutropenia occurred during the combination-treatment period than during the venetoclax monotherapy phase (54.1% vs. 11.1%). Protocol-mandated dose interruption for all grade 3 or 4 events of neutropenia occurred in 43.3% of the patients in the VEN+R group. In total, 47.9% of the patients in the VEN+R group and 43.1% of the patients in the BR group received growth factor.
[b] Two SAEs of pneumonia that resulted in death occurred in patients who had both disease progression and confirmed Richter's transformation (i.e., conversion into an aggressive lymphoma, typically diffuse large B-cell lymphoma).

B.2.10.2 TLS

TLS is the result of a sequence of metabolic abnormalities resulting from tumour cell death and is classified into two categories: laboratory and clinical TLS. Laboratory TLS is defined when two or more of the following abnormalities are met within three days before or seven days after the initiation of chemotherapy: 1) 25% decrease from baseline in serum calcium, and/or 2) 25% increase from baseline in the serum values of uric acid, potassium, or phosphorous. Clinical TLS is defined when laboratory TLS is followed by one or more of the following clinical manifestations: 1) creatinine x≥1.5 upper limit of normal (age >12 years of age or age adjusted); 2) cardiac arrhythmia or sudden death; 3) seizure. (71)

Six patients (3.1%) in the VEN+R treatment group (four assigned as medium-risk and two as high-risk for TLS) and two patients (1.1%) in the BR treatment group reported TLS (Table 24). Most reported cases of TLS were laboratory TLS (5 patients in the VEN+R group vs 1 patient in the BR group)One clinical TLS event was reported in each treatment group (VEN+R: transient increase in creatinine; BR: grade 4 acute renal failure). All six patients received treatment for the correction of metabolic abnormalities. In the VEN+R treatment group, all TLS events occurred during the venetoclax dose titration period of 4 to 5 weeks and resolved within one or two days without sequelae. All six patients who experienced a TLS event subsequently completed dose titration to reach the target dose of 400 mg of venetoclax. TLS rates, despite the different dose titrations, prophylaxis and monitoring procedures followed in the initial part of the study, proved to be manageable and were consistent with previously reported V-mono safety data. This demonstrates the established safe deliverability of VEN+R especially during the dose titration phase. (72) Importantly, no clinical TLS was reported in patients treated with the current prophylaxis and monitoring measures (including in the five-week venetoclax dose titration).

Table 24 Summary of TLS AE

TLS event, n(%)	BR (n=188)	VEN+R (n=194)
All TLS AEs	2 (1.1)	6 (3.1)
Clinical TLS	1	1[a]
Laboratory TLS	1	5
NCI-CTCAE Grade≥3 TLS AE	2	6
Serious TLS AE	1	4
TLS AE leading to discontinuation of treatment	0	0
TLS AE leading to interruption of treatment	0	4

TLS AE leading to dose reduction	1	0
TLS AE leading to death	0	0

Source: MURANO: Clinical Study Report. Data on file. (73)
Key: AE, adverse event; BR, bendamustine + rituximab; VEN+R, venetoclax + rituximab; TLS, tumour lysis syndrome
[a] One AE of TLS was reported by the investigator as clinical TLS which occurred during the former four-week venetoclax dose titration period, prior to implementation of protocol amendment to the current five-week titration (including venetoclax 20 mg for one week).

B.2.11 Ongoing studies

The MURANO trial will have further data cuts. There are no other ongoing studies for VEN+R in this patient population.

B.2.12 Innovation

R/R CLL remains incurable, despite recent advances in treatment. (52,66,67,74–77) When disease progression occurs, particularly after treatment with conventional DNA-damaging agents, CLL cells serially accumulate adverse biologic features and increasingly develop resistance to therapies. (78) In addition to this, available therapies for CLL rarely result in MRD negativity and thus a continuous pattern of relapse is observed. (79) Hence, new treatments with alternative mechanisms of action, leading to clinical efficacy with deep responses, together with an acceptable side-effect profile are needed.

Venetoclax is a first-in-class, oral, selective inhibitor of BCL-2, with a unique targeted mechanism of action that distinguishes it from other available therapies. In the MURANO trial it was shown that VEN+R, a chemotherapy-free regimen, has the potential to meet the high unmet need in R/R CLL by offering a highly effective treatment with deep responses and a safety profile that is acceptable, predictable and generally consistent with the known safety profiles of venetoclax and rituximab as single agents. (1) After a median follow up of 23.8 months, the investigator-assessed PFS was both statistically significant ($p < 0.0001$) and clinically meaningful with a considerable and meaningful reduction in the risk of disease progression or death by 83% in patients receiving treatment with VEN+R compared to patients receiving treatment with BR (stratified HR=0.17; 95% CI: 0.11, 0.25). Median PFS has not been reached in patients receiving VEN+R treatment in the MURANO trial whereas the median PFS was 17 months (95% CI: 15.5, 21.6) in patients receiving treatment with BR. (1) The KM estimates of the PFS event-free rates were 93% with VEN+R treatment and 73% with BR treatment at 1-year; and 85% and 36%, respectively, at 2-years. Furthermore, this survival benefit was maintained across all CLL risk subgroups; including the del(17p)/TP53 and non-del(17p)/TP53 subgroups.

In addition to the survival benefit conferred by treatment with VEN+R, the innovative potential of VEN+R extends to the achievement of undetectable MRD that makes fixed treatment duration for this regimen feasible. This is intended to bring a shift in the current treatment paradigm of continuous dosing of targeted therapies in R/R CLL treatment. (30,32)

MRD is an objective measure of disease status defined by the number of leukemic cells remaining in peripheral blood or bone marrow following treatment. According to current

international definitions MRD negativity equals a quantitative detection of less than one CLL cell in 10,000 leukocytes (MRD level $<10^{-4}$). Presence of undetectable MRD indicates the depth of remission and is thus considered an important clinical endpoint in CLL given that complete eradication of the leukaemia is a desired outcome. (30,32) Numerous studies have demonstrated that achieving MRD below 1 in 10,000 (10^{-4}) CLL cells per leukocyte in the blood or bone marrow corresponds to a longer PFS. (31) The importance of MRD in CLL is further supported in the recent publication of the updated iwCLL guidelines in March, 2018. (30,32) In this publication evidence from prospective clinical trials is provided; notably the evidence shows that undetectable MRD is strongly correlated with an improved clinical outcome. In the MURANO trial, the rate of clearance of MRD on the basis of peripheral blood samples at nine-months was higher in the VEN+R treatment group (62.4%; 121/194) than in the BR treatment group (13.3%; 26/195). (1) This observation with VEN+R treatment is unprecedented in trials of relapsed CLL and suggestive of improved disease control over a longer-term even when therapy is discontinued. (32)

The importance of achieving undetectable MRD and thus the potential for improved survival outcomes, even when therapy is discontinued offers a rationale for treating patients for a fixed duration. The duration of treatment must however be sufficiently long to achieve undetectable MRD. In the MURANO trial, the treatment duration for venetoclax was chosen (based on results from earlier studies) as a maximum of 2-years (or disease progression if this occurred first), recognising the potential of venetoclax to achieve undetectable MRD, whilst aiming to reduce the cumulative toxicities, patient inconvenience and more frequent hospital attendances associated with indefinite treatment periods. Moreover, a fixed treatment period might reduce the development of mechanism-induced drug resistance. 2-years was considered sufficient to maintain and potentially further improve the depth and duration of response induced in the first six months of combination treatment. Clearly, there are potential benefits to patients, clinicians and the NHS of a fixed treatment duration therapy by achieving longer treatment-free periods and thereby a reduction in the overall cost burden of therapy.

B.2.13 Interpretation of clinical effectiveness and safety evidence

As discussed above, patients with R/R CLL still have very limited treatment options, with even fewer options for del(17p) compared to non-del(17p). BCRis provide an alternative option to 2L treatment with CIT, but idelalisib is used infrequently due to toxicity concerns, leaving limited options aside from ibrutinib. BCRi therapies are highly effective, but are associated with an indefinite treatment period and do not result in high rates of undetectable MRD. There is a high unmet need for therapies demonstrating improved PFS and OS, that are effective in both del(17p)/TP53 and non-del(17p)/TP53 subpopulations and that demonstrate potential to achieve undetectable MRD. There are also benefits to patients, clinicians and the NHS if these can be achieved with a fixed treatment duration of therapy.

VEN+R offers a highly effective chemotherapy free treatment option for patients with R/R CLL. Evidence from the MURANO trial suggests that VEN+R leads to better survival outcomes. This is best illustrated by the observed KM PFS and OS curves. There is also evidence of eradication of detectable disease, i.e. undetectable MRD, which opens the prospect of time-

limited therapy in this setting. Results of the MURANO trial have demonstrated the efficacy of a truncated treatment strategy, i.e. fixed treatment duration with VEN+R for R/R CLL patients. This is expected to bring a shift in the paradigm of continuous dosing of targeted therapies such as BCRis. The fixed treatment duration of 2-years with VEN+R offers additional value as it has the potential to improve treatment adherence and thus reduce the potential risk of acquired drug resistance.

Notably, these results were observed in a multinational setting, with a safety profile of the combination that is acceptable, predictable and generally consistent with the known safety profiles of venetoclax and rituximab as single agents. Neutropenia is a known on-target effect of venetoclax, and the higher rates of grade 3 or 4 events that were observed in the VEN+R group as compared with the BR group were not unexpected, especially given the longer duration of treatment with venetoclax compared to BR. It is possible that events of neutropenia that resulted in the dose modifications of venetoclax (which were mandated by the trial protocol if an event of grade 3 or 4 neutropenia occurred) may be mitigated with improved guidance on the management of neutropenia with granulocyte colony stimulating factor. The relatively small number of patients in the VEN+R group who had TLS shows the effectiveness of the risk-mitigation procedures that were implemented during the trial and the generally manageable and safe delivery of the treatment in a multinational trial.

The MURANO trial included the BR regimen as a comparator which was appropriate given that this combination was widely used in the real-world setting at the time of study design (study conception of MURANO pre-dated the approval of BCRis). Of note is that, even though ibrutinib use has increased in clinical practice, UK clinical experts have advised that a few patients still receive BR 2L. Therefore, the MURANO trial results are generalisable to the UK. Furthermore, baseline characteristics in the trial are broadly in line with UK NHS patient characteristics.

Relative efficacy estimates for the comparators relevant to the NICE decision problem were derived using unanchored comparisons since the evidence network for treatments for R/R CLL is disconnected (see Section B.2.9). A MAIC was used to align VEN+R with the comparator using aggregate baseline characteristic data reported for the comparator trials. Results from this comparison suggest that VEN+R has a similar efficacy to ibrutinib and is more effective than idela+R. Evidence from the literature supports an equal efficacy assumption between ibrutinib and ibrutinib + BR. (68) Using this assumption with the VEN+R vs. ibrutinib + BR MAIC outcomes provides additional credence that VEN+R and ibrutinib perform similarly with the exception of achieving undetectable MRD which has a strong correlation with better clinical outcome. This is expected to facilitate a fixed treatment duration with VEN+R. These differentiators are expected to make VEN+R a cost-effective treatment for R/R CLL patients (see Section B.3.2).

The MURANO trial results are positive, but there are a number of data limitations:

1. **MURANO trial data immaturity**: Based on the first data cut (after a median follow-up period of 23.8 months), the median OS and PFS had not been reached in the VEN+R group. This indicates superiority of VEN+R over the control group as patients are event free for significantly longer. However, this may present uncertainty when interpreting the results over

a long term 30-year time horizon. Furthermore, in the MURANO trial, patients were treated for a maximum of 2-years or until disease progression (whichever came first) unless disease progression or unacceptable toxic effects occurred sooner. This introduces uncertainty in the duration of treatment effect, pending longer term follow-up data. (NB: the 2-year fixed treatment duration was chosen based on results from earlier studies indicating that venetoclax resulted in patients achieving undetectable MRD and that treatment of patients with VEN+R beyond 2-years is unlikely to achieve further reductions in the rate of undetectable MRD even years after stopping treatment. Thus, there is potential for improved disease control over a longer term even when therapy is discontinued and there are potential benefits to patients/carers, clinicians and the NHS of a fixed treatment duration therapy in the form of time off treatment and reduction of the overall cost burden of therapy*)*

2. **Disconnected network of evidence**: There are no trials comparing BR (MURANO's control group) to relevant comparators. As such, the traditional ITC methods to compare VEN+R vs. relevant comparators cannot be performed. The only option is to perform a MAIC to adjust for prognostic factors and effect modifiers. However, the absence of a link (anchor) between the trials makes the results uncertain. Applying the MAIC HRs into the model for the comparison of VEN+R vs. ibrutinib leads to an outcome that is unlikely to hold face validity: i.e. no PPS for ibrutinib. This indicates that there are unoberved differences in the trials included in the MAIC which cannot be adjusted for and hence HRs are uncertain. Of note is that, when an anchored MAIC was undertaken, using Ibrutinib+BR as a surrogate for the efficacy of Ibrutinib (in line with published evidence) (68), the HR results were broadly in line with that of the un-anchored comparison, thus corroborating the results of the un-anchored MAIC.

AbbVie acknowledges these data limitations and anticipates that more mature data cuts of MURANO will help reduce the uncertainty margins around the efficacy estimates.

In conclusion, MURANO is the first randomised trial comparing new targeted agents to treat CLL against CIT demonstrating superiority of a chemotherapy free approach in both del(17p)/TP53 and non-del(17p)/TP53 sub-populations with a manageable safety profile. In addition, it adds value in comparison to BCRis in terms of achieving undetectable MRD, thereby offering a regimen with a fixed treatment duration. VEN+R is a valuable addition to the range of available therapies in the UK.

B.3 Cost effectiveness

- This submission uses a three-state partitioned survival model, selected due to the availability of comparator data and was considered the most suitable option to provide evidence relating to the decision problem. The three-health state division (pre-progression, post-progression and death) matches well with the clinical and disease pathway for R/R CLL patients. In this framework, transitions are modelled using PFS and OS survival curves.
- MURANO trial PFS and OS curves were parameterised using the conventional models described by the NICE technical support document (TSD), however extrapolated outcomes were considered implausible based on clinical expert feedback due to the immaturity of the MURANO trial data.
- Therefore, an alternative approach was taken to make use of the data available; OS and PFS was modelled jointly. This assumes proportionality between endpoints (PFS and OS) and treatment (VEN+R and BR). Based on internal analyses using MURANO and external data sources available, proportionality was not rejected.
- Subgroup (17p-del/TP53 and non-17pdel/TP53), deterministic, probabilistic and scenario cost-effectiveness analyses were undertaken.
- The base case model selected for the joint PFS/OS model is Weibull, which results in plausible assumptions (validated by external experts and in line with longer term data from registries) of [redacted] of patients on VEN+R surviving 20 years. Time horizon of the model is 30 years as <1% of patients are alive.
- Comparator survival curves were estimated by using MAIC generated PFS and OS hazard ratios to adjust the VEN+R parametric survival curves.
- At list price, VEN+R either dominates relevant comparators or is cost-effective at the £20,000 to £30,000 willingness to pay (WTP) threshold.
- A similar pattern of dominancy or cost-effectiveness is observed (a) when the discounted price for VEN+R is used; (b) in the subgroup of patients with 17p-del/TP53 (c) in the deterministic and probabilistic sensitivity analyses, and scenario analyses results.
- In general, across all comparisons, the greatest impact on incremental costs is seen for OS and PFS MAIC HRs and the VEN+R joint model parameters.
- Longer-term follow-up of the MURANO trial is expected to reduce uncertainties in cost-effectiveness estimates.

B.3.1 Published cost-effectiveness studies

An SLR was conducted to identify studies assessing the cost-effectiveness of interventions in R/R CLL. For full details of the methods used to conduct this review, please see **Error! Reference source not found.**.

The search strategy was developed and tested as part of the a priori protocol to identify relevant studies. The search algorithms used were generated using the PICOS framework and in-line with the objective to identify clinical evidence for VEN+R and its relevant comparators from randomised and non-randomised studies described in Section B.2.1.

Across all the electronic database searches, articles with published, unpublished or on-going status were permitted. The sources that were searched are provided in Table 25. Additionally, to retrieve further studies not identified through the electronic database search, reference lists of included articles and systematic reviews were screened. Moreover, the proceedings of conferences held in 2014-2018 were also searched. All searches were conducted on 8 July, 2017 with an update of the SLR performed on 30 April, 2018, respectively. Full details of the review methodology are provided in **Error! Reference source not found.**.

Table 25 Search sources economic SLR

Type of database	Name of database	Search strategy
Electronic databases	• Medline (via ProQuest) (link) • Embase (via ProQuest) (link) • EconLit (via ProQuest) (link)	See **Error! Reference source not found.**
	• The Cochrane Library, incorporating: o EED (link) o HTA (link)	See **Error! Reference source not found.** - **Error! Reference source not found.**
Conferences proceedings	• ASH (link) • BSH (link) • ESMO (link) • ASCO (link) • ISPOR (link) • iwCLL (link) • EHA (link)	See **Error! Reference source not found.**- **Error! Reference source not found.**

Key: ASCO, American Society of Clinical Oncology; ASH, American Society of Haematology; BSH, British Society for Haematology; EED, NHS Economic Evaluation Database; HTA, Health Technology Assessment database; ISPOR, International Society For Pharmacoeconomics and Outcomes Research; iwCLL, International Workshop on Chronic Lymphocytic Leukaemia

B.3.1.1 Limits applied to the search strategy

The same limits were applied to the economic SLR as the ones in the clinical SLR reported in **Error! Reference source not found.**.

B.3.1.2 Eligibility criteria for selection

The articles identified underwent a selection process based on pre-specified criteria for inclusion and exclusion. The pre-specified eligibility criteria[2] are reported in Table 26.

Table 26 Economic evaluations review: cost-effectiveness

PICOS	Inclusion criteria	Exclusion criteria
Population	• Adult patients (≥18 years)[a] • Human • Established R/R CLL - including del(17p) R/R CLL	• Patients without established R/R CLL • Paediatric patients (<18 years) • Animal studies • In vitro studies
Intervention	• Ibrutinib • Idela +R • V-mono • VEN+R • HDMP • Lenalidomide • Acalabrutinib • Oxaliplatin • Fludarabine • Cytarabine • Rituximab • HDMP • HDMP+ Rituximab • OFA • Allogenic stem cell transplantation • Alemtuzumab • Flavopiridol • FCR • Chlorambucil • Chlorambucil + rituximab • Obinutuzumab • Obinutuzumab + chlorambucil • BR	Any interventions not specified under inclusion criteria
Comparator	• Any comparator • No treatment • Placebo	NA
Outcomes	• Total costs • QALYs • ICERs/ cost effective at some ICER threshold • Cost per life year gained • Cost per progression free year	Any outcome not specified under inclusion criteria.
Study Design	• Economic Evaluations • Economic evaluations alongside RCTs • Cost utility analysis (CUA)	• Economic evaluations not reporting outcomes of interest • Study designs not specified under inclusion criteria

[2] During the conduct of the review as the NICE scope was not yet available, the list of comparators was more comprehensive, but the NICE final scope is reflected in the eligibility criteria.

PICOS	Inclusion criteria	Exclusion criteria
	• Cost effectiveness analysis (CEA) • Cost minimization analysis (CMA)	
Publication Type	• Full-text articles • Conference proceedings from July 2014 onwards	• Any articles published before 2000 • Any conference proceedings published before July 2014[b] • Review articles[c] • Notes • Erratum • Comments • Editorials
Language	Publications in English	Other

Key: BR, bendamustine + rituximab; CEA, cost effectiveness analysis; CLL, chronic lymphocytic leukaemia; CMA, cost minimization analysis; CUA, cost utility analysis; Del(17p), deletion of 17p chromosome; FCR, fludarabine + cyclophosphamide + rituximab; HDMP, high-dose methylprednisolone; ICER, incremental cost-effectiveness ratio; Idela + R, idelalisib + rituximab; NA, not applicable; PFS, progression-free survival; QALY, quality-adjusted life year; R/R, relapsed/refractory; RCT, randomised controlled trial; VEN+R, venetoclax + rituximab; V-mono, venetoclax monotherapy.

[a] Studies which reported patient populations both above and below 18 years were included; provided stratified results for the ≥18 population were reported.

[b] This was applicable to the searches in clinical trial databases and conferences proceedings. This approach is justified based on the assumption that all research before July 2014 would have been published as full-text journal publications and would be captured via the search in Embase, Medline, EconLit and Cochrane.

[c] Review articles were included, but were not extracted: instead, these reviews were reported on a separate tab of the selection spreadsheet and were checked for relevant references that may have been missed during the literature review.

A total of 2,744 cost effectiveness studies were identified through searching the databases. After removing 65 duplicates, 2,679 publications were screened in the title/abstract selection-phase. Of these 2,679 publications, 56 full-text articles were assessed for eligibility. In total, 29 papers were deemed eligible and were included for data extraction and reporting. The PRISMA flow is shown in Figure 18.

Figure 18 PRISMA diagram of cost-effectiveness studies

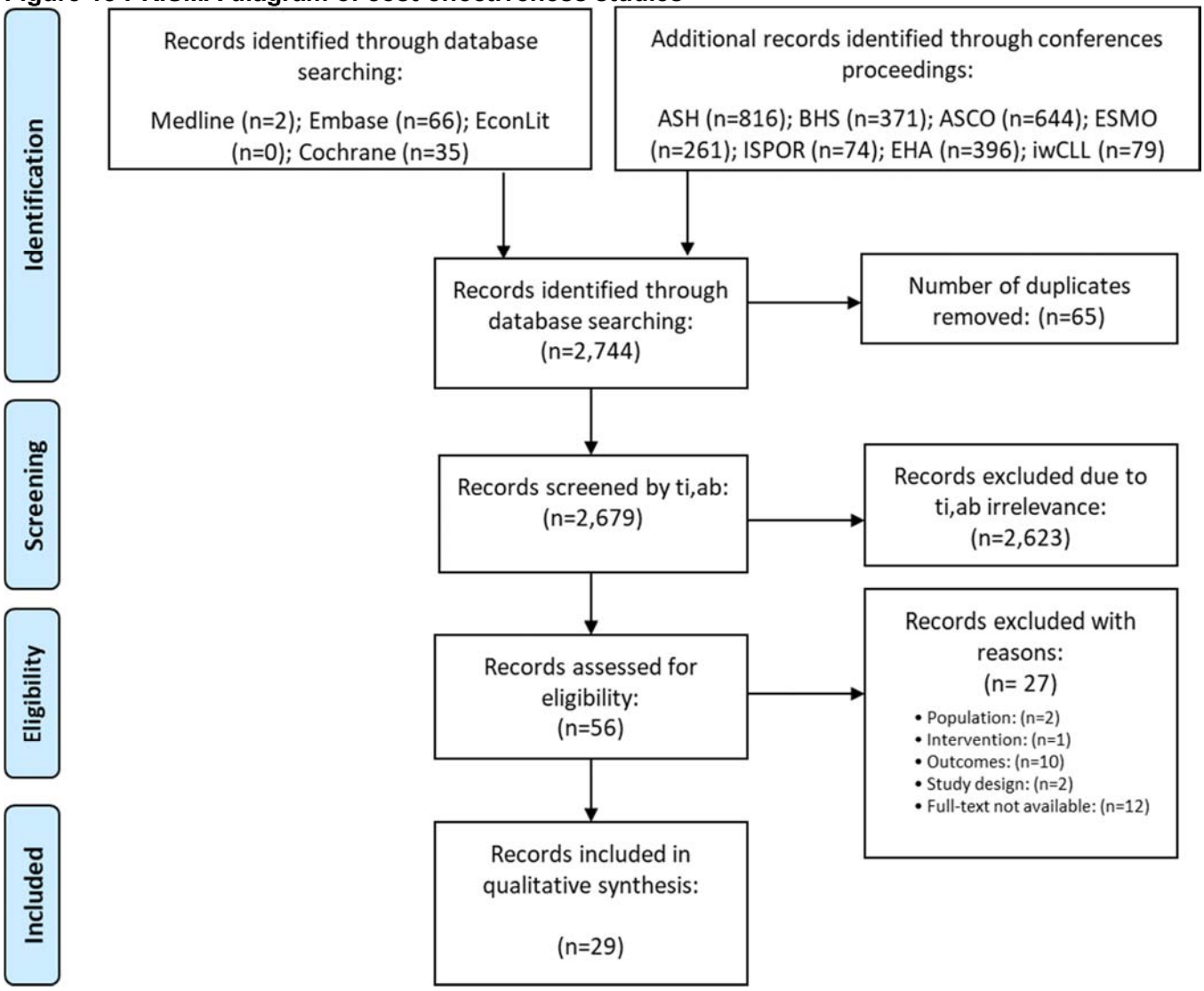


Table 27 includes the summary of the cost-effectiveness studies identified. The most frequent modelling methods were Markov (n=8) and partitioned survival (n=10). The set of health states in most cases included pre-progression, post-progression and death. Some approaches used health states to differentiate between type of treatment (e.g. oral, intravenous [IV]) and treatment line. Most studies used a lifetime horizon and cycle lengths varied between 1 day and 3 months.

Idela+R was the intervention that was most commonly investigated (n=7), although it should be mentioned that some of the included publications report on one and the same analysis or set of analyses. Additionally, several studies investigating OFA (n=5), FCR (n=4) and rituximab (n=4) were identified. There are no apparent systematic differences in the choice of economic evaluations or analytical approaches per intervention, per country of choice or by year of study. **Error! Reference source not found.** reports a complete reference list of included studies and excluded full text publications together with reasons for exclusion

Table 27 Summary list of published cost-effectiveness studies

Study and year	Summary of model		Patient population	Time horizon and cycle length	ICER (per QALY/LY gained)
	Model type	Health states			
Sullivan et al., 2015 (PQE7) (80)	Markov model	5 health states • No description of health states	Previously treated CLL	• Lifetime • Cycle length not mentioned	• Idela + R vs. rituximab: £21,224 /QALY gained
Sullivan et al., 2016 (BSH10) (81)	Markov model	5 health states • No description of health states	Previously treated CLL	• Lifetime • Cycle length not mentioned	• Idela + R vs. rituximab £26,403 per QALY • Idela + R vs. OFA: £ 10,668 per QALY • Idela + R vs. best supportive care: £ 35,275 per QALY
Silva et al., 2015 (PQE11)(82)	Partitioned survival	3 health states: • Pre-progression • Post-progression • Death	R/R CLL	• Lifetime • 1 week	Idela + R vs. rituximab: • €32,702 per QALY • € 15,935 per LY
Gouveia et al., 2015 (ISPOR25) (83)	Partitioned survival model[3]	3 health states • pre-progression • post-progression • death	R/R CLL	• Lifetime • Cycle length not mentioned	Idela + R vs. rituximab: • €32.702 per QALY • €15.935 per LYG
Marchetti et al., 2015 (ASH196) (84)	Markov model	5 health states • progression-free on IV therapy • progression-free on oral extended therapy • progression-free off-therapy • progressed disease • death	R/R CLL	NR	• Idela + R vs. FCR: € 20,441 • Idela + R vs. BR: € 26,445 • Idela + R vs. BO: €21,466 • Idela + R vs. R: €14,376 • Idela + R vs. O: €1,263
Leleu et al., 2015 (ISPOR27) (85)	Partitioned survival model	NR	CLL, not further specified	• 10 years • Cycle length not mentioned	• Idela + R vs. early relapse treatment: € 30,480/QALY • Idela+R vs late relapse treatment: € 31,312
Yu et al., 2015 (ISPOR31) (86)	Partitioned survival model	3 health states • pre-progressed • progressed	Relapsed CLL	• Lifetime • Cycle length not mentioned	Idela + R vs. rituximab: • $242,884 per QALY

[3] It is mentioned that the cost-effectiveness model adopted a lifetime horizon with three health states: 1) pre-progression; 2) post-progression and 3) death. Patients enter in the model in the pre-progression state and in each cycle (1 week length) may survive without progression; advance to post-progression or die. Remission was not considered in the model: patients in post-progression state remain there until death.

		• death			
Dretzke et al., 2010 (COE5) (87)	Partitioned survival model	3 health states • PFS • progressed • death	R/R CLL including patients with a del 17p mutation	• 25 years • Cycle length not mentioned	FCR vs. FC • £15,593
Adena et al., 2014 (COE28) (88)	Markov model with time-dependent transitions	3 health states • Unprogressed, progressed and death	R/R CLL	• 3 months cycle length • time horizon not mentioned	FCR vs. FC $42,906 per QALY
Mandrik et al., 2015 (PQE33) (89)	Markov model	• 3 health states • Stable/progression-free state • Progressed • Death	R/R CLL (Mean age 62)	• Life-time horizon • 1 month	FCR vs. FC • $11,065/QALY
Pan et al., 2014 (ISPOR15) (90)	A health state model	NR	Previously treated CLL	• 1. 5-year time horizon 2. 10-year time horizon	NR
Welten et al., 2016 (PQE19) (91)	Partitioned survival model	3 health states • PFS • PSS • Death	Relapsed CLL	• Lifetime • 3 months	• Ibrutinib vs. OFA: € 54,833 per QALY • Ibrutinib vs. indirect comparators (see column Comparators): ranged between €54,833 and €67,754 per QALY • ICER per LYG ranged from €40,051 to €51,196
Hoyle et al., 2010 (COE9) (92)	Partitioned survival model	3 health states • alive pre-progression • alive post progression • dead	Refractory CLL	NR	Ofatumumab vs. BSC £38,241 • Updated GSK's model with alternative utilities for PFS and PD, and included the 17p and 11q chromosomal deletions, the base-case ICER increased to at least £81,500 per QALY.
Hatswell et al., 2017 (PQE30) (93)	Partitioned survival model	3 health states • PFS • Progressed disease • Death	Double refractory CLL	• 10 years • 1 day	Ofatumumab vs. BSC • £63.542 per life year • £130.563 per QALY
Davies et al., 2016 (PQE23) (94)	Partitioned survival	3 health states • Progression-free	Relapsed CLL	• Lifetime • Cycle length	Ofatumumab vs observation $68,600 /QALY

	model	• Post-progression • Death		not mentioned	
Dervaux et al., 2007 (COE29) (95)	Markov model	6 health states • progression to first-line treatment without second-line treatment • progression to first-line treatment with second-line treatment • After second-line treatment, three possibilities exist: 1. Patients can be refractory to the treatment; 2. They can die; 3. They can be in remission for a while then be in progression to second-line treatment.	R/R CLL	• A 3-year time horizon • A 3-month cycle (corresponding to the frequency of follow-up of patients in remission)	NR
Scott et al., 2007 (COE30) (96)	A spreadsheet-based model	NR	R/R CLL	NR	NR
Mittmann et al., 2012 (COE31) (97)	NR	NR	R/R CLL (Median ages reported between 63 and 66)	NR	• Obinutuzumab + chlorambucil vs. chlorambucil: per € 28,028/QALY
Plommet et al., 2015 (ISPOR 22) (98)	Markov model	3 health states • Progression free survival • Remaining 2 states are not reported	CLL	• 10 years • Cycle length not mentioned	• Obinutuzumab + chlorambucil vs .rituximab + chlorambucil: € 20,484/QALY
Ho et al., 2017 (ISPOR1) (99)	Markov model	NR	CLL patients with no previous treatment, ineligible to full dose of fludarabine	• Lifetime • Cycle length not mentioned	• BR 68.955 per QALY

Hassan et al. 2017 (UPQE04) (100)	Partitioned survival model	Three health states • PFS • PD • death	RR CLL	20 years NR	Ibrutinib vs. OFA: £53,245 per QALY Ibrutinib vs. BR: £49,023 per QALY Ibrutinib vs. Idela +R: £53,644 per QALY Ibrutinib vs. Physician's choice: £52,787 per QALY
Djambazov et al. 2017 (UPQE06) (101)	Markov model	NR	R/R CLL ± del(17p)/ TP53	20 years NR	1L CLL del 17p/TP53 mut: Venetoclax vs. Idela+R (ICER 12 212 BGN/QALY) Venetoclax vs. rituximab / BEN (ICER 21 485 QALY) 2L R/R CLL ± del(17p)/ TP53 mut: Venetoclax vs. OFA/BEN (ICER 9931 BGN/QALY) Venetoclax vs. rituximab /BEN (ICER 39 085 QALY) Venetoclax vs. idelalisib/ rituximab (ICER 12 212 QALY)
Sail et al., 2017 (UPQE07) (102)	Markov model	19 health states	del(11q), del(17p) and mutated IGHV in R/R CLL	Lifetime three-months	NA
Alsaid et al., 2017 (UPQE08) (103)	Markov model	Three health states • on or off therapy • progression • death	R/R CLL del(17p)	Lifetime NR	NR
Alsaid et al., 2017 (UPQE09) (104)	Markov model	Three health states • on or off therapy • PD • Death	R/R CLL del(17p)	Three-years and lifetime NR	NR
Vreman et al., 2017 (UPQE12) (105)	Partitioned survival model	Three health states • PFS • PD • Death	CLL	Lifetime one month	NR
Yang et al., 2018 (UISPOR02) (106)	Decision tree analysis	Three health states • PFS • PD • Death	R/R CLL	One-year NR	NR
Kousoulakou et al.,	Markov	Three health states	R/R CLL	Lifetime	Obinutuzumab, €16,614 per QALY

2017 (UISPOR06) (107)	model	• NR		NR	
Casado et al., 2018(UPQE03) (108)	Partitioned survival Markov model	Three health states • PFS • PD • Death	R/R CLL	Lifetime (30 years) NR	€29 990/QALY per QALY

Key: BR, bendamustine + rituximab; CEA, cost effectiveness analysis; CLL, chronic lymphocytic leukaemia; CMA, cost minimization analysis; CUA, cost utility analysis; Del(17p), deletion of 17p chromosome; FCR, fludarabine + cyclophosphamide + rituximab; HDMP, high-dose methylprednisolone; ICER, incremental cost-effectiveness ratio; Idela+R, idelalisib + rituximab; NA, not applicable; PFS, progression-free survival; QALY, quality-adjusted life year; R/R, relapsed/refractory; RCT, randomised controlled trial; VEN+R, venetoclax + rituximab; V-mono, venetoclax monotherapy.

[a] Studies which reported patient populations both above and below 18 years were included; provided stratified results for the ≥18 population were reported.

The results of the quality assessment of the identified cost-effectiveness studies are included in Table 28, Table 29 and Table 30.

Table 28 Drummond checklist of economic studies (A)

Table A	Sullivan 2015 (PQE7)	Silva 2015 (PQE11)	Gouveia2015 (PQE12)	Marchetti 2015 (PQE18)	Welten 2016 (PQE19)	Davies 2016 (PQE23)	Leleu 2015 (PQE27)	Yu 2015 (PQE29)	Hatswell 2017 (PQE30)
The research question is stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The economic importance of the research question is stated	No	Yes	No	No	No	Yes	No	Yes	No
The viewpoint(s) of the analysis are clearly stated and justified	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes
The rational for choosing alternative programmes and interventions compared is stated	No	No	No	No	No	No	No	No	Yes
The alternatives being compared are clearly described	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table A	Sullivan 2015 (PQE7)	Silva 2015 (PQE11)	Gouveia2015 (PQE12)	Marchetti 2015 (PQE18)	Welten 2016 (PQE19)	Davies 2016 (PQE23)	Leleu 2015 (PQE27)	Yu 2015 (PQE29)	Hatswell 2017 (PQE30)
The form of economic evaluation used is stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The choice of form of economic evaluation is justified in relation to the questions addressed	No	No	No	No	No	No	No	No	No
The source(s) of effectiveness estimates used are stated	Yes	Not clear	Not clear	Yes	Yes	Yes	Not clear	Yes	Yes
Details of the design and results of effectiveness studies are given (id based on a single study)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Details on method of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies)	NA	NA	NA	NA	NA	NA	NA	NA	NA
The primary outcome measure(s) of the economic evaluation are clearly stated	No	Not clear	Yes	No	Yes	Yes	No	No	Not clear
The methods to value benefits are stated	Not clear	No	No	No	No	Yes	No	No	No
Details of the subjects from whom valuations were obtained were given	Yes	No	No	No	No	Yes	No	No	No
Productivity changes (if included) are reported separately	NA	NA	NA	NA	NA	NA	NA	NA	NA
The relevance of productivity changes to the study question is discussed	NA	NA	NA	NA	NA	NA	NA	NA	NA
Quantities of resource use are reported	No	No	No	No	No	No	No	No	No

Table A	Sullivan 2015 (PQE7)	Silva 2015 (PQE11)	Gouveia2015 (PQE12)	Marchetti 2015 (PQE18)	Welten 2016 (PQE19)	Davies 2016 (PQE23)	Leleu 2015 (PQE27)	Yu 2015 (PQE29)	Hatswell 2017 (PQE30)
separately from their unit costs									
Methods for the estimation of quantities and unit costs are described	No	Yes	No	No	No	No	No	No	No
Currency and price data are recorded	No	No	No	Yes	No	No	No	No	No
Details of currency of price adjustments for inflation or currency conversion are given	No	No	No	No	No	No	No	No	No
Details of any model used are given	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The choice of the model used and the key parameters on which it is based are justified	No	No	No	No	No	Yes	No	No	Yes
Time horizon of costs and benefits is stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The discount rate(s) is stated	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
The choice of the discount rate(s) is justified	No	Yes	Yes	No	No	No	No	No	Yes
An explanation is given if costs and benefits are not discounted	NA	NA	NA	NA	NA	NA	NA	NA	NA
Details of statistical tests and confidence intervals are given for stochastic data	No	No	No	No	No	Yes	No	No	No
The approach to sensitivity analysis is given	No	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Yes
The choice of variables of sensitivity analysis is	No	No	No	No	No	No	No	No	No

Table A	Sullivan 2015 (PQE7)	Silva 2015 (PQE11)	Gouveia2015 (PQE12)	Marchetti 2015 (PQE18)	Welten 2016 (PQE19)	Davies 2016 (PQE23)	Leleu 2015 (PQE27)	Yu 2015 (PQE29)	Hatswell 2017 (PQE30)
justified									
The range over which variables are varied is justified	No	No	No	No	No	No	No	No	No
Relevant alternatives are compared	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Incremental analysis is reported	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Major outcomes are presented in a disaggregated as well as aggregated form	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes
The answer to the study question is given	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Conclusion follow from the data reported	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Conclusions are accompanied by the appropriate caveats	No	No	No	No	No	No	No	No	Yes

Table 29 Drummond checklist of economic studies (B)

Table B	Mandrik 2015 (PQE33)	Dretzke 2010 (COE5)	Hoyle 2010 (COE9)	Adena 2014 (COE28)	Dervaux 2007 (COE29)	Scott 2007 (COE30)	Mittmann 2012 (COE31)	Sullivan 2016 (BSH10)	Ho 2017 (ISPOR1)	Welten 2016 (ISPOR6)
The research question is stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The economic importance of the research question is stated	No	No	No	No	No	No	Yes	No	No	No
The viewpoint(s) of the analysis are clearly stated and justified	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes
The rational for choosing alternative	Yes	No	No	Yes	No	Yes	No	No	No	No

Table B	Mandrik 2015 (PQE33)	Dretzke 2010 (COE5)	Hoyle 2010 (COE9)	Adena 2014 (COE28)	Dervaux 2007 (COE29)	Scott 2007 (COE30)	Mittmann 2012 (COE31)	Sullivan 2016 (BSH10)	Ho 2017 (ISPOR1)	Welten 2016 (ISPOR6)
programmes and interventions compared is stated										
The alternatives being compared are clearly described	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The form of economic evaluation used is stated	Yes	No	Yes	Yes	Yes	Yes	Not clear	Yes	Yes	Yes
The choice of form of economic evaluation is justified in relation to the questions addressed	No	No	No	No	No	No	No	No	No	No
The source(s) of effectiveness estimates used are stated	Yes	Not clear	No	Yes	Yes	Yes	Not clear	Yes	Yes	Yes
Details of the design and results of effectiveness studies are given (id based on a single study)	Yes	No	No	Yes	NA	Yes	NA	Yes	No	Yes
Details on method of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies)	NA	NA	NA	NA	Yes	NA	Yes	NA	NA	NA
The primary outcome measure(s) of the economic evaluation are clearly stated	No	Yes	Yes	Not clear	Yes	Yes	Yes	No	Yes	Yes
The methods to value benefits are stated	Yes	No	No	No	No	No	No	Not clear	No	No

Table B	Mandrik 2015 (PQE33)	Dretzke 2010 (COE5)	Hoyle 2010 (COE9)	Adena 2014 (COE28)	Dervaux 2007 (COE29)	Scott 2007 (COE30)	Mittmann 2012 (COE31)	Sullivan 2016 (BSH10)	Ho 2017 (ISPOR1)	Welten 2016 (ISPOR6)
Details of the subjects from whom valuations were obtained were given	Yes	Yes	No	Yes	No	No	No	Yes	No	No
Productivity changes (if included) are reported separately	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
The relevance of productivity changes to the study question is discussed	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Quantities of resource use are reported separately from their unit costs	Not clear	No	No	Yes	Yes	Yes	No	No	No	No
Methods for the estimation of quantities and unit costs are described	No	No	No	Yes	No	Yes	No	No	No	No
Currency and price data are recorded	Yes	No	No	Yes	No	Yes	Yes	No	No	No
Details of currency of price adjustments for inflation or currency conversion are given	Yes	No	No	No	No	Yes	No	No	No	No
Details of any model used are given	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes
The choice of the model used and the key parameters on which it is based are justified	Yes	No	No	No	No	No	No	No	No	No
Time horizon of costs and benefits is stated	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
The discount rate(s) is stated	Yes	No	Yes	Yes	No	No	No	No	No	No
The choice of the	No	No	No	No	No	NA	No	No	No	No

Table B	Mandrik 2015 (PQE33)	Dretzke 2010 (COE5)	Hoyle 2010 (COE9)	Adena 2014 (COE28)	Dervaux 2007 (COE29)	Scott 2007 (COE30)	Mittmann 2012 (COE31)	Sullivan 2016 (BSH10)	Ho 2017 (ISPOR1)	Welten 2016 (ISPOR6)
discount rate(s) is justified										
An explanation is given if costs and benefits are not discounted	NA	NA	NA	NA	NA	Yes	NA	NA	NA	NA
Details of statistical tests and confidence intervals are given for stochastic data	No	No	No	No	Yes	No	No	No	No	No
The approach to sensitivity analysis is given	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes
The choice of variables of sensitivity analysis is justified	Yes	No	No	No	No	No	No	No	No	No
The range over which variables are varied is justified	Yes	No	No	Yes	No	No	No	No	No	No
Relevant alternatives are compared	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Incremental analysis is reported	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Major outcomes are presented in a disaggregated as well as aggregated form	Yes	No	No	Yes	No	No	Yes	No	No	Yes
The answer to the study question is given	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Conclusion follow from the data reported	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Conclusions are accompanied by the appropriate caveats	Yes	No	Yes	No	No	No	No	No	No	No

Table 30 Drummond checklist of economic studies (C)

Table C	Pribylova 2015 (ISPOR7)	Pan 2015 (ISPOR15)	Paiva 2015 (ISPOR17)	Lacaine 2015 (ISPOR18)	Plommet 2015 (ISPOR22)	Gouveia 2015 (ISPOR25)	Leleu 2015 (ISPOR27)	Sullivan 2015 (ISPOR28)	Yu 2015 (ISPOR31)	Marchetti 2015 (ASH196)
The research question is stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The economic importance of the research question is stated	No	No	No	Yes	No	No	No	No	Yes	No
The viewpoint(s) of the analysis are clearly stated and justified	Yes	No	Yes	No	Not clear	Yes	No	Yes	Yes	No
The rational for choosing alternative programmes and interventions compared is stated	No	No	No	No	Yes	No	No	No	No	No
The alternatives being compared are clearly described	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The form of economic	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table C	Pribylova 2015 (ISPOR7)	Pan 2015 (ISPOR15)	Paiva 2015 (ISPOR17)	Lacaine 2015 (ISPOR18)	Plommet 2015 (ISPOR22)	Gouveia 2015 (ISPOR25)	Leleu 2015 (ISPOR27)	Sullivan 2015 (ISPOR28)	Yu 2015 (ISPOR31)	Marchetti 2015 (ASH196)
evaluation used is stated										
The choice of form of economic evaluation is justified in relation to the questions addressed	No	No	No	No	No	No	No	No	No	No
The source(s) of effectiveness estimates used are stated	No	Yes	Not clear	No	Not clear	Not clear	Not clear	Yes	Yes	Yes
Details of the design and results of effectiveness studies are given (id based on a single study)	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes
Details on method of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies)	NA	NA	NA	No	NA	NA	NA	NA	NA	NA
The primary	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No

Table C	Pribylova 2015 (ISPOR7)	Pan 2015 (ISPOR15)	Paiva 2015 (ISPOR17)	Lacaine 2015 (ISPOR18)	Plommet 2015 (ISPOR22)	Gouveia 2015 (ISPOR25)	Leleu 2015 (ISPOR27)	Sullivan 2015 (ISPOR28)	Yu 2015 (ISPOR31)	Marchetti 2015 (ASH196)
outcome measure(s) of the economic evaluation are clearly stated										
The methods to value benefits are stated	NA	No	NA	NA	Yes	No	No	Not clear	No	No
Details of the subjects from whom valuations were obtained were given	No	No	No	No	No	No	No	Yes	No	No
Productivity changes (if included) are reported separately	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
The relevance of productivity changes to the study question is discussed	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Quantities of resource use are reported separately from their unit costs	No	NA	No	No	No	No	No	No	No	No
Methods for	No	NA	No	No	No	No	No	No	No	No

Table C	Pribylova 2015 (ISPOR7)	Pan 2015 (ISPOR15)	Paiva 2015 (ISPOR17)	Lacaine 2015 (ISPOR18)	Plommet 2015 (ISPOR22)	Gouveia 2015 (ISPOR25)	Leleu 2015 (ISPOR27)	Sullivan 2015 (ISPOR28)	Yu 2015 (ISPOR31)	Marchetti 2015 (ASH196)
the estimation of quantities and unit costs are described										
Currency and price data are recorded	No	NA	No	No	Yes	No	No	No	No	Yes
Details of currency of price adjustments for inflation or currency conversion are given	No	NA	No	No	No	No	No	No	No	No
Details of any model used are given	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
The choice of the model used and the key parameters on which it is based are justified	No	No	No	No	No	No	No	No	No	No
Time horizon of costs and benefits is stated	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
The discount rate(s) is stated	No	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes
The choice of	No	No	No	No	No	Yes	No	No	No	No

Table C	Pribylova 2015 (ISPOR7)	Pan 2015 (ISPOR15)	Paiva 2015 (ISPOR17)	Lacaine 2015 (ISPOR18)	Plommet 2015 (ISPOR22)	Gouveia 2015 (ISPOR25)	Leleu 2015 (ISPOR27)	Sullivan 2015 (ISPOR28)	Yu 2015 (ISPOR31)	Marchetti 2015 (ASH196)
the discount rate(s) is justified										
An explanation is given if costs and benefits are not discounted	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Details of statistical tests and confidence intervals are given for stochastic data	No	No	No	No	No	No	No	No	No	No
The approach to sensitivity analysis is given	Yes	No	No	No	Yes	Yes	Not clear	No	Yes	Yes
The choice of variables of sensitivity analysis is justified	No	No	No	No	No	No	No	No	No	No
The range over which variables are varied is justified	No	No	No	No	No	No	No	No	No	No
Relevant alternatives are compared	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Incremental analysis is	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes

Table C	Pribylova 2015 (ISPOR7)	Pan 2015 (ISPOR15)	Paiva 2015 (ISPOR17)	Lacaine 2015 (ISPOR18)	Plommet 2015 (ISPOR22)	Gouveia 2015 (ISPOR25)	Leleu 2015 (ISPOR27)	Sullivan 2015 (ISPOR28)	Yu 2015 (ISPOR31)	Marchetti 2015 (ASH196)
reported										
Major outcomes are presented in a disaggregated as well as aggregated form	Yes	No	Yes	No	Yes	No	No	No	Yes	Yes
The answer to the study question is given	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Conclusion follow from the data reported	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Conclusions are accompanied by the appropriate caveats	No	No	Yes	No	No	No	No	No	No	No

B.3.2 Economic analysis

B.3.2.1 Patient population

The relevant population for the cost-effectiveness model is R/R CLL based on the following definitions.

- Relapsed CLL: a CLL patient who previously achieved a CR or a PR, but after a period of six or more months demonstrates evidence of disease progression. (45)
- Refractory CLL: a CLL patient who has progression within six months of the last anti-leukemic therapy. (45)

This definition is reflective of the patients included in the MURANO trial and is in-line with the intended indication for VEN+R (please refer to **Error! Reference source not found.**). More specifically, the expected positioning for VEN+R is:

- Post CIT

Moreover, the model splits the R/R CLL population into two subgroups:

- Patients WITH a deletion of chromosome 17p (del(17p) and/or TP53 mutation)
- Patients WITHOUT a deletion of chromosome 17p (non-del(17p) and/or TP53 mutation)

The process of forming these groups is to first use available assessments of del(17p). For instances where this data is missing, TP53 mutation status is used to guide allocation to a subgroup. Table 31 below includes the number of patients in each subgroup in the VEN+R arm of MURANO. Please refer to **Error! Reference source not found.** for the way the number of patients in each subgroup was calculated.

Table 31 Subgroup sample size (MURANO)

Treatment Regimen	Del(17p)/TP53	Non-Del(17p)/TP53
VEN+R	53	141

Source: MURANO trial (1)
Key: Del(17p)/TP53, deletion of 17p chromosome and/or TP53 mutation; Non-del(17p)/TP53, without deletion of 17p chromosome and/or TP53 mutation; VEN+R, venetoclax with rituximab

B.3.2.2 Model structure

The objective of the model structure is to create a framework within which the relevant outcomes can be calculated for patients undergoing treatment with VEN+R and its relevant comparators. To calculate these endpoints, a mathematical structure is developed to broadly model the patient's CLL experience, in terms of disease progression and treatment pathway. The features of the previously conducted economic evaluations in CLL are provided alongside those of this appraisal in Table 32.

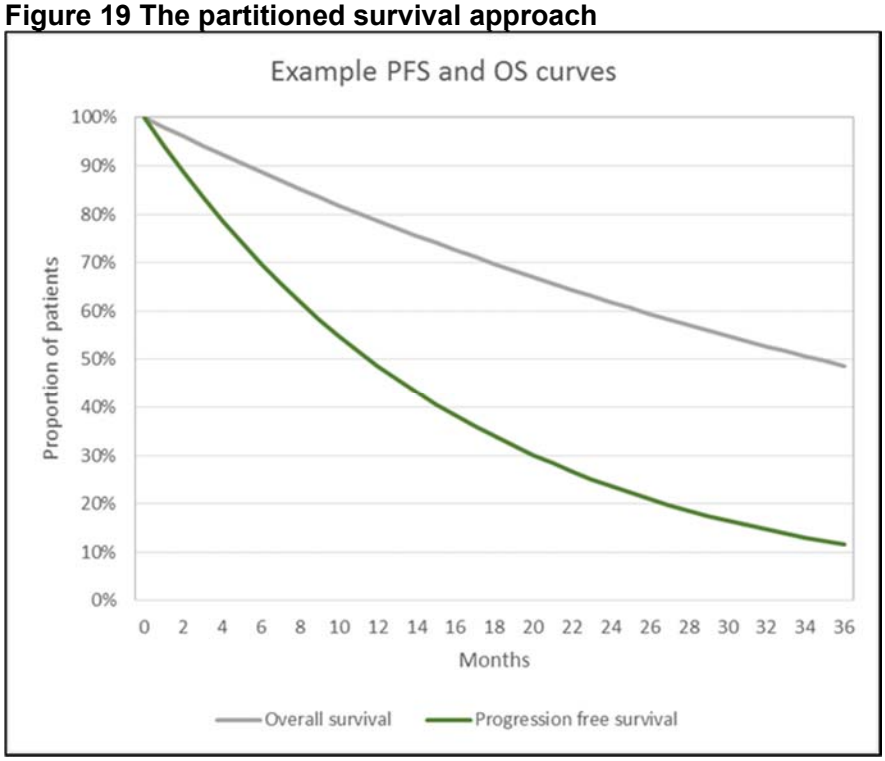
There is a precedent for usage of both Markov models and partitioned survival models. The main reason why a partitioned survival approach was selected relates to the data availability for the relevant comparators. Multi-state modelling requires estimation of transition probabilities for which patient level PFS and OS data is required. Within the partitioned survival approach, the survival of comparators can be estimated using PFS and OS hazard ratios applied to the

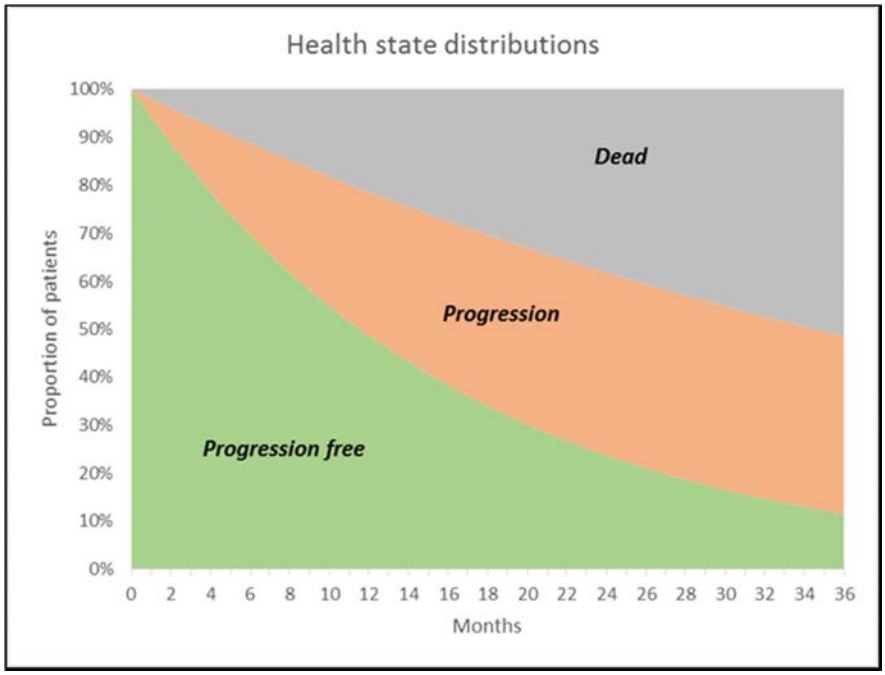
VEN+R survival curves. Therefore, the partitioned survival approach was considered the most suitable option to provide evidence relating to the decision problem.

In the partitioned survival model (PartSA) model, the patient's disease pathway is typically separated into PFS, PPS and death. Although some models have introduced health states to account for different response outcomes, that data was not available to model specific survival curves for all comparators. Moreover, data was not available to model MRD negativity using a specific health state for all comparators too. The three-health state division matches well with the clinical and disease pathway for patients with R/R CLL and it is the most common selection of health states used in previous economic models submitted to NICE (see Table 32). Area under the curve survival analysis is then used to estimate the proportion of patients in those health states over time. The patient populations within each health state over time are approximated using a PartSA modelling approach whereby health state distributions are estimated using extrapolated survival curves. This method is illustrated in Figure 19. The model's health states are associated with specific utility values and cost profiles.

This approach does not require explicit transition probabilities to be defined between health states (as required within a multi state model). Furthermore, the model incorporates two estimation methods of the comparator survival curves. Method 1. uses HRs applied to VEN+R (used in the base case analysis) whilst method 2. relaxes the proportional hazards assumption and fits individual curves to the comparators with adjustments made for baseline characteristics (tested in a scenario analysis). Although proportionality is supported to a degree in the observed period, the second method has been included since the proportional hazards assumption may not hold into the unobserved future. Moreover, method 2. was also developed due to the fact that post-progression of ibrutinib is zero when using method 1., which is very unlikely to be the case.

Figure 19 The partitioned survival approach





The model's cycle length dictates the interval between which health state distributional shifts are possible. Previous CLL models have used daily, weekly, monthly (28 days) and three-monthly cycle lengths (see Table 27 and Table 32). A cycle length of 28-days is used in this framework, as it matches the typical treatment cycle length of intervention and comparators for a more

natural implementation of regimen costs. This remains sensitive enough to capture shorter term changes in patient status. Half cycle correction is applied to adjust for the distribution of costs and benefits accrued within each cycle.

The model's base case captures a lifetime time horizon in line with the NICE reference case. This is estimated to be around 30-years. This is greater than time horizons used previously in R/R CLL since the time horizon is a result of the intervention's overall survival estimation. Over this time horizon, costs and effects are discounted at a rate of 3.5% per annum in line with the NICE reference case.

Subsequent treatment lines have been included in just two of the previous NICE appraisals. Although they are not explicitly included in this appraisal, the impact of subsequent treatment costs is included in the scenario analysis. These costs are not included in the base case as their estimation required a large amount of assumptions in the absence of the necessary data (i.e. the time on post-progression treatment for VEN+R and post progression treatment data for comparators).

Moreover, the model accounts for background mortality in the extrapolated survival curves. The method used does not add additional time-to-event hazards but instead acts as a minimum hazard rate for PFS and OS. This mechanism removes any implausibly flat tails from the intervention and comparator survival curves.

Table 32 Features of the economic analysis

	TA193 - Rituximab	TA202- OFA	TA216 - BEN	TA359 – Idela + R	TA429 - Ibrutinib	TA487- Venetoclax	ID1097 (Current appraisal)	
							Chosen Values	Justification
Date published	2009	2010	2011	2015	2017	2017	2018	NA
Perspective	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	Reference case
Indication	R/R CLL	R/R CLL (fludarabine and alemtuzumab refractory)	1L CLL	R/R CLL	1L and R/R CLL	BCRI-F CLL	R/R CLL	NA
Model type	Markov	Partitioned survival	Markov	Markov	Partitioned survival	Partitioned survival	Partitioned survival	Data limitations of multi state model
Health states	PFS, PPS and death	PFS, PPS and death	CR, PR, SD, PPS and death (duplicated health states for subsequent treatment lines)	PFS (on treatment), PFS (off treatment), PPS, terminal care and death	PFS, PPS and death	PFS, PPS and death	PFS, PPS and death	Commonly used to model disease and treatment pathway.
Utility values	PFS,0.8; PPS, 0.6	PFS,0.65; PPS, 0.47	Baseline, 0.7; CR; 0.91; PR, 0.84; No change, 0.78; PPS, 0.68	PFS (idela+R), 0.82; PFS (comparator), 0.75; PFS (off Tx), 0.8; PPS, 0.6	PFS, 0.799; PPS, 0.66	PFS, 0.853*; PPS; 0.6	PFS, 0.748 PPS, 0.600	Previously accepted values.
Cycle Length	Monthly	1 day	3 months	1 week	28 days	28 days	28 days	Accommodates dosing calculations and remains sensitive to capture short term changes

								in patient status,
Time horizon	Lifetime (25 years)	5 years	Lifetime (35 years)	Lifetime (25 years)	20 years	Lifetime (20 years)	Lifetime (30 years)	Reference case
Subsequent treatment lines	Not included	Not included	Included (FC and BSC)	Not included	Included (HDMP +/- rituximab, BSC)	Not included	Not included	Data limitations for VEN+R and comparators
Outcomes	LYs, QALYs, Costs and Incremental results	LYs, QALYs, Costs and Incremental results	LYs, QALYs, Costs and Incremental results	LYs, QALYs, Costs and Incremental results	LYs, QALYs, Costs and Incremental results	LYs, QALYs, Costs and Incremental results	LYs, QALYs, Costs and Incremental results	Reference case
Discounting of outcomes	3.5% (Annual)	3.5% (Annual)	3.5% (Annual)	3.5% (Annual)	3.5% (Annual)	3.5% (Annual)	3.5% (Annual)	Reference case

Key: 1L, first-line, BCRI-F, beta cell receptor inhibitor failure, BEN, bendamustine; BSC, best supportive care; CLL, chronic lymphocytic leukaemia; CR, complete response; FC, fludarabine + cyclophosphamide; HDMP, high-dose methylprednisolone, idela+R, idelalisib + rituximab; LY, life year; NA, not applicable; NHS, National Health Service; OFA, Ofatumumab; PFS, progression-free survival; PR, partial response; PSS, Personal Social Services; QALYS, Quality-adjusted life year; R/R, relapsed/refractory; Tx, treatment; VEN+R, venetoclax + rituximab
*Subsequently changed to 0.748 following NICE review process

B.3.2.3 Intervention

The intervention is VEN+R. Venetoclax is an oral tablet whilst rituximab is delivered via IV. Venetoclax is first delivered according to a dose titration schedule: 20 mg daily during week 1, 50mg daily during week 2, 100mg daily during week 3, 200mg daily during week 4 and 400mg daily during week 5. Following the initial dose titration, 400 mg of venetoclax is given once daily until disease progression or a 2-year maximum treatment duration. This treatment continuation rule is in-line with the MURANO clinical trial protocol and SmPC (see Appendix C**Error! Reference source not found.**). Rituximab is delivered after completion of the dose titration period at 375 mg/m^2 on day one of cycle 1 and 500 mg/m^2 on day one of cycles 2-6.

The 2-year fixed treatment duration of the VEN+R regimen is based upon the durable responses that were observed in the phase I study. (57) Since VEN+R brings about high rates of undetectable MRD, stopping treatment at 2 years may allow patients to experience a treatment free period whilst maintaining minimal disease. The rule is amenable to clinical practice in England and Wales since it is common practice to monitor disease progression and the dose sizes of venetoclax will allow prescribing of the necessary amount to terminate treatment following two years. This is a key determinant of cost-effectiveness outcomes as treatment costs are substantially reduced compared to a treat-to-progression regimen. It is assumed that the standard monitoring procedures will be maintained for all patients who discontinue at the 2 year fixed treatment duration. Any uncertainty in the longer-term health consequences of stopping treatment at two years is expected to be reduced by longer term follow-on data cuts from the MURANO trial.

B.3.2.4 Comparators

The comparators included in the model, previously described in Section B.1.3**Error! Reference source not found.**, are presented in Table 33.

Table 33 Justification of comparators included in the economic model

Comparator	Included in NICE scope?	Relevance to UK clinical practice	Rigour of data available for modelling
Ibrutinib	YES	NICE TA429 recommends ibrutinib as an option for 1L treatment of del(17p)/TP53 patients and second line in non-del(17p)/TP53 (21)	Medium – Aggregated data available
Idela+R	YES	NICE TA359 recommends idela+R for treatment of R/R CLL.(37). (*NB: although the economic model includes idela+R, note that idela+R is not considered an appropriate comparator by clinicians since it's use has been superseeded by ibrutinib as the BCRi of choice due to the toxicity profile and lesser effectiveness of idela+R relative to ibrutinib*)	Medium - Aggregated data available

Key: 1L, first-line; CLL, chronic lymphocytic leukaemia; Del(17p)/TP53: deletion of 17p chromosome and/or TP53 mutation; Idela+R, idelalisib + rituximab; non-del(17p)/TP53: without deletion of 17p chromosome and/or TP53 mutation; R/R, relapsed/refractory

Each regimen is modelled according to its SmPC. Ibrutinib 420mg and idelalisib 300mg are administered until disease progression. Rituximab is administered at 375 mg/m^2 on day 1 of cycle 1 and at 500 mg/m^2 on day 1 of cycles 2 to 6 a total of 6 doses.

B.3.3 Clinical parameters and variables

B.3.3.1 Population inputs

The population inputs were estimated based on the entire treated MURANO population (i.e. a pooled dataset of intervention and control groups) in order to use the full evidence base from MURANO. As outlined in Section B.1, the majority (58.6%) of patients in the MURANO trial had one prior therapy while 25.7% had two. The population input parameters required are age, gender distribution, and body surface area (Table 34). Age and gender distribution are used to adjust the life tables which control background mortality in the model. Body surface area features within the dosing calculations for BR containing treatment regimens (please note that BR is not a compartor in the CEM but treatment costs are only being used in the BI analysis). Body surface area is estimated using height and weight data from the trial and the Du-Bois formula (recommended by the BNF [British National Formulary]). (109)

Table 34 Cohort characteristics

Parameter	Value (SE)	Source
Mean baseline age	64.18 (0.5138)	MURANO population (VEN+R and BR groups, n=382)
% Male	73.82%	MURANO population (VEN+R and BR groups, n=382)
Body surface area	1.92(0.011)	MURANO population (VEN+R and BR groups, n=381), based on the Du-Bois method*
% Del(17p)/TP53	26.96%	MURANO population (VEN+R and BR groups, n=382)

Key: BR, bendamustine + rituximab; Del(17p)/TP53, del(17p)/TP53: deletion of 17p chromosome and/or TP53 mutation; SE, standard error; VEN+R, venetoclax + rituximab

*$0.20247 \cdot \mathrm{Height}_{\mathrm{m}}^{0.725} \cdot \mathrm{Weight}_{\mathrm{kg}}^{0.425}$, a scenario is conducted using an alternative body surface estimated using UK specific SACT data. (110)

B.3.3.2 Background mortality

Background (or general population) mortality is estimated from the latest UK life tables published by the Office for National Statistics (ONS, 2017). (111) Age and gender adjustment is applied to match the MURANO trial population. Background mortality is applied such that the hazards of PFS and OS events must always be equal or greater than background mortality hazards. This ensures that any flat tails of the parametric survival models do not lead to implausibly long-term survival outcomes. Furthermore, it ensures the parametric survival extrapolations that were validated by clinical experts closely match those that are used in the model (see Section B.3.10).

B.3.3.3 VEN+R survival curves

Although the observed survival outcomes for VEN+R in MURANO are extremely positive, the immaturity of the data provides difficulties when attempting to extrapolate outcomes beyond the trial period to a lifetime horizon. This would be improved by subsequent trial data cuts.

The cost effectiveness model requires the PFS and OS curves to be parameterised for three primary reasons: A) to estimate long term outcomes beyond the observed period through extrapolation; B) to allow outcomes to be synthesised with data from comparators and C) to facilitate a probabilistic analysis of uncertainty. The approach to parameterise the VEN+R survival curves is presented, in full, in **Error! Reference source not found.**.

Firstly, the conventional parameterisation methods were followed according to the NICE technical support documentation. (112) The following distributions, as recommended, are used: exponential, Weibull, Gompertz, log-logistic, log-normal, gamma, and generalised gamma. In addition, to provide a more flexible parameterisation, a 3-knot (hazard based) cubic spline function was tested, based on the model presented in Royston and Parmar 2002. (113) A 3 knot spline model was selected in order provide greater flexibility than the standard models. Due to the data immaturity, assessments of model fit such as cumulative hazard plots and Akaike Information Criterion (AIC) are largely redundant if the extrapolated outcomes do not hold face validity. As a means of validating the parametric extrapolation models, a multistate modelling approach was also tested. A 3-state model was prototyped, with states ‘pre-progression’, ‘progression’ and ‘dead’. 3 transitions were included: T1, pre-progression to progression; T2, pre-progression to death; T3, progression to death. The full multi-state modelling methods are included in **Error! Reference source not found.**.

Figure 20 presents the OS and PFS extrapolations for VEN+R, over a 20-year time horizon. The model coefficients are presented in Appendix L.

Figure 20 OS and PFS extrapolation of VEN+R

Due to the immature data, there is a large degree of variability and volatility in the fitted survival curves. To put these outcomes into perspective, UK general population mortality for an age-matched population would result in ~50% of individuals being alive at 20-years. For VEN+R OS, 6 of the 8 models therefore predict outcomes superior to that expected from the general population. Even the most pessimistic curve (i.e. the spline model) predicts around one fifth of patients surviving to 20-years. Although it is suspected a 3-knot cubic spline fitted to a curve which features only 15 events is highly susceptible to overfitting, particularly given the observed kink in the KM curve.

The principle issue for the OS extrapolations in Figure 20 is that fitted distributions which allow for time-varying hazards are estimating decreasing hazards over time based on the (limited) observed data. This pattern is most likely down to chance and should not be generalised across the entire modelled time horizon, particularly for aging patients who are characterised as R/R for an incurable disease. Multistate analysis of the MURANO data (see Appendix L) illustrates, intuitively, that pre-progression mortality risk is much lower than post-progression mortality risk.

Subsequently this dynamic should result in the OS curve exhibiting increasing hazards as gradually more patients transition to the post-progression state.

When clinical experts were presented with the extrapolated outcomes they were considered too optimistic for the patient population (i.e. R/R CLL). As a result of the implausible raw extrapolated outcomes, the conventional approaches were not considered suitable to parameterise the survival curves.

The alternative approach taken was to make use of the data available by making assumptions of proportionality between endpoints (PFS and OS) and treatment (VEN+R and BR), although there is no precedence of this approach in previous NICE appraisals. Based on internal and external data sources available, proportionality was not rejected (see **Error! Reference source not found.**).

The model specification is shown below in Equation 1**.**

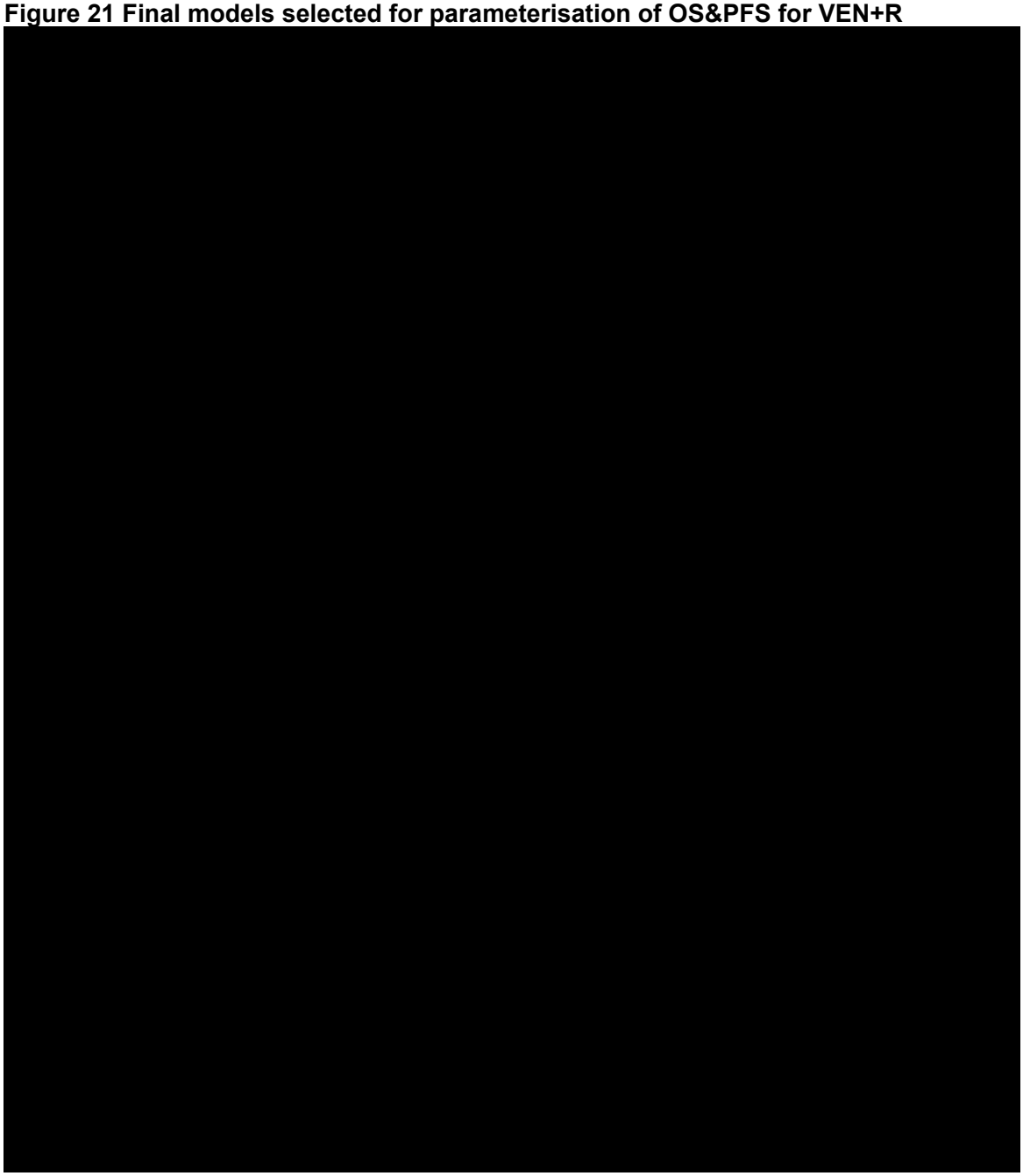
Equation 1: $\mathbf{S(t) = Tx + endpoint + del(17p) + Tx * endpoint + del(17p) * endpoint}$

The reference categories for "Tx" and "endpoint" and "del(17p)" were BR, OS and del(17p)/TP53 respectively. The subgroup coefficient controls the subgroup specific analysis in the model. Furthermore, an interaction term is included between treatment allocation and survival endpoint, as the KM data in **Error! Reference source not found.** suggests that PPS (i.e. the difference between OS and PFS) may be larger for BR, which the model should account for. An interaction term is also included between del(17p)/TP53 status and survival endpoint, to allow del(17p)/TP53 status to have a different impact on PFS vs. OS. The coefficients of the jointly estimated models are presented in Table 35 and the extrapolated curves are presented in Figure 21. In order to make plausible estimations, clinical experts were consulted as part of an advisory board process and external evidence with greater follow up was used to make comparisons. The clinical advisory process is described in detail in **Error! Reference source not found.**. To guide discussions around plausible survival estimates, 20-year outcomes were assessed. Clinical expert opinion, alternative modelling approaches and external evidence led to a selection of models that were considered plausible; the jointly estimated models using Weibull, gamma, log-logistic, log-normal, generalised gamma. Although 20-years was used as the long-term outcome to assess the time-to-event parameterisations, outcomes are extrapolated to a duration of 30-years in the model to reflect a lifetime horizon.

Table 35 VEN+R survival model coefficients

Distribution	Parameter	Point estimate	SE	95% low	95% high
Generalised gamma	Shape	[redacted]	[redacted]	[redacted]	[redacted]
	Log Scale	[redacted]	[redacted]	[redacted]	[redacted]
	Q	[redacted]	[redacted]	[redacted]	[redacted]
	EndpointPFS	[redacted]	[redacted]	[redacted]	[redacted]
	txR199	[redacted]	[redacted]	[redacted]	[redacted]
	Del(17p)/TP53	[redacted]	[redacted]	[redacted]	[redacted]
	Interaction(PFS&VENR)	[redacted]	[redacted]	[redacted]	[redacted]
	Interaction (PFS&Del(17p)/TP53)	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Shape	[redacted]	[redacted]	[redacted]	[redacted]
	Scale	[redacted]	[redacted]	[redacted]	[redacted]
	EndpointPFS	[redacted]	[redacted]	[redacted]	[redacted]
	txR199	[redacted]	[redacted]	[redacted]	[redacted]
	Del(17p)/TP53	[redacted]	[redacted]	[redacted]	[redacted]
	Interaction(PFS&VENR)	[redacted]	[redacted]	[redacted]	[redacted]
	Interaction (PFS&Del(17p)/TP53)	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	Shape	[redacted]	[redacted]	[redacted]	[redacted]
	Scale	[redacted]	[redacted]	[redacted]	[redacted]
	EndpointPFS	[redacted]	[redacted]	[redacted]	[redacted]
	txR199	[redacted]	[redacted]	[redacted]	[redacted]
	Del(17p)/TP53	[redacted]	[redacted]	[redacted]	[redacted]
	Interaction(PFS&VENR)	[redacted]	[redacted]	[redacted]	[redacted]
	Interaction (PFS&Del(17p)/TP53)	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	Meanlog	[redacted]	[redacted]	[redacted]	[redacted]
	Sdlog	[redacted]	[redacted]	[redacted]	[redacted]
	EndpointPFS	[redacted]	[redacted]	[redacted]	[redacted]
	txR199	[redacted]	[redacted]	[redacted]	[redacted]
	Del(17p)/TP53	[redacted]	[redacted]	[redacted]	[redacted]
	Interaction(PFS&VENR)	[redacted]	[redacted]	[redacted]	[redacted]
	Interaction (PFS&Del(17p)/TP53)	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	Shape	[redacted]	[redacted]	[redacted]	[redacted]
	Rate	[redacted]	[redacted]	[redacted]	[redacted]
	EndpointPFS	[redacted]	[redacted]	[redacted]	[redacted]
	txR199	[redacted]	[redacted]	[redacted]	[redacted]
	Del(17p)/TP53	[redacted]	[redacted]	[redacted]	[redacted]
	Interaction(PFS&VENR)	[redacted]	[redacted]	[redacted]	[redacted]
	Interaction (PFS&Del(17p)/TP53)	[redacted]	[redacted]	[redacted]	[redacted]

Figure 21 Final models selected for parameterisation of OS&PFS for VEN+R



Key: OS, overall survival; PFS, progression-free survival; VEN+R, venetoclax + rituximab

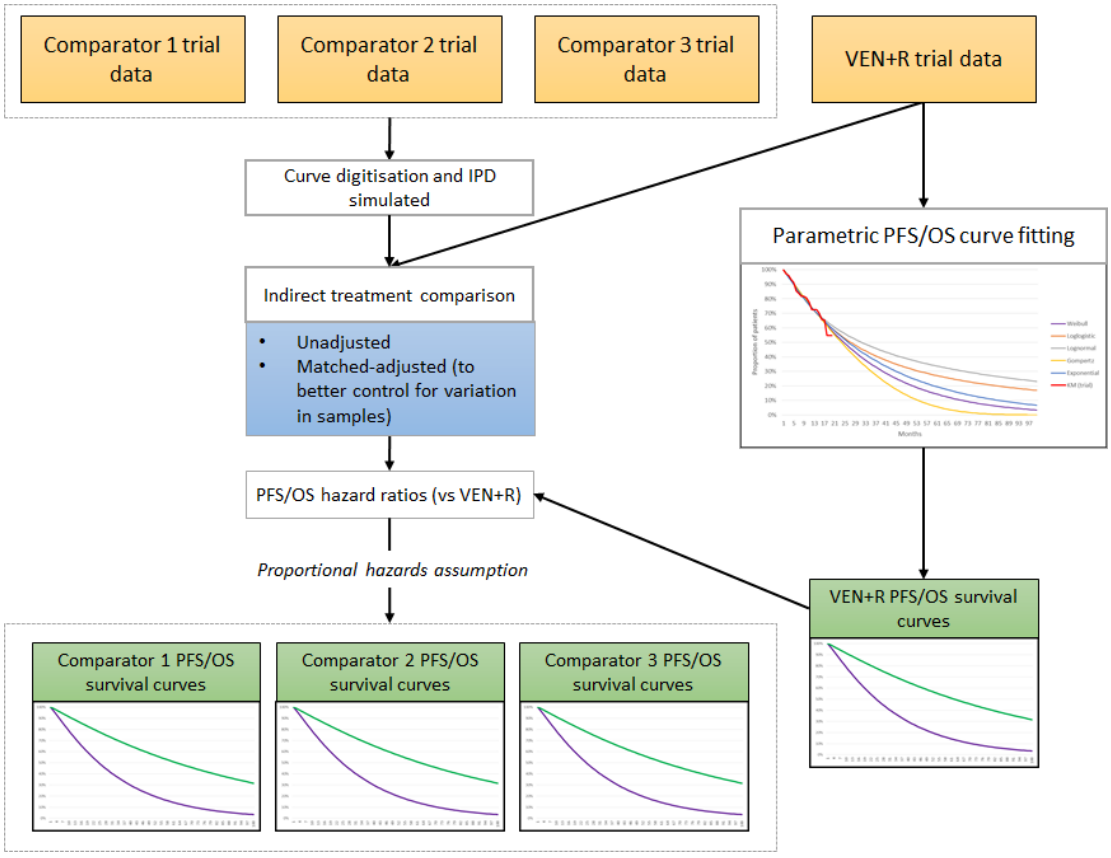
The base case model selection for the extrapolation of VEN+R PFS and OS is the Weibull. The VEN+R 20-year overall survival outcomes for this model [redacted] fall within the range of outcomes considered reasonable by clinical expert opinion and compare well to longer-term external data from clinical trials and registry sources. External data included 4-year RESONATE data, (63) FCR data with 10-year follow up (114) and 10-year registry data collected by The Haematological Malignancy Research Network (HMRN) from the Yorkshire and Humber &

Yorkshire Coast Cancer networks (115). Assessments of these sources are described in detail in greater detail in Appendix L. The model's base case assumes the treatment effect continues based on the observed data. Scenarios are performed to test this assumption by incorporating a waning effect.

B.3.3.4 Comparator survival curves

In order to estimate the comparator survival curves, estimates of relative treatment efficacy (i.e. PFS and OS hazard ratios) obtained through the MAIC are combined with the VEN+ R parametric survival curves (Figure 22). The HRs are reported in Section B.2.9**Error! Reference source not found.**. This method evokes the proportional hazards assumption.

Figure 22 Synthesis of VEN+R and comparator survival data for the economic model base case



Furthermore, a secondary method is included in the scenario analysis to estimate the comparator survival curves. This method relaxes the proportional hazards assumption by estimation of comparator survival independently from VEN+R. The KM data from the MAIC is taken and separate models are parameterised using the Weibull distribution. Using this approach, the shape parameter of the Weibull is specific to each comparator. For the methods and results please see **Error! Reference source not found.**. This approach is positioned as a

scenario as although there was no evidence to assume that the proportional hazards assumption does not hold, this assumption could be uncertain.

B.3.3.5 AE probabilities

AEs are included in the model if treatment emergent grade ≥3 events occurred in ≥5% of patients in the relevant trials. AE probabilities for each treatment are presented in Table 36. If an AE was included based on >5% for one trial, for consistency probabilities lower than 5% for that event are included for the other trials.

Table 36 AE probabilities

AE	VEN+R	ibrutinib	Idela+R
ALT/AST elevation	1.55%		5.45%
Anaemia	10.82%	4.62%	5.45%
Autoimmune haemolytic anaemia	2.58%		
Neutropenia	57.73%	16.41%	33.64%
Pneumonia	6.19%	6.67%	
Thrombocytopenia	6.19%	5.64%	10.00%
N	194	195	110
Source	MURANO (1)	RESONATE (63)	Study 116 (54)

Key: ALT/AST, Alanainine Transaminase/ Aspartate Transaminase; Idela+R, Idelalisib + rituximab; VEN+R, venetoclax + rituximab

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

A description of the EQ-5D-3L data from MURANO is provided in section B.2.6. This data was analysed to assess its feasibility for inclusion in the economic model.

B.3.4.1.1 Methods

Linear mixed effect models were fitted to the EQ-5D-3L utility data. The explanatory variables included an arm indicator, age and gender. The rationale for including an arm indicator was to observe whether there was any treatment effect on utility values, as recommended by the UK advisory board. The “lmer” function from the lme4 package in r was used to estimate the models. This model specifications tested were random intercepts and random slopes. These specifications account for the repeated measures in the data which may introduce non-independence of EQ-5D-3L reporting. The models were fitted with identical fixed effects structures and were subsequently assessed using the AIC and BIC statistics. The intercept-only model had the lowest AIC and BIC (Appendix H).

B.3.4.1.2 Results

The results of the PFS health state utility model are included in Table 37.

Table 37 Progression free survival EQ-5D-3L utility model (MURANO data)

Variable	Coefficient	SE	df	t value	Pr(>|t|)
Intercept	0.809149	0.050497	361.9	16.024	< 0.0000000000000002 ***
Group (VEN+R)	0.031553	0.014796	363.8	2.132	0.03364 *
Age	-0.00042	0.0007336	362.0	-0.568	0.57051
Gender (Male)	0.055492	0.0168313	363.4	3.297	0.00107 **
Number of observations	4166				
Number of groups (patients)	379				

Key : df, degrees of Freedom; Pr, probability ; SE, standard error ; VEN+R, venetoclax+rituximab
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Table 38 provides a summary of this data and its suitability for using within the economic evaluation of this appraisal. The results of the EQ-5D-3L analysis were not used in the model's base case since they were considered to lack plausibility when compared to external data sources (the comparative data are reported in Section B.3.4.5) as the MURANO data leads to very high utility values. The EQ-5D-3L based utility value from study 116 has been included in two previous NICE submissions. (116,117) The source is in alignment with the reference case and is used within the economic model.

Table 38 HRQoL data and suitability (MURANO)

	MURANO
HRQoL instrument	EQ-5D-3L
Measurement points	Day 1 of 28-day VEN+R dose titration cycle and cycles 1-7, 28 days after last dose of study treatment, 12 weeks after day 1 of last cycle of combination therapy, Every 12 weeks until 3-years then every 24 weeks until 5-years.
Valuation method	TTO
Reference case consistency	YES
Appropriate for economic evaluation	No -Utility values considered to be implausibly high
Results with CIs	See section: B.2.6

Key: CI, confidence interval; EQ-5D-3L, European Organisation for Research and Treatment of Cancer Version 3.0;, HRQOL, Health-related quality of life; TTO, time trade-off; VEN+R, venetoclax + rituximab

B.3.4.2 Mapping

No mapping methods have been implemented as part of this submission.

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify studies assessing the health-related quality-of-life studies of interventions in R/R CLL. For full details of the methods used to conduct this review, please see **Error! Reference source not found.**.

The results of the health-related quality of life (HRQoL) studies are reported in Appendix H. Four of the sources included utility values. Two of which included the PFS utility value used in the model's base case (i.e. PFS: 0.748). (116,117) The remaining two sources report on the same data and included health state utility values for PFS (subject to numerous criteria such as treatment type/line) and for progression or relapse health states. The PFS values specific to treatment line cannot be directly used in the economic model as the model's PFS health state is not treatment line specific. The PFS values ranged between 0.82 and 0.55 and progression

/relapse between 0.66 and 0.42. The health state utility values used in the economic analysis of this submission fall within these values (Table 42).

Table 39 Health related quality of life study results

First author, Year, Study ID, Study acronym	Tool used to measure HRQoL / Elicitation method	Data source for utilities	Disease (Disutility) state / Method of estimation	(Dis)utility values
Sullivan et al., 2016 (PQU14), NCT01539512(117)	EQ-5D	NR	NR	• Idela + R: treatment effect vs. rituximab: 0.0652 • PFS on treatment: Idela+R: 0.813 Rituximab:0.748 OFA: 0.748 Best supportive care: 0.748 • PFS off treatment: Idela + R: 0.748 Rituximab:0.748 OFA: 0.748 BSC: 0.748
Munir et al., 2015 (BSH26), NCT01539512 (116)	Fact-LEU	Fact-LEU	NR	• Rituximab utility: 0.7475 (SE: 0.0159) • Idela + R: 0.8127 (no SE reported)
Ghia et al., 2014 (PQU31), NCT01539512 (118)	• The 44-item Functional Assessment of Cancer Therapy–Leukaemia (FACT-Leu) scale measured Physical-,Functional, Social and Emotional Well-being and leukaemia-specific concerns (LeuS). • Trial Outcome Index (TOI) is the sum of PWB, FWB and LeuS	NR	NR	N/A
Cramer et al., 2018 (UPQU08) (119)	FACIT-Fatigue, EORTC QLQ-C30, QLQ-CLL16, and EQ-5D-5L	NR	NR	FACIT-Fatigue: 37.2 (SD 10.4) EORTC QLQ-C30: 78.9 (SD 18.9) QLQ-CLL16: 16.7% of patients reported feeling ill 'quite a bit' or 'very much' EQ-5D-5L: 0.79 (SD 0.18)
Traina et al., 2015 (PQU16) (120)	• FACIT-Fatigue • The EORTC Quality of	NR	NR	NR

	Life Questionnaire Core 30 (EORTC QLQ-C30) version 3.0 [23] • EORTC Quality of Life Questionnaire CLL 16 item module (EORTC QLQ-CLL16) • EQ-5D-5L			
Robak et al., 2015 (ASH314), COMPLEMENT 2 (121)	• The EORTC Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) version 3.0 • EORTC Quality of Life Questionnaire Chronic Lymphocytic Leukaemia 16 item module (EORTC QLQ-CLL16)	NR	NR	N/A
Robak et al., 2017 (PQU29), COMPLEMENT 2 (122)	• EORTC QLQ-C30 v3.0 • EORTC QLQ-CLL16	NR	NR	N/A
Robak et al. 2017 (UPQU17) (122)	The EORTC QLQ-C30 and EORTC QLQ-CLL16 were collected at baseline, day 1 of cycle 4, at the 1-month follow-up visit, and every 3 months during follow-up.	NR	N/A	EORTC QLQ-C30 GHS/HRQoL scores over time form the screening visit until the 18-month follow-up visit OFA +FC: Screening:(n=178) 60.9 mean score cycle 4 day 1: (n=142) 68.5 mean score 1-month follow-up: (n=139) 69.1 mean score 3-month follow-up: (n=144) 67.2 mean score 6-month follow-up: (n=126) 71.5 mean score 9-month follow-up: (n=113) 71.5 mean score 12-month follow-up: (n=111) 72.8 mean score 15-month follow-up: (n=94) 72.9 mean score 18-month follow-up: (n=94) 74.4 mean score FC: Screening:(n=172) 57.6 mean score cycle 4 day 1: (n=125) 63.9 mean score 1-month follow-up: (n=123) 63.5 mean score 3-month follow-up: (n=107) 70.3 mean score 6-month follow-up: (n=101) 71.5 mean score 9-month follow-up: (n=85) 69.2 mean score

				12-month follow-up: (n=76) 68.5 mean score 15-month follow-up: (n=63) 70.6 mean score 18-month follow-up: (n=61 68.2 mean score
Jain et al., 2017 (PQU20) NCT02131584 (123)	• Brief Fatigue Inventory (BFI) • MDASI (MD Anderson Symptom Inventory (MDASI))	N/A	NR	N/A
Shingler et al., 2014 (PQU2) (124)	TTO	NR	• Disutility: TTO • Type: NR	• PFS without therapy (mean utility=0.82); • PFS on initial oral therapy (0.71) • PFS on initial IV therapy (0.67) • apart from PFS on initial therapy with increased hospital visits (0.55) • Mean utility for disease progression after 1st line therapy was 0.66 • PFS without 2nd line therapy was 0.71 • further progression (0.59) • PFS on 2ndline therapy (0.55) • relapsed lines of treatment (0.42)
Kosmas et al., 2015 (PQU3) (125)	TTO and VAS	TNR	• Disutility: TTO VAS • Type: NR	<u>TTO mean utility:</u> • PFS without therapy: 0.82 • PFS without second line therapy: 0.71 • PFS on initial therapy oral treatment: 0.71 • PFS on initial therapy IV treatment: 0.67 • Progression after first line treatment: 0.66 • Further progression:0.59 • PFS on second line therapy:0.55 • PFS on initial therapy with increased: 0.55 hospital visits • Relapsed lines of treatment: 0.42 <u>VAS Mean:</u> • PFS without therapy: 65.5 • PFS without second line therapy:53.0 • PFS on initial therapy oral treatment: 52.1 • PFS on initial therapy IV treatment: 47.3 • Progression after first line treatment: 44.8 • Further progression: 40.3 • PFS on second line therapy: 42.8

				• PFS on initial therapy with increased: 43.9 hospital visits • Relapsed lines of treatment: 27.5
Wierda et al., 2016 (EHA151) (126)	EORTC-QLQ-C30 and EORTC-QLQ-CLL16	NR	NR	Global Health status Week 4 (70)- BL mean: 55.2; visit mean: 64.4 week 24 (73): - BL mean: 58.6; visit mean: 67.9 Emotional functioning Week 4 (73)- BL mean: 72; visit mean: 81.2 week 24 (76)- BL mean: 74.6; visit mean: 82.4 Role functioning Week 4 (70):- BL mean: 64.3; visit mean: 73.6 week 24 (74):- BL mean: 68; visit mean: 79.1 Social functioning Week 4 (73)- BL mean: 64.6; visit mean: 71.5 week 24 (76)- BL mean:69.1; visit mean: 80.9 Fatigue Week 4 (74)- BL mean: 42.4; visit mean: 35.7 week 24 (77)- BL mean:37.1; visit mean: 30.6 EORTC-QLQ-CLL16 Future health Week 4 (73)- BL mean: 56.6; visit mean: 39.7 week 24 (73)- BL mean:54.8; visit mean: 32.9 Fatigue Week 4 (75)- BL mean: 34; visit mean: 24 week 24 (77)- BL mean:29.7; visit mean: 21.1
Wierda et al., 2017 (EHA1) (127)	EORTC-QLQ-C30 and EORTC-QLQ-CLL16	NR	NR	Global Health status (n) Week 24 (40)- BL mean: 62.9; visit mean: 75 week 48 (33): - BL mean: 64.2; visit mean: 71 Role functioning Week 24 (40):- BL mean: 74.2; visit mean: 87.9 week 48(34):- BL mean: 77.5 ; visit mean: 91.7 Social functioning Week 24 (73)- BL mean: 75; visit mean: 85.8 week 48 (76)- BL mean: 77.9; visit mean: 86.3 Fatigue Week 4 (74)- BL mean: 38.1; visit mean: 23.7 week 48 (77)- BL mean:35.3; visit mean: 22.5 EORTC-QLQ-CLL16 (n)

				Fatigue Week 24 (40)- BL mean: 35.4; visit mean: 20.0 week 24 (34)- BL mean:33.3; visit mean: 20.1

Furthermore, the HRQoL data collected in the relevant clinical trials is summarised in Table 40.

Table 40 HRQoL and suitability (Comparator trials)

	RESONATE	Study 116
HRQoL instrument	EQ-5D-5L	EQ-5D-3L
Measurement points	Screening/week1 (baseline), every 4 weeks in the first 24 weeks, every 12 weeks starting from the week 24 visit until disease progression was confirmed by IRC, and at the last treatment visit before treatment discontinuation	Baseline and at Weeks 2, 4, 6, 8, 12, 16, 20, 24, 30, 36, 42, and 48, at every 12 weeks thereafter prior to progression and at the end of treatment.
Valuation method	Mapped to EQ-5D-3L values	TTO
Reference case consistency	YES	YES
Appropriate for economic evaluation	NO. The committee overseeing the ibrutinib appraisal concluded that the EQ-5D may not have captured the experience of people with CLL.	YES
Results with CIs	N/A	PFS: 0.748

The EQ-5D-3L based utility value from study 116 has been included in two previous NICE submissions. (6,37) The EQ-5D was a tertiary endpoint in Study 116 which compared idela + R vs. rituximab + placebo. Measurements were taken at baseline, and at weeks 2, 4, 6, 8, 12, 16, 20, 24, 30, 36, 42, and 48, at every 12 weeks thereafter prior to progression and at the end of treatment. EQ-5D data were not collected once patients had progressed. Compliance rates for EQ-5D completion were good across all time points. The source is in alignment with the reference case and is used within the economic model.

Table 41 EQ-5D compliance in study 116

Visit	Treatment	N	Compliance Rate (%)
Week 2	Idela+R	110	96
	rituximab + placebo	108	94
Week 4	Idela+R	108	95
	rituximab + placebo	106	93
Week 6	Idela+R	107	90
	rituximab + placebo	106	90
Week 8	Idela+R	106	89
	rituximab + placebo	100	92
Week 12	Idela+R	99	84
	rituximab + placebo	93	85
Week 16	Idela+R	85	82
	rituximab + placebo	71	75
Week 20	Idela+R	72	85
	rituximab + placebo	54	76
Week 24	Idela+R	59	86
	rituximab + placebo	40	78
Week 30	Idela+R	51	77
	rituximab + placebo	31	81
Week 36	Idela+R	39	80
	rituximab + placebo	25	72
Week 42	Idela+R	30	90
	rituximab + placebo	15	67

Week 48	Idela+R	26	81
	rituximab + placebo	10	70

Source: NICE TA359, table 68 (37)
Key: Idela + R, Idelalisib + rituximab

B.3.4.4 Adverse reactions

The impact of AEs on HRQoL is included in the economic evaluation. Literature estimates of disutility and duration of each AE are combined multiplicatively to estimate a QALY decrement (see the model inputs in the next section, Table 43).

This QALY decrement is applied during the first model cycle only. This is a simplifying assumption since estimating the exact timing of AEs is not possible for all comparators relevant to the decision problem. This assumption is not a large driver of model results.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

A qualitative description of the disease is provided in Section B.1.3. In order to model the disease and treatment pathway the health states used are progression, post-progression and death. The death health state has a zero-utility value whilst the two living health states can vary from negative values (worse than death) to 1 (equivalent to perfect health).

The MURANO trial data was first assessed for suitability. The trial collected EQ-5D-3L data at regular intervals within a patient's pre-progression period, once at progression and once at the first assessment following progression. The trial EQ-5D-3L data was combined with the published UK value sets to obtain utility values for each assessment. (62) The utility values ranged between -0.594 and 1. The utility values reported were heavily skewed towards the upper value of 1 or "Perfect health". Attempts to model a PFS health state utility value based on this data lead to high values that lack validity when compared to general population norms. Surveys for England show that a healthy population, aged between 60 and 65, have a utility value around 0.9373. (128) For the entire population, irrespective of health condition this was 0.8041 and for cancer patients in general 0.6737 (this group was not stratified further by cancer type which limits its generalizability to R/R CLL). Based on these comparative data and previous submissions made to NICE in CLL, the MURANO EQ-5D-3L data was not used to estimate the base case PFS utility value. (6,56)

The health state utility values used in the model bases case are taken from literature sources that were used in the NICE committees preferred model for V-mono (TA487) and idela+R (TA359). (6,37) The health state utility values are reported in Table 42. The pre-progression utility value was based on the data from study 116 which administered the EQ-5D-3L during a patient's pre-progression period (0.748). The post-progression health state utility is estimated from the literature; an ERG report by Dretzke et al. on the cost effectiveness of rituximab in which the mean post-progression utility was 0.600. (87)

Table 42 Summary of health state utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% CI (assuming SE=10% of the mean)	Reference in submission (section and page number)
Pre-progression	0.748	0.589-0.879	Section: Health-related quality-of-life data used in the cost-effectiveness analysis
Post-progression	0.600	0.480-0.714	Section: Health-related quality-of-life data used in the cost-effectiveness analysis

Key: HS, health state; CE, cost-effectiveness; CI, Confidence Interval

The parameters for each AE are informed by previous NICE technology appraisals and the literature (see Table 43). The QALY decrement (i.e. disutility*duration) is applied during the first model cycle.

Table 43 AE disutility, duration and QALY decrement

AE	Disutility Value	Reference	Duration (months)	Reference	QALY decrement
ALT/AST elevation	0.050	NICE TA347(129)- Assumption	0.690	NICE TA347(129)- Assumption	0.003
Anaemia	0.090	NICE TA344(40) – Value form Beusterien et al. 2010 (130)	0.763	NICE TA359 (37)- Assumed equal to thrombocytopenia	0.006
Autoimmune haemolytic anaemia	0.090	Assumed equal to anaemia. Assumed equal to infection disutility from Tolley et al. 2013 (131)	0.763	Assumed equal to anaemia. NICE TA359 (37)- Assumed equal to thrombocytopenia	0.006
Hypophosphatemia	0.000	Assumption	0.000	Assumption	0.000
Infusion related reaction	0.200	NICE TA344 (40)	0.115	NICE TA344 (40)	0.002
Neutropenia	0.163	Tolley et al 2013 (131)	0.496	NICE TA306 (132)	0.007
Pneumonia	0.195	Assumed equal to infection disutility from Tolley et al.2013 (131)	0.598	NICE TA359 (37) - Study 116	0.010
Thrombocytopenia	0.108	NICE TA359 (37)– Tolley et al 2013 (131)	0.763	NICE TA306 (132)	0.007

The NICE decision support unit (DSU) TSD for the use of health state utility values in decision models recommends that utility values be age adjusted. (64) This is due to the increasing prevalence of comorbidities in older aged cohorts and the negative effect on HRQoL directly associated with age. This relationship has been documented in analyses of large UK survey data. (128,133) To account for this relationship over the time horizon of the model, a multiplicative adjustment is applied to the health state utility values of the cohort. This age dependency is applied for both pre- and post-progression health states. The data used to inform the adjustment is taken from a study which pooled data from four consecutive health surveys for England (2003-2006). (128) Within this survey, self-reported EQ-5D (3 level) data were reported. Table 23 reports the mean utility values by age group, irrespective of health status, from a sample of 11,982 members of the general population in England. The inputs used to make the adjustment are presented in Table 44. The economic model assumes that patients enter with an average age of 64.18 and hence the age bracket '60 to ≤ 65' is used as the baseline group. As the model simulates patients over time, those who survive and enter the remaining age brackets receive age deteriorated health state utility values for progression free and progressed health states. The deteriorated health state utility values are presented in

Table 45.

Table 44 Age related utility deterioration

Age bracket	N	Mean	95% CI	Adjustment from baseline
60-≤65	2739	0.8072	(0.793,0.821)	1
66-≤70	2993	0.8041	(0.790,0.817)	0.996
71-≤75	2501	0.779	(0.766,0.791)	0.965
76-≤80	1895	0.7533	(0.739,0.767)	0.933
81-≤85	1199	0.6985	(0.677,0.719)	0.865
86+	655	0.6497	(0.624,0.675)	0.805
Total	11,982			

Table 45 Pre and post-progression utilities adjusted by age

Age bracket	Adjustment from baseline	Pre-progression age adjusted utilities	Post-progression age adjusted utilities
60-≤65	1	0.748	0.60
66-≤70	0.996	0.745	0.598
71-≤75	0.965	0.722	0.579
76-≤80	0.933	0.698	0.560
81-≤85	0.865	0.647	0.519
86+	0.805	0.602	0.483

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify studies assessing the cost and healthcare resource use studies in R/R CLL. For full details of the methods used to conduct this review, please see Appendix I.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.2 Active treatment

Drug costs are obtained from the BNF and are presented in Table 46. The treatment regimens are presented in Table 47. Venetoclax is available in five different pack sizes which accommodate for the initial dose titration and a pack for 28 days of treatment thereafter. Treatment in the model's base case is assumed to follow the protocols laid out in

Table 47.

Table 46 Drug acquisition costs

Drug	Pack size	Pack Cost	Per mg Cost	Source
Venetoclax	14 x 10mg	£59.87	£0.43	BNF – 10, 50 and 100 mg tablets (AbbVie Ltd)
	7 x 50mg	£149.67	£0.43	
	7 x 100mg	£299.34	£0.43	
	14 x 100mg	£598.68	£0.43	
	112 x 100mg	£4,789.47	£0.43	
Rituximab (IV)	1 x 500mg	£785.84	£1.57	BNF - Truxima 500mg/50ml concentrate for solution for infusion vials (Napp Pharmaceuticals Ltd)
Rituximab (SC)	1 x 1,400mg	£1,344.65	£0.96	NICE Evidence summary ESNM46 (2014) (134)
Ibrutinib	90 x 140mg	£4,599.00	£0.37	BNF - Imbruvica 140mg capsules (Janssen-Cilag Ltd)
Idelalisib	60 x 150mg	£3,114.75	£0.35	BNF - Zydelig 150mg tablets (Gilead Sciences International Ltd)

Key: BNF, British National Formulary; IV, Intravenous; SC, Subcutaneous

Table 47 Treatment regimens

Regimen	Drug	Admin	Dosing schedule
VEN+R	Venetoclax	Oral	Daily dose, 20 mg week 1, 50mg week 2, 100mg week 3, 200mg week 4, 400 mg week 5 and beyond until disease progression or 2-year maximum treatment duration.
	Rituximab	IV	375 mg/m^2 D1 C1, 500 mg/m^2 D1 C2-C6 for a total of 6 doses.
Ibrutinib	Ibrutinib	Oral	Daily dose of 420mg until disease progression.
Idela + R	Idelalisib	Oral	Daily dose of 300mg until disease progression.
	Rituximab	IV	375 mg/m^2 D1 C1, 500 mg/m^2 D1 C2-C6 for a total of 6 doses.

Key: Idela + R, Idelalisib + rituximab; IV, intravenous; Dx, day x; Cx, cycle x; VEN+R, venetoclax + rituximab

The drug administration costs are shown in Table 48. Millar et al. found that the dispensing of drugs administered intravenously takes on average 12 minutes each. (135) One hour of pharmacist time performing patient related activities (accounting for overheads, qualifications, and salary on costs) is estimated to cost £45 (Hospital-based scientific and professional staff band 6). (136) Hence 12 minutes of pharmacist time is associated with a cost of £9 per infusion (£45*12/60).

Table 48 Drug administration costs

Drug	Cost	Currency code	Description
Rituximab (IV standard)	£313.47	SB15Z	IV administration cost from NHS Reference Costs 2016-17; Total HRGs, SB15Z: deliver subsequent elements of a chemotherapy cycle. This is supplemented by the cost of pharmacist time for dispensing the IV drugs (£9.00).
Rituximab (IV Rapid)	£250.07	SB12Z	IV administration cost from NHS Reference Costs 2016-17; Total HRGs, SB12Z: deliver Simple Parenteral Chemotherapy at First Attendance (£241.07). This is supplemented by the cost of pharmacist time for dispensing the IV drugs (£9.00).

Key: HRG, Healthcare Resource Group ; NHS, National Health Service, IV, intravenous

The model's base case accounts for the alternative delivery methods. Standard and rapid IV infusion methods maintain the same dosing regimens as shown in Table 47 but vary in terms of the cost per administration. The underlying assumption is that the cost of a rapid infusion would be similar to a simple chemotherapy delivery included in the NHS reference costs. The model's base case assumes all rituximab containing treatment regimens use a 30:70 ratio between standard and rapid IV infusions. This is based on a survey that was conducted within 20 UK trusts regarding their administration policies. (137)

Given the regimens specified in

Table 47 and any associated administration costs, the drug costs per 28-day model cycle are shown in Table 49. No wastage costs are included in the model framework since vial sharing is common clinical practice in the UK. (6)

Table 49 Total treatment costs per cycle

Treatment cycle*	VEN+ R	Ibrutinib	Idela+R
1	[redacted]	£4,292	£4,307
2	[redacted]	£4,292	£4,684
3	[redacted]	£4,292	£4,684
4	[redacted]	£4,292	£4,684
5	[redacted]	£4,292	£4,684
6	[redacted]	£4,292	£4,684
7 onwards	[redacted]	£4,292	£2,907

Key: Idela + R, Idelalisib + rituximab; VEN+R, venetoclax + rituximab
*Each cycle in the model includes 28 days. The model uses 13 cycles to represent a year (i.e. 364 days).

The base case includes only one line of treatment. In order to test this assumption, a scenario is included which incorporates post progression treatment costs. The methods used to estimate this cost are included in **Error! Reference source not found.**. These costs are not included in the base case as their estimation required a large amount of assumptions in the absence of the necessary data (i.e. the time on post-progression treatment data).

B.3.5.3 Treatment specific monitoring (i.e. TLS)

Since venetoclax can cause rapid death of CLL cells and tumour reduction, there is potential for TLS to occur. TLS is a result of the cellular contents of dying cells being released into the blood stream. TLS is well categorised and effectively preventable with guided monitoring and

prophylaxis treatment that is tailored towards a patient's risk of TLS occurring. The risk categories are based upon the size of lymph nodes and absolute lymphocyte counts. The prophylaxis regimen consists of an oral acid reducer such as allopurinol, oral hydration and serum chemistry monitoring. TLS prophylaxis is an important part of the treatment regimen VEN+R. The costs of TLS prophylaxis are modelled at baseline taking account of the TLS risk distribution from the MURANO trial.

The costs for laboratory TLS prophylaxis are obtained based on an algorithm (see **Error! Reference source not found.**) factoring TLS risk distribution of patients from the treated MURANO population. Specifically, patients were first divided into patients at lower and greater risk based on the tumour mass and absolute lymphocyte count (ALC) (i.e. lower risk: lymph node with a diameter ≤5 cm and ALC <25 x 10^9/L; greater risk included all other patients). Patients in the lower risk group included 18.06% of all patients (69 patients out of 382 treated MURANO patients). Patients in the greater risk included 81.94% of all patients (313 patients out of 382). The greater risk group was subdivided into two groups according to Creatinine Clearance. The TLS risk group distribution is shown below in Table 50 and is applied to VEN+R treatment in the model.

Table 50 TLS risk distribution

Lower Risk (node diameter ≤5 cm and ALC <25 x 10^9)	**Greater Risk (node diameter >5 cm or ALC >25 x 10^9)**	
	CRCL > 80 mL/min	**CRCL ≤ 80 mL/min**
18.06%	32.20%	49.74%

Key: ALC, absolute lymphocyte count; CRCL, creatinine clearance

Table 51 Per cycle TLS prophylaxis cost by risk group

Low Tumour Burden	**Greater Risk (CRCL>=80)**	**Greater Risk (CRCL<80)**
£1,430.40	£2,016.54	£2,146.81

Key: ALC, absolute lymphocyte count; CRCL, creatinine clearance

Based on the TLS risk distribution and the prophylaxis algorithm, the cost of TLS prophylaxis applied to VEN+R in the first cycle is £1,975.46.

B.3.5.4 Health-state unit costs and resource use

The 'routine care and monitoring' category is in place to account for the routine monitoring visits and procedures which occur during a CLL patient's treatment pathway. The selection of resources and their frequency of use was guided by those used in a previous NICE submission of ibrutinib, sourced from expert opinion of 50 NHS haematologists and oncologists who actively make treatment decisions for CLL patients. (21) These were further refined based on the comments provided by four clinical advisors via an online survey preceding the UK advisory board (see section 2.10). Resources include: full blood counts, LDH tests, chest X-rays, bone marrow exams, haematologist visits, inpatient non-surgical medical visits, blood and platelet transfusions. Unit cost estimates are taken from the NHS reference costs 2016/17 and are presented in Table 52.

Table 52 Routine care and monitoring unit costs

Visit/procedure	Cost	Source
Full blood count	£3.06	National schedule of reference costs 2016/17: DAPS05- Haematology
LDH	£1.13	National schedule of reference costs 2016/17: DAPS04 - Clinical biochemistry
Chest X-ray	£18.71	National schedule of reference costs 2016/17: IMAGDA- Imaging: Outpatient (IMAGOP)
Bone marrow exam	£512.59	National schedule of reference costs 2016/17: Diagnostic Bone Marrow Extraction (SA33Z)
Haematologist visit	£169.64	National schedule of reference costs 2016/17: Outpatient Attendances Data: 303- Clinical haematology
Inpatient non-surgical/medical visit	£536.07	National schedule of reference costs 2016/17: Weighted average of day case SA32A, SA32B, SA32C and SA32D= £401.07 PSSRU 2016: Medical consultant hour (including qualification costs) = £135
Full blood transfusion	£171.58	National schedule of reference costs 2015/16: Outpatient Procedures- 303, Clinical Haematology, single plasma exchange or other IV blood transfusion, 19-years and over

Key: IV, intravenous; LDH, Lactate Dehydrogenase; PSSRU, Personal Social Services Research Unit

The ERG reviewing the ibrutinib submission disagreed with response stratified resource use in pre-progression. Therefore, annual resource use frequencies are stratified by pre- and post-progression only (see Table 53). Feedback from the clinical experts suggested that the pre-progression health state resource use would include full blood counts, LDH tests and haematologist visits. For post-progression, resources use would include full blood counts, chest X-rays, bone marrow exams, haematologist visits, inpatient non-surgical medical visits and full blood transfusions. The annual frequencies lead to substantially lower per cycle costs for the pre-progression health state compared to post-progression.

Table 53 Routine care and monitoring resource use

Resource/procedure	Annual pre-progression frequency	Annual post-progression frequency
Full blood count	4	8
LDH test	2	0
Chest X-ray	0	2
Bone marrow exam	0	1
Haematologist visit	2	6
Inpatient non-surgical medical visit	0	4
Full blood transfusion	0	11
Total annual cost	£353.78	£5,624.03
Per cycle cost	**£27.12**	**£431.14**

Key: **LDH, Lactate Dehydrogenase**

B.3.5.5 Adverse reaction unit costs and resource use

The AE costs are taken from the National Schedule of Reference Costs 2016/17. When a cost was only available in an older version of the National Schedule of Reference Costs, the Hospital and Community Health Services (HCHS) Prices index has been used to inflate the price to

2016/17 prices (i.e. the most recent year available in this index). (136) Previous submissions made to NICE are also used to inform the selection of unit costs.

Table 54 AE costs

AE	Cost	Reference
ALT/AST elevation	£0.00	NICE TA193: No intervention
Anaemia	£1,170.78	NHS Reference Costs 2016-17: Total HRGs, weighted average of Haemolytic Anaemia CC score 0-2 and 3+ (SA03G and SA03H)
Autoimmune Haemolytic anaemia	£1,170.78	Assumed equal to Anaemia
Neutropenia	£119.49	NICE TA359: NHS Reference Costs 2016-17: Total HRGs, Neutropenia Drugs, Band 1 (XD25Z)
Pneumonia	£6,149.58	NHS Reference Costs 2016-17; Total - HRGs, Lobar, Atypical or Viral Pneumonia, with multiple interventions (weighted average of DZ11K-DZ11M)
Thrombocytopenia	£621.34	NHS Reference Costs 2016-17; Total - HRGs, Thrombocytopenia (weighted average of SA12G-SA12K)

Key: AE: adverse event; ALT/AST, Alanainine Transaminase/ Aspartate Transaminase; HRGs, Healthcare Resource Group; NHS, National Health Service; NICE National Institute for Health and Care Excellence

B.3.5.6 Terminal Care costs

The costs associated with terminal care are included in the model. These are applied to all patients who transition to the death health state as a one-off cost. The costs of terminal care were based on a published study of end of life care for solid tumour cancer patients. (138) The specific cost used was guided by the NICE ibrutinib appraisal. (21) Clinical experts advising on the ibrutinib submission process had suggested that the costs of terminal care would be similar between solid tumour and haematology patients.

The terminal care costing study incorporated Bayesian modelling using data from the literature and publicly available datasets. Four types of cancer were considered: Breast, Colorectal, Lung and Prostate. Mean costs were presented for health care, social care, charity care and informal care. The cost used within the economic model only considers the direct costs borne by the health and social care sectors, in line with the perspective recommended in the NICE reference case. (139) The costs are presented below in Table 55. The total cost for terminal care per patient was £6,601.23 (inflated to 2016-17 prices). (136)

Table 55 Terminal care cost

Resource category	Mean costs (2013-14)	HCHS annual price inflation multiplier (to 2016-17)	Mean total cost (2016-17)
Health care	£4,254	1.017*1.027*1.039= 1.085	**£6,601.23**
Social care	£1,829		
Total	£6,083		

Key: HCHS, Hospital and Community Health Services

B.3.6 Summary of base-case analysis inputs and assumptions

Table 56 Summary of variables included in the economic model

Variable	Value (ref.to table/figure)	Lower CI	Upper CI	Distribution	Ref. to submission section
Discount rate of costs	0.035	0.028	0.042	Beta	Section B.3.2.2
Discount rate of outcomes	0.035	0.028	0.042	Beta	Section B.3.2.2
Starting age	64.18	63.18	65.19	Gamma	Section B.3.3.1
Proportion male	0.738	0.582	0.868	Beta	
Body surface area	1.918	1.898	1.939	Gamma	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Section B.2.9
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
AE probabilities	See Table 33	NR	NR	Beta	Section B.3.3.5
Drug acquisition: Venetoclax (week 1)	59.87	N/A	N/A	N/A	Section B.3.5.2
Drug acquisition: Venetoclax (week 2)	149.67	N/A	N/A	N/A	
Drug acquisition: Venetoclax (week 3)	299.34	N/A	N/A	N/A	
Drug acquisition: Venetoclax (week 4)	598.68	N/A	N/A	N/A	
Drug acquisition: Venetoclax (28-day, week 5+)	4,789.47	N/A	N/A	N/A	
Drug acquisition: Ibrutinib (90*140mg pack)	4,599	N/A	N/A	N/A	
Drug acquisition: Idelalisib (60*150mg pack)	3,114.75	N/A	N/A	N/A	
Drug acquisition: Rituximab (IV) (1*500mg vial)	785.84	N/A	N/A	N/A	
Drug acquisition: Rituximab (RAPID IV) (1*500mg vial)	785.84	N/A	N/A	N/A	
Drug admin: Rituximab (IV)	313.47	255.05	377.82	Gamma	
Drug admin: Rituximab (RAPID IV)	250.07	203.47	301.41	Gamma	
Routine costs: Pre- progression	28.48	23.17	34.32	Gamma	Section B.3.5
Routine costs: Post progression	452.69	368.33	545.63	Gamma	
One-off cost: ALT/AST elevation	0.00	0.00	0.00	Gamma	Section B.3.5.5
One-off cost: Anaemia	1,170.78	952.59	1,411.13	Gamma	
One-off cost: Autoimmune Haemolytic Anaemia	1,170.78	952.59	1,411.13	Gamma	
One-off cost: Neutropenia	119.49	97.22	144.01	Gamma	

One-off cost: Pneumonia	6149.58	5003.54	7412.02	Gamma	
One-off cost: Thrombocytopenia	621.34	505.55	748.90	Gamma	
Venetoclax + R: TLS prophylaxis	1,975.46	1607.31	2,381.00	Gamma	Section B.3.5.3
Venetoclax: TLS prophylaxis	1,975.46	1,607.31	2,381.00	Gamma	
Terminal care cost	6,601.23	5,371.02	7,956.39	Gamma	Section B.3.5.6
Utility: progression free	0.748	0.589	0.879	Beta	Section B.3.4.5
Utility: post-progression	0.600	0.480	0.714	Beta	
Disutility: ALT/AST elevation	0.003	0.002	0.003	Beta	
Disutility: Anaemia	0.006	0.005	0.007	Beta	
Disutility: Autoimmune Haemolytic Anaemia	0.006	0.005	0.007	Beta	
Disutility: Neutropenia	0.007	0.005	0.008	Beta	
Disutility: Pneumonia	0.010	0.008	0.012	Beta	
Disutility: Thrombocytopenia	0.007	0.006	0.008	Beta	
VEN+R/BR Joint model PFS/OS hazard rate	N/A	N/A	N/A	Weibull	Section B.3.3.3

Key: ALT/AST, Alanainine Transaminase/ Aspartate Transaminase; CI, confidence interval; HR, hazard ratio; Idela+R, Idelalisib + rituximab; IV,Intravenous ; OS, overall survival; PFS, progression-free survival; TLS: tumour lysis syndrome; VEN+R, venetoclax + rituximab

B.3.6.1 Assumptions

Table 57 List of model assumptions (base case)

Model feature	Source/assumption	Justification
Efficacy		
VEN+R extrapolation model, section B.3.3	Proportionality between treatments	Not rejected based on observed MURANO data.
	Proportionality between survival endpoints (i.e. PFS and OS)	Not rejected based on observed MURANO data. Not rejected based on external data.
	Proportionality between del(17p)/TP53 and non-del(17p)/TP53	Not rejected based on observed MURANO data.
	The Weibull distribution is used to extrapolate PFS and OS outcomes into the future.	See Appendix L: Final model selections
PFS and OS hazard ratios (MAIC), section B.2.9	All prognostic and effect modifiers are accounted for in the matching procedure.	The method aims to strike a balance between matching for all possible variables and maintaining a large enough effective sample size to estimate the Hazard Ratios with minimal uncertainty.
	Proportionality between VEN+R and comparator over time.	The data available from the MURANO trial and the comparator literature is insufficient to estimate time-varying hazard ratios. Particularly for extrapolation.
Utility		
PFS and PPS utility values, section B.3.4	There is no difference in health state utility values across treatments.	There are no randomised data comparing VEN+R directly with the relevant comparators in terms of HRQoL.
AE disutility, section B.3.4	The negative impact of AEs on quality of life is applied in the first model cycle.	AEs are not a driver of the incremental results. This is a simplifying assumption.
Costs		
ToT, section B.3.5	Treatment follows protocol for intervention and comparators. i.e. dose intensity and adherence are assumed to be 100%	This approach can be applied consistently across comparators.
TLS prophylaxis, section B.3.5	TLS prophylaxis is conducted in line with the key clinical trials for VEN.	
Routine care and monitoring costs, section B.3.5	Applied uniformly to the health state as opposed to treatment status (e.g. on/off treatment)	
Post-progression treatment costs, section B.3.5	No post-progression treatment costs are included	Data limitations lead to many assumptions.

Key: AE, adverse event; del(17p)/TP53, 17p deletion or tumour protein 53 mutation; HRQoL, health related quality of life; MAIC; Matching Adjusted Indirect Comparison; OS, overall survival; PFS, progression free survival; PPS, post progression survival; TLS, tumour lysis syndrome; ToT, Time on treatment; VEN+R, venetoclax+ rituximab

B.3.7 Base-case results

B.3.7.1 Health state distributions over time

Figure 23, Figure 24 & Figure 25 show the distribution of patients within the PFS and PPS health states over 30-years for VEN+R, ibrutinib and idela+R respectively. The hazard ratios applied to Ibrutinib lead to PFS exceeding OS (which is restricted in the model to be equal or lower than OS). This results in a zero post-progression period. This lacks face validity, and is predominantly a consequence of the large uncertainty margins surrounding the MAIC estimates.

Figure 23 VEN+R health state distribution over a lifetime horizon (R/R CLL)

R, Rituximab; PFS, Progression Free Survival; PPS, Post-Progression Survival

Figure 24 Ibrutinib health state distribution over a lifetime horizon (R/R CLL)

PFS, Progression Free Survival; PPS, Post-Progression Survival

Figure 25 Idela+R health state distribution over a lifetime horizon (R/R CLL)

R, Rituximab; PFS, Progression Free Survival; PPS, Post-Progression Survival

B.3.7.2 Time on treatment (ToT)

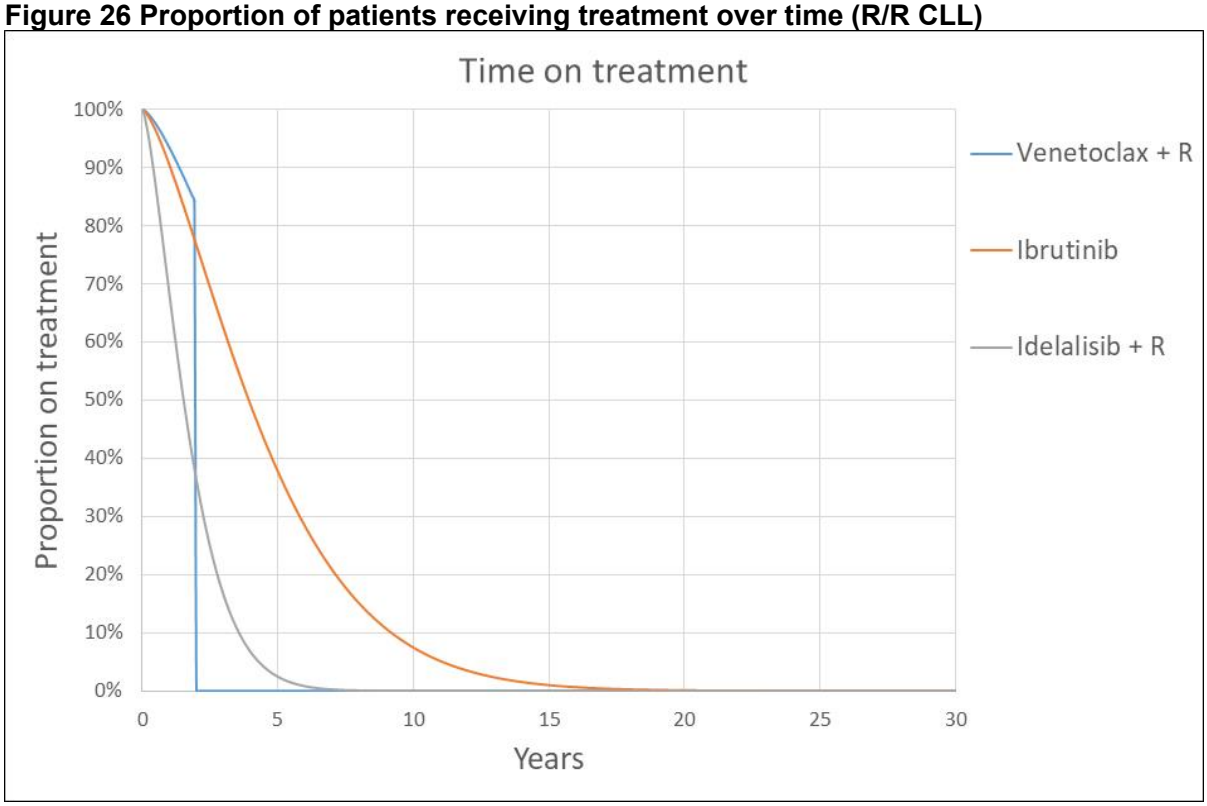
Table 58 includes the average ToT for each regimen included in the model inclusive of survival events. Figure 26 shows VEN+R ToT follows the PFS curve until 2 years at which point all patients stop treatment. All other regimens follow a treat to progression rule.

Table 58 Average time on treatment (R/R CLL)

Treatment	Average ToT (mean years)
VEN+R	1.859
Ibrutinib	4.661
Idela+R	1.833
Venetoclax	2.458

Key: Idela+R, idelalisib+rituximab; VEN+R, venetoclax+Rituximab;

Figure 26 Proportion of patients receiving treatment over time (R/R CLL)



Key: R, Rituximab

B.3.7.3 Costs

Table 59 presents the total per patient treatment costs, discounted over a lifetime time horizon. For all treatments the largest cost category is active treatment. This is followed by the routine costs of care applied to patients in the post-progression health state.

Table 59 Per patient costs by category, discounted over a lifetime horizon (R/R CLL)

Treatment	Active treatment	Treatment admin	PFS health state costs	PPS health state costs	Terminal care costs	Treatment specific monitoring	AEs	Total
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Idela+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: VEN+R, Venetoclax+Rituximab; Idela+R, Idelalisib+Rituximab; PFS, Progression Free Survival; PPS, Post Progression Survival; AE, adverse event.

[redacted]

B.3.7.4 QALYs

Life years and QALYs over a lifetime horizon are presented in Table 60. VEN+R had the highest value of life years in both the PFS and PPS health states. After applying the health state utility values VEN+R had the greatest number of QALYS. The impact of AE related disutility values has a very small impact on total QALYs.

Table 60 Total per patient life years (undiscounted) and QALYs (discounted) over a lifetime horizon (R/R CLL)

	Undiscounted Life years			**Discounted QALYs**			
Treatment	PFS	PPS	Total life years	Progression free QALYs	Post-progression QALYs	AE disutility	Total QALYs
VEN+R	6.101	4.687	10.788	3.885	1.787	0.006	5.666
Ibrutinib	4.635	0.000	4.635	3.069	0.000	0.002	3.067
Idela+R	1.800	1.985	3.785	1.285	1.026	0.003	2.307

Key: VEN+R, venetoclax+Rituximab; Idela+R, Idelalisib+rituximab; PFS, Progression Free Survival; PPS, Post Progression Survival; AE, Adverse Event

B.3.7.5 Incremental cost-effectiveness analysis results

The results of the incremental comparison are presented in Table 61, Table 62, Figure 27 and Figure 28. In summary, for list price to list price comparisons VEN+R either dominates relevant comparators or is cost-effective at the £20,000 WTP threshold. The same pattern of dominancy or cost-effectiveness is observed when VEN+R discounted prices are used. It is expected that the ERG will undertake similar comparisons using the confidential discounted prices for Idela+R and ibrutinib and that this will be shared with the appraisal committee.

For list price comparisons, when compared to the lowest cost regimen (Idela+R), the ICER for VEN+R was [redacted]. When making a pairwise comparison with VEN+R, ibrutinib is dominated.

Table 61 Base-case results (R/R CLL, list price)

Technologies	Total costs (£)	Total LYG (undisc)	Total QALYs (disc)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)	Pairwise ICER vs. VEN+R (£/QALY)
Idela+R	[redacted]	3.78	2.307	[redacted]	-	-	[redacted]	[redacted]
VEN+R	[redacted]	10.79	5.666	[redacted]	-7.003	-3.358	[redacted]	[redacted]
Ibrutinib	[redacted]	4.64	3.067	[redacted]	-0.851	-0.759	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; Idela+R, idelalisib+rituximab; LYG, life years gained; QALYs, quality-adjusted life years; VEN+R, venetoclax+rituximab;

The cost effectiveness frontier shows the ICER between idela+R and VEN+R through the gradient of the connected points. This value is [redacted].

Figure 27 Cost-effectiveness frontier (R/R CLL, list price)

Key: QALY, quality adjusted life year

The results are presented below based on discounted prices. [redacted]

Table 62 Base-case results (R/R CLL, net price)

Technologies	Total costs (£)	Total LYG (undisc)	Total QALYs (disc)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Pairwise ICER VS VEN+R (£/QALY)
Idela+R	[redacted]	3.78	2.307	-	-	-	-	£2,625
VEN+ R	[redacted]	10.79	5.666	-£8,816	-7.003	-3.358	£2,625	-
Ibrutinib	[redacted]	4.64	3.067	-£147,377	-0.851	-0.759	£194,048	Dominated

Key: ICER, incremental cost-effectiveness ratio; Idela+R, Idelalisib+rituximab; LYG, life years gained; QALYs, quality-adjusted life years; VEN+R, Venetoclax+Rituximab;

Figure 28 Cost-effectiveness frontier (R/R CLL, net price)

Key: QALY, quality adjusted life year

The clinical outcomes and disaggregated results of the model are presented in Section B.3.7.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

The PSA involves drawing values for each variable from its individual uncertainty distribution. This is performed for each parameter simultaneously and the resulting incremental results are recorded. This constitutes one 'simulation'. One thousand simulations were performed, which gives a distribution of incremental results, and consequently, an idea of the overall uncertainty surrounding cost-effectiveness. The parameters varied and the distributions used are reported in Table 63. For event rates and utilities, a beta distribution is used to restrict draws to the 0-1 space. For costs and resource use estimates, a gamma distribution is fitted to prevent values less than zero. Treatment costs remain fixed. HRs are logged and assumed to follow a normal distribution. For the estimated venetoclax parametric extrapolations outlined, the covariance matrix is used to estimate the joint uncertainty between model parameters. Values are sampled by decomposing the covariance matrix using Cholesky decomposition. (140)

Using the NMB approach, the probability of each treatment to be cost-effective at different levels of WTP per QALY are presented in a cost-effectiveness acceptability curve (CEAC). This NMB approach uses the following formula and involves estimating the cost-effectiveness of each treatment, given WTP threshold per QALY.

$$NMB^{Treatment\ X} = (WTP * QALYs^{Treatment\ X}) - Costs^{Treatment\ X}$$

For a given WTP per QALY threshold, the treatment with the highest NMB is the most cost-effective.

Table 63 Model parameters varied in PSA

Parameter	Distribution
Starting age	Gamma
Proportion male	Beta
Body surface area	Gamma
PFS HR: VEN+R vs. Ibrutinib	Normal
PFS HR: VEN+R vs. Idela + R	Normal
OS HR: VEN+R vs. Ibrutinib	Normal
OS HR: VEN+R vs. Idela + R	Normal
Drug admin: Venetoclax (week 1)	Gamma
Drug admin: Venetoclax (week 2)	Gamma
Drug admin: Venetoclax (week 3)	Gamma
Drug admin: Venetoclax (week 4)	Gamma
Drug admin: Venetoclax (28 day, week 5+)	Gamma
Drug admin: Ibrutinib	Gamma
Drug admin: Idelalisib	Gamma
Drug admin: Rituximab (IV)	Gamma
Drug admin: Rituximab (SC)	Gamma
Drug admin: Rituximab (RAPID IV)	Gamma

Routine costs: Pre progression	Gamma
Routine costs: Post progression	Gamma
One-off cost: ALT/AST elevation	Gamma
One-off cost: Anaemia	Gamma
One-off cost: Anaemia (Autoimmune haemolytic)	Gamma
One-off cost: Hypophosphatemia	Gamma
One-off cost: Infusion related reaction	Gamma
One-off cost: Neutropenia	Gamma
One-off cost: Pneumonia	Gamma
One-off cost: Thrombocytopenia	Gamma
VEN+R: TLS prophylaxis	Gamma
Terminal care cost	Gamma
Utility: progression free	Beta
Utility: post-progression	Beta
Disutility: ALT/AST elevation	Beta
Disutility: Anaemia	Beta
Disutility: Anaemia (Autoimmune haemolytic)	Beta
Disutility: Hypophosphatemia	Beta
Disutility: Neutropenia	Beta
Disutility: Pneumonia	Beta
Disutility: Thrombocytopenia	Beta
Ven+R/BR Joint model PFS/OS hazard rate	Normal

Key: ALT/AST, Alanainine Transaminase/ Aspartate Transaminase; BR, bendamustine + rituximab, Idela+R, Idelalisib + rituximab; OS, overall survival, IV, intravenous; PFS, Progression Free Survival; SC, Subcutanous; TLS, Tumour Lysis Syndrome; VEN+R, venetoclax + rituximab

Table 64 presents the base case probabilistic results. The probabilistic results reinforce the deterministic results in that the ICER vs idela+R is similar and dominance is maintained vs Ibrutinib.

Figure 29 shows the scatter plot of probabilistic simulations on the cost-effectiveness plane for the included treatment regimens. The spread of the points shows that most of the uncertainty for VEN+R falls on the QALY side. This is a direct result of the uncertainty in survival extrapolation. The largest cost category for VEN+R is active treatment costs, and it is concentrated to the first 2-years of the model's time horizon (and hence is less sensitive to variations in extrapolation). In contrast, QALYs are accrued gradually over the model time horizon and hence total QALYs remain anchored to the full duration of the survival curve. For the comparator regimens, active treatment is influenced to a greater degree by the PFS extrapolations, which explains the much wider variance in costs for the comparators vs VEN+R.

Table 64 Base-case results (probabilistic, list price)

Technologies	Total costs (£), (95% CI)	Total QALYs, (95% CI)	Incremental. costs (£), (95% CI)	Incremental QALYs, (95% CI)	ICER versus baseline (£/QALY), (95% CI)	Pairwise ICER VS VEN+R (£/QALY), (95% CI)
Idela+R	[redacted]	2.410 (1.195 - 4.337)	[redacted]	-	[redacted]	[redacted]
VEN+R	[redacted]	5.678 (4.051, 7.396)	[redacted]	-3.268 (-4.944, -1.643)	[redacted]	[redacted]
Ibrutinib	[redacted]	3.073 (1.485, 5.222)	[redacted]	-0.663 (-2.645, 1.248)	[redacted]	[redacted]

Key: Idela+R, idelalisib+rituximab; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; VEN+R, venetoclax+rituximab

Figure 29 Cost-effectiveness plane (R/R CLL, list price)

Key: QALY, quality adjusted life year; R, rituximab

Table 65 Base-case results (probabilistic, net price)

Technologies	Total costs (£), (95% CI)	Total QALYs, (95% CI)	Incremental. costs (£), (95% CI)	Incremental QALYs, (95% CI)	ICER versus baseline (£/QALY), (95% CI)	Pairwise ICER VS VEN+R (£/QALY), (95% CI)
Idela+R	[redacted]	2.437 (1.161 - 4.318)	-	-	-	£1,225 (-£15,475 - £10,967)
VEN+R	[redacted]	5.674 (4.060 - 7.308)	-£5,588 (-£37,232 - £37,642)	-3.236 (-4.893 - -1.551)	£1,225 (-£15,475 - £10,967)	-
Ibrutinib	[redacted]	1.400 (0.971 - 1.905)	£81,534 (£51,242 - £122,256)	1.038 (-0.090 - 2.805)	£154,717 (-£235,150 - £824,823)	£20,743 (£16,382 - £26,488)

Key:; ICER, incremental cost-effectiveness ratio; Idela+R, Idelalisib+Rituximab; QALYs, quality-adjusted life years; VEN+R, Venetoclax+Rituximab;

Figure 30 Cost-effectiveness plane (R/R CLL, net price)

Key: QALY, quality adjusted life year; R, rituximab

All cost-effectiveness acceptability curves are presented in Figure 31 (list price) and Figure 32 (net price). Figure 31 shows that VEN+R has [redacted] and [redacted] probability of being cost-effective vs. idela+R and ibrutinib, respectively, at a WTP of £30,000 using list price. Using net price, VEN+R has 100% probability of being cost-effective vs. all comparators at a WTP of [redacted]

Figure 31 Cost-effectiveness acceptability curves (R/R CLL, list price)

Key: QALY, quality adjusted life year, R, rituximab

Figure 32 Cost-effectiveness acceptability curves (R/R CLL, net price)

Key: QALY, quality adjusted life year, R, rituximab

B.3.8.2 Deterministic sensitivity analysis

To identify model drivers and key areas of uncertainty, variables for which values were uncertain were tested in a one-way sensitivity analysis (OWSA). The low and high values are based upon the 95% CI. When the CI of an input was unknown an assumption was made to

construct an interval assuming a standard error of 10% of the input value. The low and high values are presented in Table 66.

Table 66 Model parameters varied in deterministic sensitivity analysis

Parameter	Base Case	Low	High
Discount rate of costs	0.035	0.028	0.042
Discount rate of outcomes	0.035	0.028	0.042
Background mortality adjustment	1.000	1.000	1.000
Starting age	64.180	63.177	65.191
Proportion male	0.738	0.582	0.868
Body surface area	1.918	1.898	1.939
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Drug admin: Rituximab (IV)	313.466	255.048	377.817
Drug admin: Rituximab (RAPID IV)	250.072	203.468	301.409
Routine costs: Pre progression	27.121	22.066	32.688
Routine costs: Post progression	431.137	350.790	519.645
One-off cost: Anaemia	1170.777	952.591	1411.125
One-off cost: Anaemia (Autoimmune haemolytic)	1170.777	952.591	1411.125
One-off cost: Hypophosphatemia	378.657	308.090	456.391
One-off cost: Neutropenia	119.486	97.218	144.015
One-off cost: Pneumonia	6149.581	5003.544	7412.025
One-off cost: Thrombocytopenia	621.340	505.547	748.895
VEN+R: TLS prophylaxis	1975.461	1607.314	2381.002
Terminal care cost	6601.228	5371.023	7956.391
Utility: progression free	0.748	0.589	0.879
Utility: post-progression	0.600	0.480	0.714
Disutility: ALT/AST elevation	0.003	0.002	0.003
Disutility: Anaemia	0.006	0.005	0.007
Disutility: Anaemia (Autoimmune haemolytic)	0.006	0.005	0.007
Disutility: Hypophosphatemia	0.000	0.000	0.000
Disutility: Neutropenia	0.007	0.005	0.008
Disutility: Pneumonia	0.010	0.008	0.012
Disutility: Thrombocytopenia	0.007	0.006	0.008
Ven+R/BR Joint model PFS/OS hazard rate	**Error! Reference source not found.**		

Key: ALT/AST, Alanine Transaminase/ Aspartate Transaminase; PFS, Progression Free Survival; OS, Overall Survival; IV, Intravenous; SC, Subcutaneous; TLS, Tumour Lysis Syndrome; VEN+R, venetoclax + rituximab

The results of the one-way sensitivity analyses are presented using tornado plots. These plots show how parameter uncertainty influences key model results: incremental costs, incremental

QALYs and NMB. The top 6 parameters that create the widest range in each result are displayed.

In general, across all the comparisons, the OWSA demonstrates that variance in the VEN+R joint model hazard rates and ITC hazard ratios have the biggest influence on key model results. This is in line with expectations, as aside from being large model drivers (structurally), the ITC hazard ratios and survival extrapolations have very wide uncertainty margins in light of the data immaturity issues discussed previously.

For the comparison with ibrutinib the greatest impact on incremental costs is seen for the OS and PFS hazard ratios and the VEN+R joint model parameters. It is these parameters that drive the VEN+R and ibrutinib survival curves which are a key determinant of incremental costs (both with list and net prices). The next 3 parameters, which have a much lower impact, are routine costs in post progression (which affects VEN+R only), the discount rate of costs and VEN+R TLS prophylaxis costs (which affects VEN+R only). The largest driver of incremental QALYs is the OS HR which led to VEN+R having a much longer post-progression period compared to ibrutinib. Secondly the utility values for the PFS and OS health states are a key driver of incremental QALYs. The low estimate has the impact of weighting QALYs to a greater degree. The next parameters, with a much lower impact are the discount rate of outcomes, the PFS HR, the VEN+R joint model parameters and the starting age which affects background mortality. These parameters appear in the tornado plot for NMB since this is a function of both incremental costs and QALYs

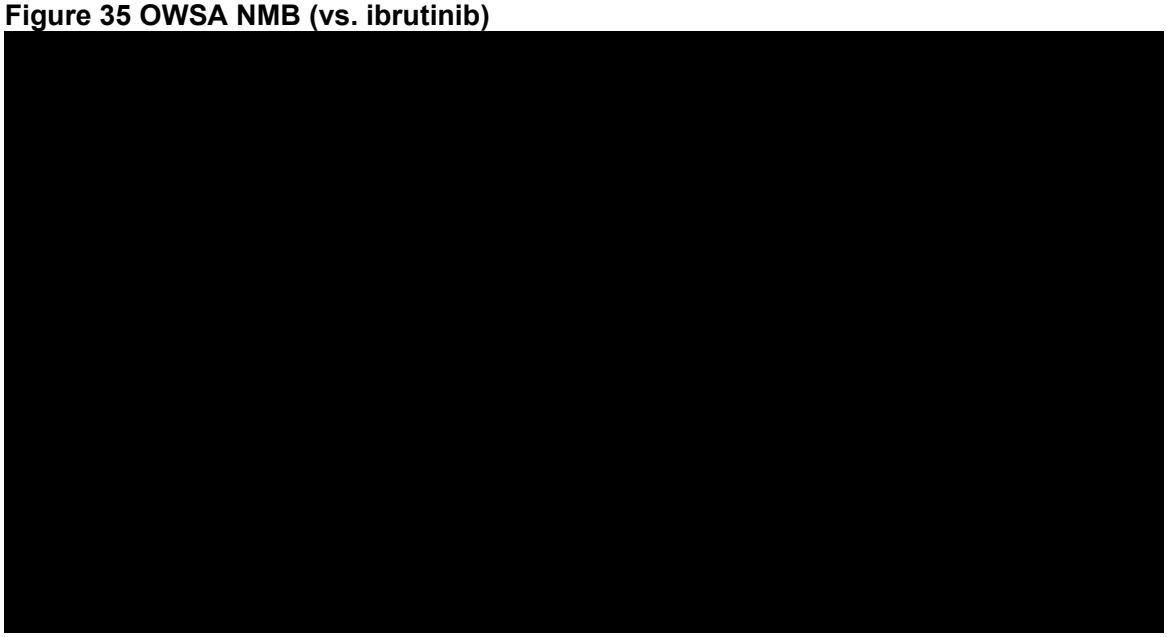
Figure 33 OWSA costs (vs. ibrutinib)

Key: BR, bendamustine+rituximab; HR, hazard ratio; OS, overall survival; PFS, progression free survival; TLS, tumour lysis syndrome; VEN+R, venetoclax+rituximab

Figure 34 OWSA QALYs (vs. ibrutinib)

Key: BR, bendamustine+rituximab; HR, hazard ratio; OS, overall survival; PFS, progression free survival; TLS, tumour lysis syndrome; VEN+R, venetoclax+rituximab

Figure 35 OWSA NMB (vs. ibrutinib)



Key: BR, bendamustine+rituximab; HR, hazard ratio; OS, overall survival; PFS, progression free survival; TLS, tumour lysis syndrome; VEN+R, venetoclax+rituximab

The OWSA is repeated using the venetoclax net price for incremental costs and NMB (net prices have no impact on incremental QALYs). The results in Figure 36 and Figure 37 differ

from list price results as the base case value has shifted. There are no changes to the magnitude or ordering of model drivers as venetoclax prices are not varied in the one-way sensitivity analysis.

Figure 36 OWSA costs (vs. ibrutinib, net price)

Key: BR, bendamustine+rituximab; HR, hazard ratio; OS, overall survival; PFS, progression free survival; TLS, tumour lysis syndrome; VEN+R, venetoclax+rituximab

Figure 37 OWSA NMB (vs ibrutinib, net price)

Key: BR, bendamustine+rituximab; HR, hazard ratio; OS, overall survival; PFS, progression free survival; TLS, tumour lysis syndrome; VEN+R, venetoclax+rituximab

For idela+R the greatest impact on incremental costs is seen for OS and PFS hazard ratios and the VEN+R joint model parameters. It is these parameters that drive the VEN+R and idela+R survival curves which are a key determinant of incremental costs. The next 3 parameters, which have a much lower impact, are routine costs in post progression, the discount rate of costs and VEN+R TLS prophylaxis costs (which affects VEN+R only). The largest driver of incremental QALYs is the OS HR which led to VEN+R having a much higher post-progression period compared to idela+R. Secondly the utility values for the PFS and OS health states are a key driver of incremental QALYs. The low estimate has the impact of weighting QALYs to a greater degree. The next parameters, with a much lower impact are the VEN+R joint model parameters, the discount rate of outcomes, the PFS HR and the starting age which affects background mortality. These parameters appear in the tornado plot for NMB since this is a function of both incremental costs and QALYs.

Figure 38 OWSA costs (vs. idela + R)

Key: BR, bendamustine+rituximab; HR, hazard ratio; OS, overall survival; PFS, progression free survival; TLS, tumour lysis syndrome; VEN+R, venetoclax+rituximab

Figure 39 OWSA QALYs (vs. idela+R)

Key: BR, bendamustine+rituximab; HR, hazard ratio; OS, overall survival; PFS, progression free survival; TLS, tumour lysis syndrome; VEN+R, venetoclax+rituximab

Figure 40 OWSA NMB (vs. idela+R)

Key: BR, bendamustine+rituximab; HR, hazard ratio; OS, overall survival; PFS, progression free survival; TLS, tumour lysis syndrome; VEN+R, venetoclax+rituximab

The OWSA is repeated using the venetoclax net price for incremental costs and NMB (net prices have no impact on incremental QALYs). The results in Figure 41 and Figure 42 differ from list price results as the base case value has shifted. There are no changes to the magnitude or ordering of model drivers as venetoclax prices are not varied in the one-way sensitivity analysis.

Figure 41 OWSA costs (vs. idela + R, net price)

Key: BR, bendamustine+rituximab; HR, hazard ratio; OS, overall survival; PFS, progression free survival; TLS, tumour lysis syndrome; VEN+R, venetoclax+rituximab

Figure 42 OWSA NMB (vs. idela+R, net price)

Key: BR, bendamustine+rituximab; HR, hazard ratio; OS, overall survival; PFS, progression free survival; TLS, tumour lysis syndrome; VEN+R, venetoclax+rituximab

B.3.8.3 Scenario analysis

A set of exploratory scenario analyses provide insight into model parameters and their relationship with key model outcomes. They also test the rigor and strength of model assumptions. Table 67 presents the scenario analyses conducted.

Table 67 Scenario analyses

Scenario	Description
Discount rates	The discount rates associated with costs and outcomes is varied between 0 and 6%
Time horizon	The time horizon is set to 1, 2, 5, 10, 15 and 25 years
VEN+R survival models	These scenarios fit the survival models that are not selected as the base case; the same model is consistently applied to PFS and OS.
VEN+R survival post treatment discontinuation	The VEN+R treatment effect following treatment discontinuation will be explored by manipulating the VEN+R hazards. This is done by incorporation of a waning effect assumed to start immediately after treatment cessation. PFS and OS hazards increase by 20, 50 and 100% until they hit a target percentage, 3-years after treatment cessation. This is the 5th-year of the model, which has also been the chosen year in previous NICE submissions in this disease area. (21),(37)
Comparator survival curves	The comparator survival curves will be estimated using individual curve estimation (with and without adjustment).
OS/PFS HRs for the VEN+R vs ibrutinib	Alternative HRs are tested for ibrutinib making the assumption of equal efficacy to ibrutinib + BR.
VEN TLS prophylaxis costs	The TLS prophylaxis costs are halved, doubled and removed.
Routine Costs of Care	The routine cost of care pre- and post-progression are halved, doubled and removed. Secondly, the routine costs of care resource use frequencies from the ibrutinib NICE submission are used. (21)
Terminal care costs	Terminal care costs are increased by 5,10,15 and 20%.
Observed MURANO Time on Treatment (ToT)	The observed time on treatment from MURANO is used (i.e. 1.753 years).
Body surface area	The body surface area is changed to a source from the UK general population (SACT dataset). (110) This parameter affects the drug costs for treatment regimens inclusive of rituximab.
Rituximab administration method	Scenarios test the effect of the three methods of rituximab administration: (i) IV infusion for rituximab as per SmPC (ii) IV infusion for rituximab: 'faster' infusion (90min rather than licensed rate) (iii) Subcutaneous injection
AEs	The AE rates are halved, doubled and removed.
Costs of next line treatment	To account for treatment post-progression, an annual cost will be applied based on the costs available evidence for VEN+R, BR, ibrutinib and idela+R. Ibrutinib incurs no cost in instances where the PPS period is zero.
Utilities	Alternative pre-and post-progression utility values are tested. Secondly, the difference between pre-and post-progression utility values is varied between 0.1 and 0.5.

Key: AE, adverse event; BR, bendamustine+rituximab; HR, hazard ratio; OS, overall survival; PFS, progression free survival; PPS, post progression survival; idela+R, idelalisib+R; IV, intravenous; NICE, The National Institute for Health and Care Excellence; SmPC, summary of product characteristics; TLS, tumour lysis syndrome; ToT, time on treatment; UK, United Kingdom; VEN+R, venetoclax+rituximab

B.3.8.4 Summary of scenario analyses results

The scenario analysis results are presented in Table 68 (list price) and Table 69 (net price). A total of 51 scenarios are performed. In general, the model outcomes remain reasonably robust to the scenario analyses. VEN+R remains dominant against ibrutinib for all scenarios, with the exception of extremely low time horizons (i.e. 1 and 2-year time horizons).

Using different pairings of discount rates leads to moderate movements in the incremental results which is anticipated in a model that makes estimates over a life-time horizon. The removal of discounting improves incremental QALYs for all comparisons since VEN+R produces the most QALYs. The effect on incremental costs is an improvement for the comparison with ibrutinib but a worsening vs. idela+R where VEN+R was a more expensive treatment. The reverse applies for scenarios that increase discount rates.

Scenarios that shorten the time horizon to 1-5 years have a large impact on model results since VEN+R accrues far fewer incremental QALYs over the shorter time period whilst the majority of VEN+R costs are captured within the first 2-years.

The effect of using alternative distributions for the joint survival model leads to fairly modest changes in incremental results. This is because the scenario impacts on both intervention and comparator curves estimated by a HR. Furthermore, using a multi-state approach to model VEN+R survival has a modest effect on incremental results. The scenarios that manipulate the post FTD hazards of VEN+R have the effect of reducing VEN+R QALYs, whilst the impact on the cost side is low. The scenarios have no impact on the comparator survival curves. Therefore, these scenarios lead to a slight increase in ICERs vs. idela+R.

Opting to use individually estimated PFS and OS curves for the comparators leads to large variation in cost-effectiveness results, particularly for the ibrutinib comparison. The impact of the adjustment factor can be seen by comparing the scenarios with and without its inclusion. However, we would caution against strong interpretation of these outcomes. Allowing such flexibility in individually fitted curve parameters (and from separate samples) may lead to widely spurious outcomes as time goes on.

Under the assumption that the efficacy of ibrutinib is similar to that of ibrutinib+BR, the anchored HR of VEN+R vs. ibrutinib+BR can be used as a proxy for VEN+R vs. ibrutinib. Under these assumptions, VEN+R remains dominant, an outcome which is robust to whether the HR is match-adjusted or not.

Varying the cost of TLS prophylaxis and removing it entirely has a very small impact on model results. Furthermore, increasing the cost of terminal care between 5% and 20% has a low impact. Larger variation is seen when routine costs of care are halved, doubled and removed (routine costs of care were next largest cost category following active treatment). When using the KM data from MURANO to model ToT, leads to a reduction in active treatment costs for VEN+R and an improvement in cost-effectiveness results. This scenario makes no change to comparator ToT.

The scenarios altering body surface area, rituximab administration approach, AE rates, wastage, utility values and disutility value have small impacts on models results. The impact of including post-progression treatment costs worsens cost-effectiveness outcomes vs. all comparators. The comparison with ibrutinib includes zero post-progression costs as there is no post-progression period resulting in an unfair comparison but VEN+R still remains dominant vs. ibrutinib.

Table 69 shows the results based on the venetoclax discounted price. The discount affects only incremental costs and improves cost-effectiveness results.

Table 68 Scenario analysis (R/R CLL, list price)

	VS. Ibrutinib			VS. Idela+R		
	Inc. costs (£)	**Inc. QALYs**	**ICER (£)**	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£)**
Base case	[redacted]	**2.599**	[redacted]	[redacted]	**3.358**	[redacted]
Discount rate. Costs: 0%, QALYs: 0%	[redacted]	3.677	[redacted]	[redacted]	4.592	[redacted]
Discount rate. Costs: 0%, QALYs: 6%	[redacted]	2.087	[redacted]	[redacted]	2.760	[redacted]
Discount rate. Costs: 6%, QALYs: 6%	[redacted]	2.087	[redacted]	[redacted]	2.760	[redacted]
Discount rate. Costs: 6%, QALYs: 0%	[redacted]	3.677	[redacted]	[redacted]	4.592	[redacted]
Time horizon: 1 year	[redacted]	0.015	[redacted]	[redacted]	0.038	[redacted]
Time horizon: 2 year	[redacted]	0.085	[redacted]	[redacted]	0.181	[redacted]
Time horizon: 5 year	[redacted]	0.568	[redacted]	[redacted]	0.980	[redacted]
Time horizon: 10 year	[redacted]	1.560	[redacted]	[redacted]	2.256	[redacted]
Time horizon: 15 year	[redacted]	2.181	[redacted]	[redacted]	2.933	[redacted]
Time horizon: 25 year	[redacted]	2.562	[redacted]	[redacted]	3.321	[redacted]
PFS/OS extrapolation: Generalised Gamma (Joint model)	[redacted]	2.336	[redacted]	[redacted]	3.069	[redacted]
PFS/OS extrapolation: Log-logistic (Joint model)	[redacted]	3.066	[redacted]	[redacted]	3.837	[redacted]
PFS/OS extrapolation: Gamma (Joint model)	[redacted]	2.884	[redacted]	[redacted]	3.690	[redacted]
PFS/OS extrapolation: Log-normal (Joint model)	[redacted]	3.540	[redacted]	[redacted]	4.405	[redacted]
PFS/OS extrapolation: Multi-state approach	[redacted]	2.190	[redacted]	[redacted]	2.693	[redacted]
VEN+R Waning effect: PFS/OS Hazards increase by 20%, 3 years after tx disc.	[redacted]	2.236	[redacted]	[redacted]	2.996	[redacted]
VEN+R Waning effect: PFS/OS Hazards increase by 50%, 3 years after tx disc.	[redacted]	1.820	[redacted]	[redacted]	2.579	[redacted]
VEN+R Waning effect: PFS/OS Hazards increase by 100%, 3 years after tx disc.	[redacted]	1.336	[redacted]	[redacted]	2.095	[redacted]
Assumption IBRUTINIB efficacy = IBRUTINIB +BR (Adjusted)	[redacted]	1.210	[redacted]	[redacted]	N/A	[redacted]
Assumption IBRUTINIB efficacy = IBRUTINIB +BR (Unadjusted)	[redacted]	0.845	[redacted]	[redacted]	N/A	[redacted]
Individual curve estimation for PFS and OS (adjusted)	[redacted]	0.943	[redacted]	[redacted]	3.337	[redacted]
Individual curve estimation for PFS and OS (naive)	[redacted]	1.262	[redacted]	[redacted]	3.529	[redacted]
TLS prophylaxis cost halved	[redacted]	2.599	[redacted]	[redacted]	3.358	[redacted]

TLS prophylaxis cost doubled	[redacted]	2.599	[redacted]	[redacted]	3.358	[redacted]
TLS prophylaxis cost removed	[redacted]	2.599	[redacted]	[redacted]	3.358	[redacted]
Pre and post-progression routine costs of care halved	[redacted]	2.599	[redacted]	[redacted]	3.358	[redacted]
Pre and post-progression routine costs of care doubled	[redacted]	2.599	[redacted]	[redacted]	3.358	[redacted]
Pre and post-progression routine costs of care removed	[redacted]	2.599	[redacted]	[redacted]	3.358	[redacted]
Pre and post-progression routine costs of care frequency from ibrutinib submission	[redacted]	2.599	[redacted]	[redacted]	3.358	[redacted]
Terminal care cost + 5%	[redacted]	2.599	[redacted]	[redacted]	3.358	[redacted]
Terminal care cost + 10%	[redacted]	2.599	[redacted]	[redacted]	3.358	[redacted]
Terminal care cost + 15%	[redacted]	2.599	[redacted]	[redacted]	3.358	[redacted]
Terminal care cost + 20%	[redacted]	2.599	[redacted]	[redacted]	3.358	[redacted]
VEN+R follows observed ToT from MURANO	[redacted]	2.599	[redacted]	[redacted]	3.358	[redacted]
SACT BSA = 1.895	[redacted]	2.599	[redacted]	[redacted]	3.358	[redacted]
All treatments use standard IV infusion of Rituximab	[redacted]	2.599	[redacted]	[redacted]	3.358	[redacted]
All treatments use rapid IV infusion of Rituximab	[redacted]	2.599	[redacted]	[redacted]	3.358	[redacted]
All treatments use subcutaneous injection of Rituximab	[redacted]	2.599	[redacted]	[redacted]	3.358	[redacted]
AE rates halved	[redacted]	2.601	[redacted]	[redacted]	3.360	[redacted]
AE rates doubled	[redacted]	2.596	[redacted]	[redacted]	3.356	[redacted]
AE removed	[redacted]	2.602	[redacted]	[redacted]	3.361	[redacted]
Post-progression treatment costs included	[redacted]	2.599	[redacted]	[redacted]	3.358	[redacted]
Utilities: Dretzke et al (PFS:0.800, PPS:0.600)	[redacted]	2.656	[redacted]	[redacted]	3.539	[redacted]
Utilities: Beusterien et al (PFS:0.819, PPS:0.680)	[redacted]	2.915	[redacted]	[redacted]	3.707	[redacted]
Diff. between pre and post-progression utility: 0.1	[redacted]	2.742	[redacted]	[redacted]	3.419	[redacted]
Diff. between pre and post-progression utility: 0.2	[redacted]	2.444	[redacted]	[redacted]	3.292	[redacted]
Diff. between pre and post-progression utility: 0.3	[redacted]	2.146	[redacted]	[redacted]	3.166	[redacted]
Diff. between pre and post-progression utility: 0.4	[redacted]	1.848	[redacted]	[redacted]	3.039	[redacted]
Diff. between pre and post-progression utility: 0.5	[redacted]	1.551	[redacted]	[redacted]	2.912	[redacted]
Disutilities doubled	[redacted]	2.596	[redacted]	[redacted]	3.356	[redacted]
Disutilities removed	[redacted]	2.602	[redacted]	[redacted]	3.361	[redacted]

Key: AE, adverse event; BR, bendamustine+rituximab; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; idela+R, idelalisib+rituximab; Inc., incremental; IV, intravenous; OS, overall survival; PFS, progression free survival; PPS, post progression survival; QALY, quality adjusted life year; R, rituximab; TLS, tumour lysis syndrome; ToT, time on treatment; VEN+R, venetoclax+rituximab

Table 69 Scenario analysis (R/R CLL, net price)

	VS. Ibrutinib			VS. Idela+R		
	Inc. costs (£)	**Inc. QALYs**	**ICER (£)**	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£)**
Base case	-138,561	2.599	Dominated	**8,816**	**3.358**	**2,625**
Discount rate. Costs: 0%, QALYs: 0%	-154,801	3.677	Dominated	16,327	4.592	3,556
Discount rate. Costs: 0%, QALYs: 6%	-154,801	2.087	Dominated	16,327	2.760	5,916
Discount rate. Costs: 6%, QALYs: 6%	-127,847	2.087	Dominated	5,794	2.760	2,099
Discount rate. Costs: 6%, QALYs: 0%	-127,847	3.677	Dominated	5,794	4.592	1,262
Time horizon: 1 year	-7,827	0.015	Dominated	2,955	0.038	77,691
Time horizon: 2 year	-22,617	0.085	Dominated	12,523	0.181	69,318
Time horizon: 5 year	-105,208	0.568	Dominated	-4,880	0.980	Dominated
Time horizon: 10 year	-141,923	1.560	Dominated	-1,403	2.256	Dominated
Time horizon: 15 year	-142,717	2.181	Dominated	3,957	2.933	1,349
Time horizon: 25 year	-139,081	2.562	Dominated	8,293	3.321	2,497
PFS/OS extrapolation: Generalised Gamma (Joint model)	-126,713	2.336	Dominated	10,309	3.069	3,359
PFS/OS extrapolation: Log-logistic (Joint model)	-140,496	3.066	Dominated	4,829	3.837	1,259
PFS/OS extrapolation: Gamma (Joint model)	-145,624	2.884	Dominated	7,802	3.690	2,115
PFS/OS extrapolation: Log-normal (Joint model)	-149,419	3.540	Dominated	1,582	4.405	359
PFS/OS extrapolation: Multi-state approach	-101,449	2.190	Dominated	-2,622	2.693	Dominated
VEN+R Waning effect: PFS/OS Hazards increase by 20%, 3 years after tx disc.	-139,978	2.236	Dominated	7,399	2.996	2,470
VEN+R Waning effect: PFS/OS Hazards increase by 50%, 3 years after tx disc.	-141,701	1.820	Dominated	5,676	2.579	2,200
VEN+R Waning effect: PFS/OS Hazards increase by 100%, 3 years after tx disc.	-143,785	1.336	Dominated	3,592	2.095	1,714
Assumption IBRUTINIB efficacy = IBRUTINIB +BR (Adjusted)	-246,051	1.210	Dominated	N/A	N/A	N/A

Assumption IBRUTINIB efficacy = IBRUTINIB +BR (Unadjusted)	-201,254	0.845	Dominated	N/A	N/A	N/A
Individual curve estimation for PFS and OS (adjusted)	-223,649	0.943	Dominated	16,943	3.337	5,077
Individual curve estimation for PFS and OS (naive)	-170,926	1.262	Dominated	18,536	3.529	5,252
TLS prophylaxis cost halved	-139,547	2.599	Dominated	7,830	3.358	2,331
TLS prophylaxis cost doubled	-136,587	2.599	Dominated	10,790	3.358	3,213
TLS prophylaxis cost removed	-140,534	2.599	Dominated	6,843	3.358	2,038
Pre and post-progression routine costs of care halved	-147,606	2.599	Dominated	4,180	3.358	1,245
Pre and post-progression routine costs of care doubled	-120,471	2.599	Dominated	18,090	3.358	5,387
Pre and post-progression routine costs of care removed	-156,651	2.599	Dominated	-457	3.358	Dominated
Pre and post-progression routine costs of care frequency from ibrutinib submission	-148,161	2.599	Dominated	11,669	3.358	3,475
Terminal care cost + 5%	-138,612	2.599	Dominated	8,758	3.358	2,608
Terminal care cost + 10%	-138,663	2.599	Dominated	8,699	3.358	2,590
Terminal care cost + 15%	-138,714	2.599	Dominated	8,640	3.358	2,573
Terminal care cost + 20%	-138,683	2.599	Dominated	8,675	3.358	2,583
VEN+R followsobserved ToT from MURANO	-142,699	2.599	Dominated	4,678	3.358	1,393
SACT BSA = 1.895	-138,664	2.599	Dominated	8,812	3.358	2,624
All treatments use standard IV infusion of Rituximab	-138,299	2.599	Dominated	8,827	3.358	2,628
All treatments use rapid IV infusion of Rituximab	-138,673	2.599	Dominated	8,812	3.358	2,624
All treatments use subcutaneous injection of Rituximab	-139,508	2.599	Dominated	8,767	3.358	2,611
AE rates halved	-138,627	2.601	Dominated	8,574	3.360	2,552
AE rates doubled	-138,428	2.596	Dominated	9,301	3.356	2,771
AE removed	-138,693	2.602	Dominated	8,332	3.361	2,479
Post-progression treatment costs included	-65,389	2.599	Dominated	34,581	3.358	10,297
Utilities: Dretzke et al (PFS:0.800, PPS:0.600)	-138,561	2.915	Dominated	8,816	3.707	2,379
Utilities: Beusterien et al (PFS:0.819, PPS:0.680)	-138,561	2.742	Dominated	8,816	3.419	2,578
Diff. between pre and post-progression utility: 0.1	-138,561	2.444	Dominated	8,816	3.292	2,678
Diff. between pre and post-progression utility: 0.2	-138,561	2.146	Dominated	8,816	3.166	2,785
Diff. between pre and post-progression utility: 0.3	-138,561	1.848	Dominated	8,816	3.039	2,901
Diff. between pre and post-progression utility: 0.4	-138,561	1.551	Dominated	8,816	2.912	3,028

Diff. between pre and post-progression utility: 0.5	-138,561	2.596	Dominated	8,816	3.356	2,627
Disutilities doubled	-138,561	2.602	Dominated	8,816	3.361	2,623
Disutilities removed	-138,561	2.599	Dominated	8,816	3.358	2,625

Key: AE, adverse event; BR, bendamustine+rituximab; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; idela+R, idelalisib+rituximab; Inc., incremental; IV, intravenous; OS, overall survival; PFS, progression free survival; PPS, post progression survival; QALY, quality adjusted life year; R, rituximab; TLS, tumour lysis syndrome; ToT, time on treatment; VEN+R, venetoclax+rituximab

B.3.9 Subgroup analysis

In accordance with the decision problem (see section B.1), the model splits the R/R CLL population into two subgroups:

- Patients WITH a deletion of chromosome 17p (del(17p) and/or TP53 mutation)
- Patients WITHOUT a deletion of chromosome 17p (non-del(17p) and/or TP53 mutation).

Deletion of the chromosome 17p and TP53 mutation are known to negatively affect a patient's prognosis. Therefore, the economic analysis has been programmed to estimate PFS and OS outcomes according to del(17p)/TP53 status. This is performed by leveraging the del(17p) coefficient included in the survival analysis regression (see section B.3.3). Only the VEN+R baseline PFS and OS curves are adjusted, with the comparator curves following due to being anchored to the VEN+R curves via their hazard ratios. Because we use the same hazard ratios as in the base case, relative treatment effects remain unchanged.

B.3.9.1 Del(17p)/TP53

B.3.9.1.1 Health state distributions over time

The survival for del(17p)/TP53 patients is lower than the R/R CLL and non-del(17p)/TP53 patient groups, as shown in figures Figure 43,

Figure 44 and Figure 45. Applying the ibrutinib MAIC hazard ratio in this population leads to a very small PPS period. This is a result of the PFS and OS HR which, when applied to the del(17p)/TP53 VEN+R curves, lead to very similar results.

Figure 43 VEN+R health state distribution over a lifetime horizon (del(17p)/TP53)

Key: PFS, progression-free survival; PPS, PPS, Post-progression survival; R, rituximab

Figure 44 Ibrutinib health state distribution over a lifetime horizon (del(17p)/TP53)

Key: PFS, progression-free survival; PPS, PPS, Post-progression survival

Figure 45 Idela+R health state distribution over a lifetime horizon (del(17p)/TP53

Key: PFS, progression-free survival; PPS, PPS, Post-progression survival; R, rituximab

B.3.9.1.2 Time on treatment

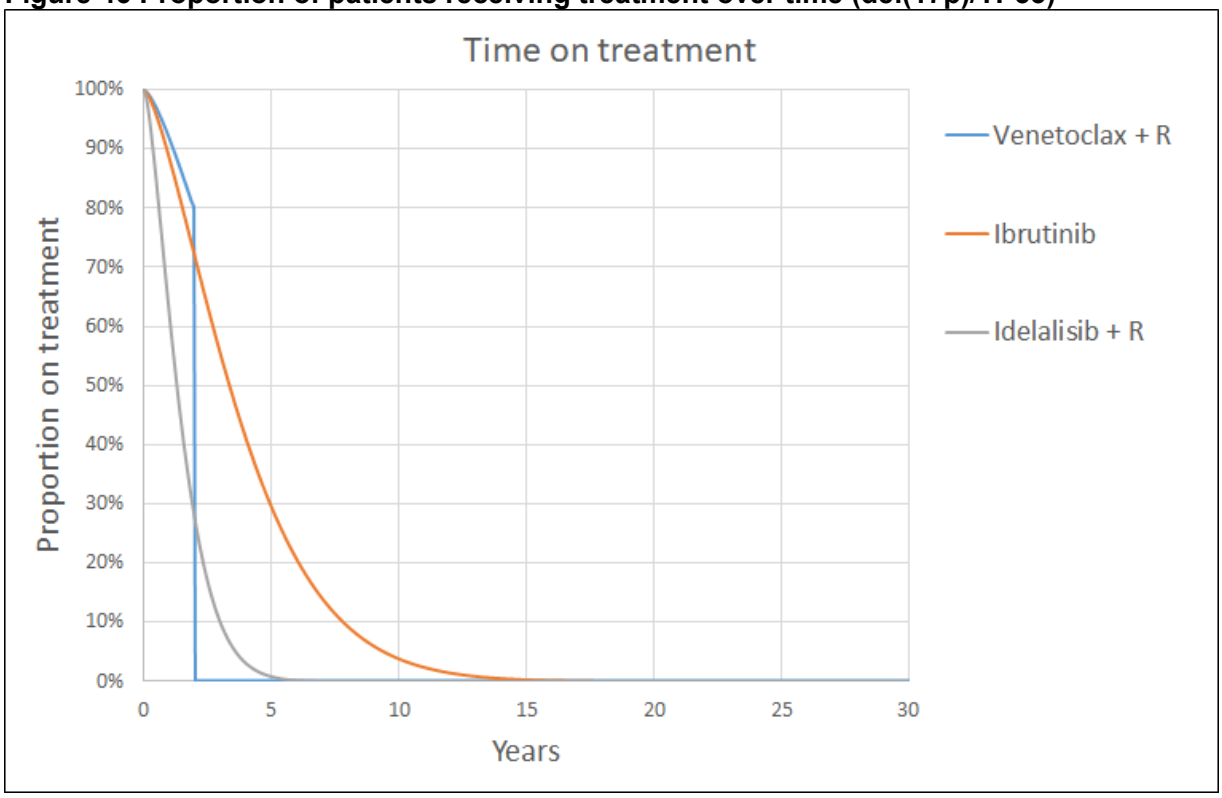
Table 70 shows the average ToT for the treatment regimens inclusive of survival events. The average ToT is lowest in the del(17p)/TP53 subgroup as patients in this subgroup are estimated to have a shorter time to disease progression. VEN+R ToT is less affected due to its fixed treatment duration. The ToT curves are displayed in Figure 46.

Table 70 Average time on treatment (del(17p)/TP53)

Treatment	Average time on treatment (Mean years)
VEN+R	1.823
Ibrutinib	3.965
Idela+R	1.535

Key: Idela+R, idelalisib + rituximab; VEN+R, venetoclax + rituximab

Figure 46 Proportion of patients receiving treatment over time (del(17p)/TP53)



Key: R, rituximab

B.3.9.1.3 Costs

The total costs over the lifetime horizon are presented in Table 71 for the Del(17p)/TP53 population. The active treatment costs for the treat to progression regimens are lower due to the steeper PFS curves.

Table 71 Per patient costs by category, discounted over a lifetime horizon (del(17p)/TP53)

Treatment	Active treatment	Treatment admin	PFS health state costs	PPS health state costs	Terminal care costs	Treatment specific monitoring	AEs	Total
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Idela+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; Idela+R, idelalisib + rituximab; PFS, progression free survival; PPS, post progression survival; VEN+R, venetoclax + rituximab

[redacted]

B.3.9.1.4 QALYs

Table 72 shows the life year and QALY outcomes for the del(17p)/TP53 subgroup. Both the PFS and PSS periods are lower compared to R/R CLL and non-del(17p)/TP53.

Table 72 Total per patient life years (undiscounted) and QALYs (discounted) over a lifetime horizon (del(17p)/TP53)

	Undiscounted Life years			Discounted QALYs			
Treatment	Progression free survival	Post-progression survival	Total life years	Progression free QALYs	Post-progression QALYs	AE disutility	Total QALYs
VEN+R	5.088	4.497	9.586	3.329	1.809	0.006	5.132
Ibrutinib	3.938	0.149	4.087	2.657	0.072	0.002	2.726
Idela+R	1.501	1.836	3.337	1.080	0.969	0.003	2.045

Key: AE, adverse event; Idela+R, idelalisib+rituximab; QALY, quality adjusted life year; VEN+R venetoclax+rituximab

B.3.9.1.5 Incremental cost-effectiveness analysis results

The incremental results for the del(17p)/TP53 subgroup are presented in Table 73 using the VEN+R list price. When VEN+R is compared with ibrutinib, VEN+R is still dominant.

Table 73 Base-case results (del(17p)/TP53, list price)

Technologies	Total costs (£)	Total LYG (undisc)	Total QALYs (disc)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Pairwise ICER VS. VEN+R (£/QALY)
Idela+R	[redacted]	3.34	2.045	[redacted]	-	-	[redacted]	[redacted]
VEN + R	[redacted]	9.59	5.132	[redacted]	-6.249	-3.087	[redacted]	[redacted]
Ibrutinib	[redacted]	4.09	2.726	[redacted]	-0.750	-0.681	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; Idela+R, idelalisib+rituximab; LYG, life years gained; QALY, quality-adjusted life year; VEN+R, venetoclax plus rituximab

Figure 47 Cost-effectiveness frontier (del(17p)/TP53, list price)

[redacted]

Key: QALY, quality adjusted life year

The incremental results for the del(17p)/TP53 subgroup are presented in Table 74 using the venetoclax net price. [redacted]

Table 74 Base-case results (del(17p)/TP53, net price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Pairwise ICER VS VEN+R (£/QALY)
Idela + R	[redacted]	3.34	2.045	-	-	-	-	£6,013
VEN+ R	[redacted]	9.59	5.132	-£18,558	-6.249	-3.087	£6,013	-
Ibrutinib	[redacted]	4.09	2.726	-£127,669	-0.750	-0.681	£187,556	Dominated

Key: Idela+R, idelalisib+rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; VEN+R, venetoclax+rituximab

Figure 48 Cost-effectiveness frontier (del(17p)/TP53, net price)

Key: QALY, quality adjusted life year

Non-Del(17p)/TP53

B.3.9.1.6 Health state distributions over time

The survival for non-del(17p)/TP53 patients is greater than R/R CLL and del(17p)/tp53 populations as shown in Figure 49, Figure 50 and Figure 51. Applying the ibrutinib hazard ratio in this population leads to a zero PPS period (when PFS exceeds OS, PFS is set equal to OS in the model).

Figure 49 VEN+R health state distribution over a lifetime horizon (non-del(17p)/TP53)

Key: PFS, progression-free survival; PPS, PPS, Post-progression survival; R, rituximab

Figure 50 Ibrutinib health state distribution over a lifetime horizon (non-del(17p)/TP53)

Key: PFS, progression-free survival; PPS, PPS, Post-progression survival; R, rituximab

Figure 51 Idela+R health state distribution over a lifetime horizon (non-del(17p)/TP53)

Key: PFS, progression-free survival; PPS, PPS, Post-progression survival; R, rituximab

B.3.9.1.7 Time on treatment

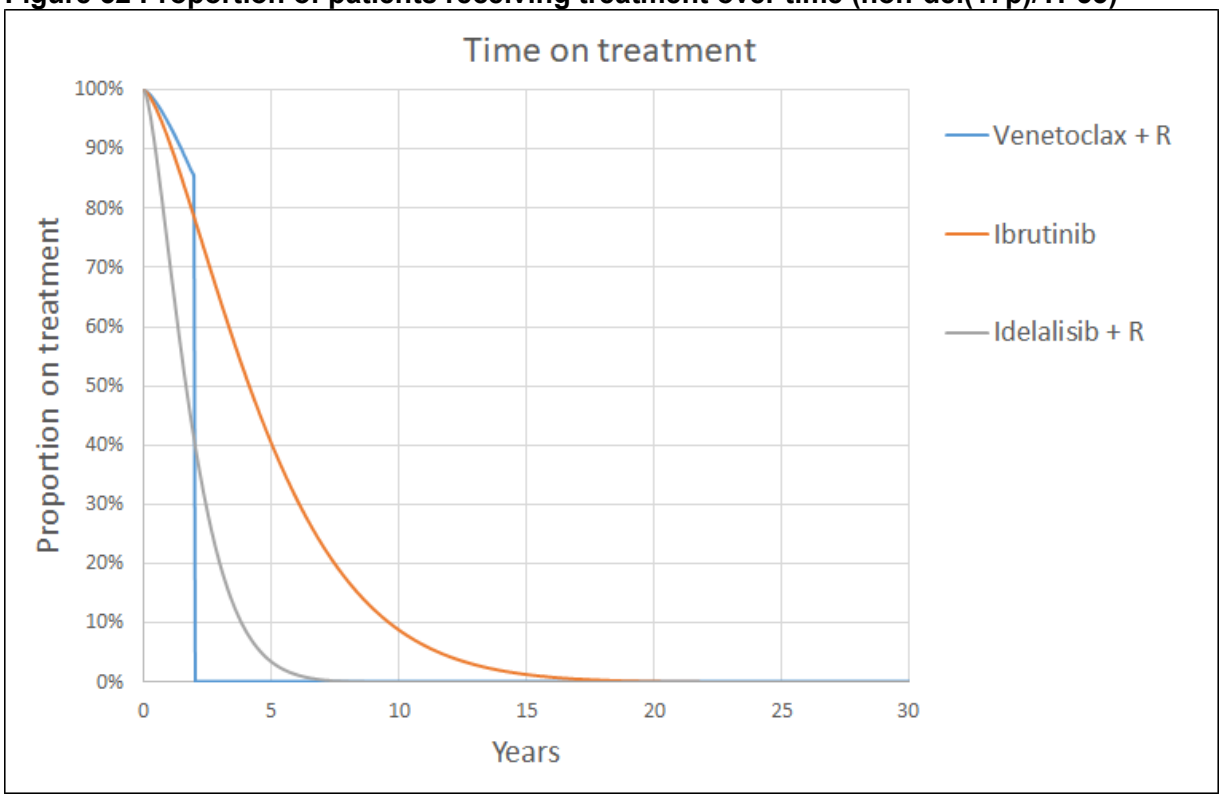
Table 75 shows the average ToT for the treatment regimens inclusive of survival events. The average ToT is greatest in the non-del(17p)/TP53 subgroup as patients in this subgroup are estimated to have the longest time to disease progression. VEN+R ToT is less affected due to its fixed treatment duration. The ToT curves are displayed in Figure 52.

Table 75 Average time on treatment (Non-del(17p)/TP53)

Treatment	Average ToT (Mean years)
VEN+R	1.871
Ibrutinib	4.880
Idela+R	1.957

Key: Idela+R, idelalisib+rituximab; ToT, time on treatment; VEN+R, venetoclax+rituximab

Figure 52 Proportion of patients receiving treatment over time (non-del(17p)/TP53)



Key: R, rituximab

B.3.9.1.8 Costs

The total costs over a lifetime horizon are presented in Table 76 for the non-del(17p)/TP53 population. The active treatment costs, particularly for the treat to progression regimens, are higher due to a longer time to progression.

Table 76 Per patient costs by category, discounted over a lifetime horizon (non-del(17p)/TP53)

Treatment	Active treatment	Treatment admin	PFS health state costs	PPS health state costs	Terminal care costs	Treatment specific monitoring	AEs	Total
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Idela+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; Idela+R, idelalisib+rituximab; PFS, progression free survival; PPS, post progression survival; VEN+R, venetoclax+rituximab

[redacted]

B.3.9.1.9 QALYs

Table 77 shows the life year and QALY outcomes for the non-del(17p)/TP53 subgroup. Both the progression free survival and PSS periods are higher compared to R/R CLL and del(17p)/TP53.

Table 77 Total per patient life years (undiscounted) and QALYs (discounted) over a lifetime horizon (non-del(17p)/TP53)

	Undiscounted Life years			**Discounted QALYs**			
Treatment	PFS	PPS	Total life years	Progression free QALYs	Post-progression QALYs	AE disutility	Total QALYs
VEN+R	6.523	4.728	11.251	4.107	1.767	0.006	5.869
Ibrutinib	4.855	0.000	4.855	3.196	0.000	0.002	3.193
Idela+R	1.924	2.040	3.964	1.370	1.045	0.003	2.411

Key: AE, adverse event; Idela+R, idelalisib+rituximab; PFS, progression free survival; PPS, post progression survival; VEN+R, venetoclax+rituximab

B.3.9.1.10 Incremental cost-effectiveness analysis results

The incremental results for the non-del(17p)/TP53 subgroup are presented in Table 78 using the venetoclax list price. The VEN+R regimen has lower costs than VEN. When VEN+R is compared with Idela+R, the ICER is slightly lower compared to the broad R/R CLL population (R/R ICER=[redacted]).

Table 78 Base-case results (non-del(17p)/TP53, list price)

Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER vs. baseline (£/QALY)**	**Pairwise ICER vs. VEN+R (£/QALY)**
Idela+ R	[redacted]	3.96	2.411	[redacted]	-	-	[redacted]	[redacted]
VEN + R	[redacted]	11.25	5.869	[redacted]	-7.287	-3.458	[redacted]	[redacted]
Ibrutinib	[redacted]	4.86	3.193	[redacted]	-0.891	-0.782	[redacted]	[redacted]

Key: Idela+R, idelalisib+rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; VEN+R, venetoclax+rituximab

Figure 53 Cost-effectiveness frontier (non-del(17p)/TP53,list price)

Key: QALY, quality adjusted life year; R, rituximab

The incremental results for the non-del(17p)/TP53 subgroup are presented in Table 79 using the VEN+R net price.

Table 79 Base-case results (non-del(17p)/TP53, net price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (£/QALY)	Pairwise ICER vs. VEN+R (£/QALY)
Idela + R		3.96	2.411	-	-	-	-	£1,333
VEN+ R		11.25	5.869	-£4,608	-7.287	-3.458	£1,333	-
Ibrutinib		4.86	3.193	-£152,538	-0.891	-0.782	£194,985	Dominated

Key: Idela+R, idelalisib+rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; VEN+R, venetoclax+rituximab

Figure 54 Cost-effectiveness frontier (non-del(17p)/TP53, net price)

Key: QALY, quality adjusted life year

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

The model has been validated using numerous methods. These are presented using the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) format below. (141)

Table 80 AdViSHE tool

Part A: Validation of the conceptual model
A1/ Face validity testing (conceptual model): Have experts been asked to judge the appropriateness of the conceptual model? If yes, please provide information on the following aspects: - Who are these experts? - What is your justification for considering them experts? - To what extent do they agree that the conceptual model is appropriate? If no, please indicate why not.
The face-validity of the conceptual model has been assessed by health economic experts. Firstly, the model's technical specification was independently reviewed [redacted] Secondly, feedback was provided during an advisory board attended by both health economic and clinical experts. The health economic experts were [redacted]. This group of advisors collectively hold a vast amount of experience in health economic modelling. The conceptual model, i.e. a 3-state partitioned survival model, was considered appropriate to the decision problem taking account of the data available.
A2/ Cross validity testing (conceptual model): Has this model been compared to other conceptual models found in the literature or clinical textbooks? If yes, please indicate where this comparison is reported. If no, please indicate why not.
Yes, this comparison is reported in Table 32.
Part B: Input data validation
B1/ Face validity testing (input data): Have experts been asked to judge the appropriateness of the input data? If yes, please provide information on the following aspects: - Who are these experts?

- What is your justification for considering them experts? - To what extent do they agree that appropriate data have been used? If no, please indicate why not. *Aspects to judge may include but are not limited to: potential for bias; generalizability to the target population; availability of alternative data sources; any adjustments made to the data.*
Yes, as part of the advisory board process the clinical advisors received a web-based survey which was designed to elicit feedback on numerous modelling inputs. Furthermore, feedback relating to survival outcomes was received during face to face discussions. The feedback has been integrated into the model's routine costs and survival outcomes. The clinical advisors were [redacted]. Moreover, [redacted] has provided feedback on the survival extrapolations. These clinical experts have many years of experience treating CLL patients and conducting clinical trials in CLL. The clinical experts were presented with the background material for the MURANO trial and the survival analysis materials presented in **Error! Reference source not found.**L.
B2/ Model fit testing: When input parameters are based on regression models, have statistical tests been performed? If yes, please indicate where the description, the justification and the outcomes of these tests are reported. If no, please indicate why not. *Examples of regression models include but are not limited to: disease progression based on survival curves; risk profiles using regression analysis on a cohort; local cost estimates based on multi-level models; metaregression; quality-of-life weights estimated using discrete choice analysis; mapping of disease-specific quality of-life weights to utility values. Examples of tests include but are not limited to: comparing model fit parameters (R2, AIC), Bayesian information criterion (BIC)); comparing alternative model specifications (covariates, distributional assumptions); comparing alternative distributions for survival curves (Weibull, lognormal, logit); testing the numerical stability of the outcomes (sufficient number of iterations); testing the convergence of the regression model; visually testing model fit and/or regression residuals.*
Relevant statistical tests have been performed for survival **Error! Reference source not found.** and HRQoL (Table 37) regression analyses.
Part C: Validation of the computerized model
C1/ External review: Has the computerized model been examined by modelling experts? If yes, please provide information on the following aspects: - Who are these experts? - What is your justification for considering them experts? - Can these experts be qualified as independent? - Please indicate where the results of this review are reported, including a discussion of any unresolved issues. If no, please indicate why not. *Aspects to judge may include but are not limited to: absence of apparent bugs; logical code structure optimized for speed and accuracy; appropriate translation of the conceptual model.*
The computerized model has been assessed by senior modeller. The findings of this quality check are reported in Table 81**Error! Not a valid result for table.**. An issue was identified through implementation of extreme testing of the background mortality rates. This caused the hazard rates of comparators to exceed 100%. This problem has been corrected.
C2/ Extreme value testing: Has the model been run for specific, extreme sets of parameter values in order to detect any coding errors? If yes, please indicate where these tests and their outcomes are reported. If no, please indicate why not. *Examples include but are not limited to: zero and extremely high (background) mortality; extremely beneficial,extremely detrimental, or no treatment effect; zero or extremely high treatment or healthcare costs.*
Yes. The list of quality checks are reported in Table 81.
C3/ Testing of traces: Have patients been tracked through the model to determine whether its logic is correct? If yes, please indicate where these tests and their outcomes are reported. If no, please indicate why not. *In cohort models, this would involve listing the number of patients in each disease stage at one, several, or all time points (e.g., Markov traces). In individual patient simulation models, this would*

involve following several patients throughout their natural disease progression.
Yes, each model trace sheet contains a logic test to ensure no patients are gained/lost over the model's time horizon. The reporting of this test is seen directly in the economic model on the "Tx" sheets. When the text "TRUE" is returned, the model trace produces logical outcomes.
C4/ Unit testing: Have individual sub-modules of the computerized model been tested? If yes, please provide information on the following aspects: - Was a protocol that describes the tests, criteria, and acceptance norms defined beforehand? - Please indicate where these tests and their outcomes are reported. If no, please indicate why not. *Examples include but are not limited to: turning sub-modules of the program on and off; altering global parameters; testing messages (e.g., warning against illegal or illogical inputs), drop-down menus, named* *areas, switches, labelling, formulas and macros; removing redundant elements.*
Yes. The various components of the model have been tested individually. The reporting of these tests can be found in Table 81. Furthermore, dropdowns, user input cells and hyperlinks have been tested.
Part D: Operational validation
D1/ Face validity testing (model outcomes): Have experts been asked to judge the appropriateness of the model outcomes? If yes, please provide information on the following aspects: - Who are these experts? - What is your justification for considering them experts? - To what extent did they conclude that the model outcomes are reasonable? If no, please indicate why not. *Outcomes may include but are not limited to: (quality-adjusted) life years; deaths; hospitalizations; total costs.*
Yes, as part of the advisory board process the clinical advisors provided feedback relating to survival outcomes of the PFS and OS extrapolation models. The feedback has been integrated into the model (see survival outcomes section 9.4.9). The clinical advisors were [redacted] Moreover, [redacted] has provided feedback on the survival extrapolations. These clinical experts have many years of experience treating CLL patients and conducting clinical trials in CLL. An acceptable range of survival outcomes was identified and subsequently incorporated into the economic model.
D2/ Cross validation testing (model outcomes): Have the model outcomes been compared to the outcomes of other models that address similar problems? If yes, please provide information on the following aspects: - Are these comparisons based on published outcomes only, or did you have access to the alternative model? - Can the differences in outcomes between your model and other models be explained? - Please indicate where this comparison is reported, including a discussion of the comparability with your model. If no, please indicate why not. *Other models may include models that describe the same disease, the same intervention, and/or the same population.*
Cross validation with the results of existing models in this indication has not been explicitly conducted. However, a model comparison is provided in Table 32.
D3/ Validation against outcomes using alternative input data: Have the model outcomes been compared to the outcomes obtained when using alternative input data? If yes, please indicate where these tests and their outcomes are reported. If no, please indicate why not. *Alternative input data can be obtained by using different literature sources or datasets, but can also be constructed by splitting the original data set in two parts, and using one part to calculate the model outcomes and the other part to validate against*
Yes. Scenario analyses incorporating alternative input data are presented in B.3.8.3. Furthermore, external data sources were used to calibrate survival extrapolations towards a plausible range (see **Error! Reference source not found.**).
D4/ Validation against empirical data: Have the model outcomes been compared to empirical data? If yes, please provide information on the following aspects:

- Are these comparisons based on summary statistics, or patient-level datasets? - Have you been able to explain any difference between the model outcomes and empirical data? - Please indicate where this comparison is reported. If no, please indicate why not.
D4.A/ Comparison against the data sources on which the model is based (dependent validation).
Yes. Dependent validation when regression models are fitted using AIC/BIC.
D4.B/ Comparison against a data source that was not used to build the model (independent validation).
The data from MURANO is the most robust source of data for the VEN+R treatment regimen. Furthermore, external data sources were used to calibrate survival extrapolations towards a plausible range (see Appendix L).
Part E: Other validation techniques
E1/ Other validation techniques: Have any other validation techniques been performed? If yes, indicate where the application and outcomes are reported, or else provide a short summary here. *Examples of other validation techniques: structured "walk-throughs" (guiding others through the conceptual* *model or computerized program step-by-step); naïve benchmarking ("back-of-the-envelope" calculations);* *heterogeneity tests; double programming (two model developers program components independently and/or the model is programmed in two different software packages to determine if the same results are obtained).*
Model walkthroughs have been conducted providing a guide to the conceptual model and offer a guide to each sheet.

Key: AIC ,Akaike information criterion; BIC, Bayesian information criteria; CLL, chronic lymphocytic leukaemia; ERG, evidence review group; NICE, the National Institute for Health and Care Excellence; STA, single technology appraisal; VEN+R, venetoclax+rituximab

[redacted]

The excel model has undergone a quality check performed by a senior economic modeller. The tests conducted, results and any actions taken are provided in Table 81.

Table 81 Quality check procedure

Test	Expected effect	Observed effect	Action required?	Action taken
Set all efficacy data equal for treatment and control and set disutility associated with treatment related AEs to 0	Same QALY estimates for treatment and control	As expected	NO	N/A
Set mortality rate to 100% at all ages	All patients dead at cycle 1 but still generate expected costs and QALYs	When background mortality is set to ~99% the model is using 65% per cycle. This has to do with a conversion to take account cycle length.	YES	No. Using the current model formula, annual background mortality of exactly 99% converts to a rate of mortality ~29% per cycle which works as intended.
Set mortality rate to 100% at age 70	All patients dead after x years (starting age 70 - x) but still generate expected costs and QALYs	Results are as expected however graphs on the GEN settings sheet are not displaying correctly (whereas on the results sheet they are).	YES	The hazards for comparators exceeded 100% for extreme scenarios such as this. A MIN function is added to ensure a cap of 100%. Columns M and O of comparator sheets contain this edit.
Increase mortality rate	Reduced costs	As expected	NO	N/A
Health state utilities and AEs all set to 0	Total QALYs = 0 for treatment and comparator	As expected	NO	N/A
Health state utilities for states all set to 1 and AEs all set to 0, age-adjusted utilities are excluded	Total QALYs same as life years	As expected	NO	N/A
Unit costs of treatments set to 0	Total cost of treatment = 0	As expected	NO	N/A
Doubled unit costs of treatment	Treatment costs doubled	As expected	NO	N/A
Unit costs of routine care, monitoring , and AEs set to 0	Costs for routine care, monitoring , and AEs are 0	Costs for routine care, monitoring, and AEs are 0	NO	N/A

Doubled unit costs of routine care, monitoring, and AEs	Costs for routine care, monitoring, and AEs double	Doubled costs for routine care, monitoring, and AEs	NO	N/A
Unit costs of terminal care and tx admin set to 0	Terminal care costs and admin = 0	Terminal care costs and admin = 0	NO	N/A
Alter time horizon	Total costs and QALYs to increase/decrease in accordance with longer/shorter durations	As expected	NO	N/A
Discount rates set to 100%	Costs and QALYs should be significantly reduced	As expected	NO	N/A
Discount rates set to 0%	Undiscounted and discounted results should be the same	This cannot be checked since undiscounted results are not separately displayed.	NO	N/A
Check navigation buttons		All buttons work correctly	NO	N/A

Key: AE, adverse event; QALY, quality adjusted life year
*The model quality check has been conducted by an internal senior modeller who was not involved in the model's development.

B.3.11 Interpretation and conclusions of economic evidence

- Based on the currently available data, VEN+R shows evidence of being considered cost-effective vs. its comparators. This finding is observed, largely due to the early trial results from the MURANO trial showing strong PFS and OS outcomes and the 2-year fixed treatment duration which lead to substantial cost saving vs. treat to progression regimens.
- However, there is uncertainty in the required inputs leading to this conclusion.
- Further data collection of VEN+R survival outcomes via additional data cuts will act to reduce the most prominent areas of uncertainty.

In general, the economic modelling is supportive of the conclusion that VEN+R is cost-effective vs. the comparators included in the scope. In the wider R/R population, VEN+R is estimated to be dominant (lower costs, additional QALYs) against ibrutinib, and cost-effective against idela+R, with an ICER of [redacted]. These results also generalise to subpopulations of patients with and without del(17p)/TP53.

However, it is important to evaluate these conclusions within the context of the economic model's limitations.

B.3.11.1 Limitations and uncertainties

The economic modelling of VEN+R in a R/R CLL patient population presents a number of challenges.

Firstly, and most prominently, is the lack of mature RCT data for VEN+R. The aim of the economic evaluation is to estimate incremental impacts over a lifetime horizon. In order to make such estimates, a large proportion of this time horizon is handled by an extrapolation as the median follow-up in MURANO is only ~2 years. This mismatch between the observed period, and the required degree of extrapolation, has had consequences on the validity of the modelled survival curves. Substantial efforts have been made to calibrate survival extrapolations to a range that is considered plausible by experts in the field and other sources of external evidence where follow-up periods are greater. However, the true judge of such extrapolations involves further follow-up of the MURANO patients. Moreover, a key feature of the VEN+R regimen is the 2-year FTD. Currently, there is only limited trial data to gauge the impact of treatment termination on the treatment effect. Subsequent data cuts containing patients who have experienced considerable treatment-free periods are required to make more informed estimations regarding the continuation of a treatment effect over a longer time horizon.

Secondly, the data used to estimate the relative efficacy of the comparators to VEN+R in this indication is generated from a largely disconnected evidence network comprised of heterogenous trials. For the comparisons without an anchor, MAICs have been implemented in order to adjust for trial differences. However, this method only permits one to make adjustments based upon observable characteristics, leaving the potential for unobserved characteristics to create residual bias. Furthermore, it is possible that the methods used to measure, identify

and/or define observed characteristics are subject to a degree of heterogeneity. This may be a result of differences in the trial methods/protocol, due to cross temporal and geographical differences for example. On top of these methodological concerns, the immature trial data for VEN+R further affects the precision of all comparisons.

In summary, the uncertainty surrounding the estimated VEN+R extrapolations and comparator HRs contribute substantially to variations in the modelled cost-effectiveness results. This is best illustrated in the OWSA tornado plots and the PSA CIs, particularly surrounding incremental QALYs which are principally driven by the OS extrapolations. This is a direct consequence of the short follow-up in MURANO.

To support the modelling framework, it has been necessary to make a number of assumptions. For example, the analysis of the EQ-5D-3L data from MURANO led to utility values that were considered too high to have face validity. Therefore, it was necessary to source these inputs from the literature. The survival extrapolations have been assumed to follow a Weibull distribution and cost-categories such as routine care and TLS prophylaxis follow uncertain resource use algorithms.

To test some of these modelling assumptions, we explored various scenario analyses. In contrast to the parameter uncertainty surrounding the survival modelling, the model results remain reasonably robust when exploring the various scenario analyses. Aside from extremely short time horizons (1 and 2 years) and inclusion of post-progression treatment costs, especially for the idela+R comparison, the scenario analyses did not significantly alter the incremental results.

B.3.11.2 Conclusions

Venetoclax in combination with rituximab offers a highly effective chemotherapy free treatment for patients with R/R CLL. Currently available evidence suggests that VEN+R leads to better survival outcomes. This is best illustrated by the observed KM PFS and OS curves, as well as the high levels of undetectable MRD, which are expected to lead to long lasting and durable responses. In comparison to BCRis, VEN+R adds value in terms of offering a regimen with a fixed treatment duration and achieving undetectable MRD.

VEN+R's potency is reflected in the encouraging deterministic cost-effectiveness results. In the wider R/R population, VEN+R is estimated to be dominant (lower costs, additional QALYs) against ibrutinib and cost-effective against idela+R, with an ICER of [redacted]. These results also generalise to subpopulations of patients with and without del(17p)/TP53.

However, there are data limitations, which mean that there is a degree of uncertainty in the modelled efficacy and cost-effectiveness results. AbbVie anticipates that more mature data cuts of MURANO will reduce the uncertainty in the results.

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Single technology appraisal

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]

Dear AbbVie,

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have looked at the submission received on 2nd July 2018 from AbbVie. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

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

Please provide your written response to the clarification questions by 5pm on Thursday 2 August 2018. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Julia Sus, Technical Lead (julia.sus@nice.org.uk). Any procedural questions should be addressed to Stephanie Callaghan, Project Manager (stephanie.callaghan@nice.org.uk).

Yours sincerely

Sally Doss
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

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On behalf of:
Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

Section A: Clarification on effectiveness data

A1. **Priority question:** Please clarify what proportion of patients were relapsed/refractory to ibrutinib or idelalisib in the MURANO trial.

A2. **Priority question**: Please clarify the Rai staging at diagnosis for the 64 patients in the venetoclax plus rituximab (VEN+R) group and the 55 patients in bendamustine plus rituximab (BR) group who are not listed in table 12 (page 42) (or listed as 'unknown at diagnosis').

A3. **Priority question:** Results from adjusted comparisons using matching adjusted indirect comparison (MAIC) methods suggest the risk of death is reduced by 70% with VEN+R compared to ibrutinib (hazard ratio (HR) 0.297, 95% CI 0.129-0.684). Indirect comparisons using the MURANO results based on the MAIC would suggest a far better outcome on overall survival (OS) for BR compared to ibrutinib. This would contradict the indirect comparison of single agent ibrutinib and BR by Hillmen et al (Blood 2015) that reports ibrutinib reduces the risk of death by 55% compared to BR (hence suggesting relatively similar effectiveness between VEN+R and ibrutinib based on OS). Please can you provide the individual-level patient data from the MURANO trial together with summary data of effect modifying and prognostic variables from the competitor trials (HELIOS, RESONATE and Study 116) in a format suitable for running the MAIC R code provided in the appendix for both OS and progression-free survival (PFS) MAIC analyses in order to allow a cross-validation of the MAIC.

A4. **Priority question:** Please provide any analysis that you may have performed comparing minimal residual disease (MRD) status between VEN+R and ibrutinib or VEN+R and idelalisib+R.

A5. Please provide the number of patients from a) the UK and b) the EU (including UK), who were enrolled in the MURANO trial and if possible, split by treatment group.

A6. In section B.2.4.1 (page 39), it is noted that 74 patients discontinued from the study, however the description in the text only provides reasons for 70 patients. Please provide details on the remaining four patients.

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A7. Figure 3 (page 41), please confirm that a total of 61 patients discontinued full treatment in the venetoclax group (this includes 13 patients who discontinued on rituximab, in addition to the 48 who discontinued venetoclax). If not, please can you provide a clearer explanation of the discontinuations.

A8. Page 73 (end of Section B.2.9.6) states: "The MAIC results suggest that VEN+R has a similar efficacy to ibrutinib and is more effective than idelalisib+R." Please explain which MAIC results this statement is referring to in relation to table 20.

A9. Please provide anchored MAIC results for the comparison of VEN+R to idelalisib+BR, both adjusted and unadjusted for table 21 (page 68).

A10. Please clarify why the base case HRs for PFS and OS (table 56, page 137) were taken from the unanchored MAIC analysis (table 20 page 68) instead of the anchored MAIC estimates (table 21 page 68) as recommended in NICE decision support unit (DSU) technical support document (TSD) 18 page 7 *"When connected evidence with a common comparator is available, only "anchored" forms of population adjustment may be used."*

A11. Please provide the number of patients on VEN+R who achieved MRD negative status, broken down by age group (aged 50 and younger, aged over 50).

A12. Please provide the EQ-5D-3L data in the format as shown in table 17 (page 57) and figure 11 (page 60) from the MURANO study comparing by treatment group and for each time point the data was collected.

Literature searches

A13. Please supply a list of the 181 included studies in the clinical effectiveness systematic review. Please also highlight and provide PDFs of the 49 studies considered eligible for the MAIC.

Section B: Clarification on cost-effectiveness data

Survival analyses

B1. Please provide graphs demonstrating the implausibility of the non-jointly fitted parametric time-to-event curves. Please show both treatment groups of the MURANO trial on each of the following graphs:
   1: PFS with no relationship between treatment or PFS/OS.
   2: OS with no relationship between treatment or PFS/OS.
   3: PFS with relationship between treatment but not PFS/OS.
   4: OS with relationship between treatment but not PFS/OS.
   5: PFS with relationship between PFS/OS but not treatment
   6: OS with relationship between PFS/OFS but not treatment

B2. A rationale was provided for why model fit statistics was not presented for parameterisation used to generate survival curves in the base-case economic model.

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Nevertheless, the ERG would like the option to be able to assess appropriateness of alternative parametric fits to the data based on the AIC and BIC values. Please provide the Akaike information criterion (AIC) and Bayesian information criterion (BIC) values for the OS and PFS curves for VEN+R as shown in figure 20 (page 113) and figure 21 (page 116).

B3. In section B.3.3.3, the third paragraph on page 114 states the following about the joint model used to estimate the OS and PFS curves for the economic model: *"The alternative approach taken was to make use of the data available by making assumptions of proportionality between endpoints (PFS and OS) and treatment (VEN+R and BR), although there is no precedence of this approach in previous NICE appraisals."* Please provide the option to implement non-joint survival models (i.e. fit separate models for PFS and OS) within the economic model in order to investigate the effect of relaxing the proportionality assumptions between endpoints (OS and FPS) and treatments (VEN+R and BR) underlying the joint model on the cost-effectiveness results.

B4. Please provide log cumulative hazard (log(−log(S(t))) plots demonstrating the proportionality between PFS, OS and the treatment groups of MURANO.

B5. Please provide the plausible range of 20-year PFS and OS extrapolations as suggested by your clinical experts.

B6. Please provide hazard plots of fitted parametric curves, corresponding with those included in the economic model, compared to the observed data from MURANO (like figure 76, page 174 in appendix L, with smoothed Kaplan–Meier data overlayed).
1: PFS of VEN+R
2: OS of VEN+R
3: PFS of BR
4: OS of BR

Cost-effectiveness analyses

B7. **Priority question**: Figure 24 (page 142) suggests that the model predicts no patients were alive in post-progression state of the ibrutinib group, thus implying that all patients in the ibrutinib group died without disease progression. This seems like an implausible assumption that is unlikely to reflect clinical practice in the UK. Please clarify whether this is due to error in the model or provide rationale to justify appropriateness of this structural assumption.

B8. Please clarify whether cycle 7 in table 49 for VEN+R and idelalisib+R includes costs of rituximab?

B9. Please provide the cost-effectiveness planes plotted as incremental costs and incremental effectiveness, in addition to those provided in figures 29-30 (page 153/154), which looked at total costs and total effectiveness.

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Section C: Textual clarifications and additional points

C1. Do reference numbers 149 to 183 relate to a section in document B that was removed? If not, please state where in the document these references are cited and provide PDFs of the full papers.

C2. Some reference numbers cited in the appendices, which appear to refer to the bibliography in submission document B, are inconsistent. For example:
   a. 115 in the bibliography (Badoux et al. (2011)) is cited as 114 in the appendices.
   b. 147 and 148 in the bibliography are cited in the appendices as 146 and 147.

   Please review the referencing to ensure that citations in the submission and appendices correspond to the correct references in the bibliography.

C3. Throughout the appendices PSS is used when referring to patient survival. Please confirm that this should instead be post-progression survival (PPS).

AbbVie Ltd
AbbVie House
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Maidenhead
SL6 4UB

Frances Sutcliffe
Level 1A City Tower
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2nd August 2018

Dear Frances,

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097] - Response to Clarification Questions

Thank you for reviewing AbbVie's submission for the above appraisal and for acknowledging that the submission was clear and well-presented.

We welcome the opportunity to provide further clarity on the clinical and cost-effectiveness data and are fully committed to providing a comprehensive response: please see our responses to the clarification questions below (after this letter). Appendices are included at the end of this document.

Thank you for your time and please do not hesitate to contact me using the details below if you would like to discuss further.

Yours sincerely,

[redacted]

Head of Health Technology Assessments
PHONE [redacted]

EMAIL [redacted]

Contents

<table>
<tr><th></th><th>AbbVie Response to Clarification Questions</th></tr>
<tr><td>A1</td><td>
Priority question: Please clarify what proportion of patients were relapsed/refractory to ibrutinib or idelalisib in the MURANO trial.

Company response:

In the MURANO trial, 5 patients received a prior BCRi. The detailed breakdown is presented below:
<table>
<tr><th></th><th>VEN+R
(n=194)</th><th>BR
(n=195)</th></tr>
<tr><td>Patients receiving a prior BCRI, n (%)</td><td></td><td></td></tr>
<tr><td>Ibrutinib monotherapy</td><td>3 (1.5)</td><td>1 (0.5)</td></tr>
<tr><td>Idelalisib</td><td>nil</td><td>1 (0.5)</td></tr>
</table>
</td></tr>
<tr><td>A2</td><td>
Priority question: Please clarify the Rai staging at diagnosis for the 64 patients in the venetoclax plus rituximab (VEN+R) group and the 55 patients in bendamustine plus rituximab (BR) group who are not listed in table 12 (page 42) (or listed as ‘unknown at diagnosis’).

Company response:

In the MURANO trial, CLL staging at diagnosis was based on either the Rai OR Binet staging system (not both). Of note is that CLL staging at diagnoses based on the Rai or Binet staging system was generally balanced between the treatment arms.

Staging details in Table 12 (page 42) of the company submission have now been updated as follows:
<table>
<tr><th></th><th>VEN+R
(n=194)</th><th>BR
(n=195)</th></tr>
<tr><td>Rai staging at diagnosis, n (%)</td><td></td><td></td></tr>
<tr><td>N</td><td>130</td><td>140</td></tr>
<tr><td>Stage 0–II</td><td>88 (67.7)</td><td>103 (73.6)</td></tr>
<tr><td>Stage III–IV</td><td>30 (23.1)</td><td>18 (12.9)</td></tr>
<tr><td>Unknown</td><td>12 (9.2)</td><td>19 (13.6)</td></tr>
<tr><td>Binet staging at diagnosis, n (%)</td><td></td><td></td></tr>
<tr><td>N</td><td>58</td><td>51</td></tr>
<tr><td>Stage A</td><td>29 (50.0)</td><td>25 (49.0)</td></tr>
<tr><td>Stage B</td><td>20 (34.5)</td><td>16 (31.4)</td></tr>
<tr><td>Stage C</td><td>7 (12.1)</td><td>7 (14.7)</td></tr>
<tr><td>Unknown</td><td>2 (3.4)</td><td>3 (5.9)</td></tr>
<tr><td>Missing staging information</td><td></td><td></td></tr>
<tr><td>N</td><td>6</td><td>4</td></tr>
</table>
</td></tr>
<tr><td>A3</td><td>
Priority question: Results from adjusted comparisons using matching adjusted indirect comparison (MAIC) methods suggest the risk of death is reduced by 70% with VEN+R compared to ibrutinib (hazard ratio (HR) 0.297, 95% CI 0.129-0.684). Indirect comparisons using the MURANO results based on the MAIC would suggest a far better outcome on overall survival (OS) for BR compared to ibrutinib. This would contradict the indirect comparison of single agent ibrutinib and BR by Hillmen et al (Blood 2015) that reports ibrutinib reduces the risk of death by 55% compared to BR (hence suggesting relatively similar effectiveness between VEN+R and ibrutinib based on OS). Please can you provide the individual-level patient data from the MURANO trial together with summary data of effect modifying and prognostic variables from the competitor trials (HELIOS, RESONATE and Study
</td></tr>
</table>

	116) in a format suitable for running the MAIC R code provided in the appendix for both OS and progression-free survival (PFS) MAIC analyses in order to allow a cross-validation of the MAIC. **Company response:** [redacted] Table 19 under section B.2.9.4 (page 64) of the submission, as well as Table 101 (page 71, Appendix) and Table 104 (page 77, Appendix) provide summaries of all the prognostic factors and effect modifiers AbbVie adjusted to perform the MAIC. As explained in our response to A8 below, AbbVie acknowledge the uncertainties around the OS MAIC results (as a result of the immaturity of the MURANO trial OS data) [redacted] Considering the findings from Hillmen et al., it is assumed that the relative efficacy of VEN+R vs. ibrutinib+BR can be extended to VEN+R vs. ibrutinib single agent. Hence, the results of the anchored analysis vs. ibrutinib+BR can be extended to the ibrutinib comparison. [redacted] Moreover, as discussed on page 80 of the company submission, AbbVie acknowledges the limitations of the methodology used to synthesise the available data and there is no short- or medium-term solution for connecting the evidence network. Nevertheless, it is expected that further maturity of the MURANO trial dataset will reduce the uncertainty of the relative efficacy estimates and improve their use for decision-making. [redacted]
A4	**Priority question:** Please provide any analysis that you may have performed comparing minimal residual disease (MRD) status between VEN+R and ibrutinib or VEN+R and idelalisib+R **Company response:** Abbvie has not performed any analysis comparing MRD status between VEN+R and ibrutinib monotherapy or VEN+R and idelalisib+R as comparator data is not available. As outlined in the company submission (pages 13 and 14 of Document A), the rate of clearance of MRD on the basis of peripheral blood samples at 9 months was higher in the VEN+R treatment group (62.4%; 121/194) than in the BR treatment group (13.3%; 26/195), the higher rate of clearance of MRD on the basis of peripheral-blood samples in the VEN+R treatment group was also maintained over time and MRD status was strongly concordant in blood and bone marrow (94.8%, 308 matched/325 total samples). This observation with VEN+R treatment is unprecedented in trials of R/R CLL and suggestive of improved disease control over a longer-term even when therapy is discontinued. The economic model does not include MRD and response status of patients as comparator data is not available. Nevertheless, the high rates of undetectable MRD achieved by VEN+R provide qualitative supportive evidence of the plausibility of the modelled survival extrapolations.

A5

Please provide the number of patients from a) the UK and b) the EU (including UK), who were enrolled in the MURANO trial and if possible, split by treatment group.

Company response:
The number of patients enrolled in the MURANO trial from the UK and the Europe (including UK) are presented below. (*NB – NICE later clarified that the numbers for Europe should be presented rather than the EU*)

	VEN+R (n=194)	BR (n=195)
UK	6	4
Europe (including UK)	130	131

A6

In section B.2.4.1 (page 39), it is noted that 74 patients discontinued from the study, however the description in the text only provides reasons for 70 patients. Please provide details on the remaining four patients.

Company response:

Section B.2.4.1 (page 39) has now been updated to reflect reasons for discontinuation for all 74 patients. See below with the updated information underlined.

In total, 74 patients (19.0%) discontinued from the study at clinical cut-off date.

- The main safety reasons for study discontinuation were death (15 patients [7.7%] in the VEN+R treatment group and 26 patients [13.3%] in the BR group). 1 patient in BR group [0.5%] due to adverse event.

- The main non-safety reasons for study discontinuation were; one patient [0.3%] lost to follow up in BR group. Three patients (0.8%) were withdrawn due to physician decision (one VEN+R, two BR) and three patients [1.5%] in the BR group were due to progressive disease. The remaining 25 patients who discontinued the study (seven patients [3.6%] in the VEN+R group, 18 patients [9.2%] in the BR group) withdrew consent.

A7

Figure 3 (page 41), please confirm that a total of 61 patients discontinued full treatment in the venetoclax group (this includes 13 patients who discontinued on rituximab, in addition to the 48 who discontinued venetoclax). If not, please can you provide a clearer explanation of the discontinuations.

Company response:

The CONSORT diagram presented as figure 3 (page 41) of the company submission is accurate:

- A total of 48/194 patients discontinued all study treatment during the VEN+R combination period (including dose-titration period) and/or the venetoclax single agent treatment period.
- A total of 13/194 discontinued rituximab prior to completion of the VEN+R combination treatment period.

A8

Page 73 (end of Section B.2.9.6) states: “The MAIC results suggest that VEN+R has a similar efficacy to ibrutinib and is more effective than idelalisib+R.” Please explain which MAIC results this statement is referring to in relation to table 20.

Company response:

The above statement refers to the MAIC results presented in Table 20 (page 68) of the company submission. Table 20 of the company submission is presented below, with a justification column added.

	Adjusted Comparison		
	HR PFS (95% CI)	HR OS (95% CI)	Justification
VEN+R vs. Ibrutinib	**0.696 (0.412 – 1.178) Investigator**	0.297 (0.129 – 0.684)	Since the HR PFS is not statistically significant, it is assumed that the efficacy of VEN+R vs ibrutinib is similar. AbbVie appreciate that in terms of OS, VEN+R is statistically significant vs ibrutinib, but given the uncertainties of the unanchored MAIC approach, we have performed an anchored MAIC vs ibrutinib+BR (please refer to response to A3) which shows non-statistical significance.
VEN+R vs. Idela+R	**0.178 (0.086 – 0.368) IRC**	**0.223 (0.084 – 0.593)**	Since both the PFS and OS HRs are statistically significant, it is assumed that the efficacy of VEN+R vs idelalisib+R is superior.

A9

Please provide anchored MAIC results for the comparison of VEN+R to idelalisib+BR, both adjusted and unadjusted for table 21 (page 68).

Company response:

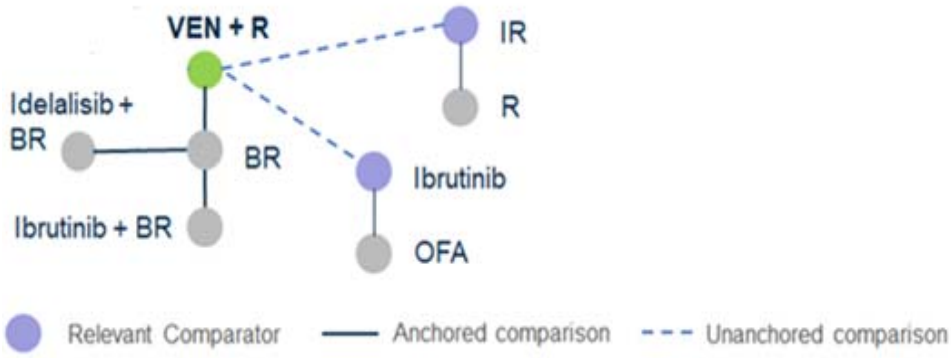
The MAIC results for the comparison of VEN+R vs idelalisib+BR (adjusted and unadjusted) are reported in the table below.

VEN+R vs.	**HR PFS (95% CI)**	**HR OS (95% CI)**	**Sample Size**
Idelalisib +BR (Unadjusted)	[redacted] IRC definition	[redacted]	VEN+R= [redacted] Idelalisib + BR = [redacted]
Idelalisib +BR (Adjusted)	[redacted] IRC definition	[redacted]	VEN+R= [redacted] Idelalisib + BR = [redacted]

AbbVie would like to highlight the following points, which are important in interpreting the MAIC results:

1. The comparator stated in the NICE Final scope is Idelalisib in combination with rituximab (Idela+R) and NOT idelalisib in combination with bendamustine + rituximab (Idela+BR)

2. As discussed on page 62 of the company submission, no connections were identified for the key comparators relevant to UK clinical practice. An unanchored MAIC vs relevant comparators was performed in line with NICE guidance on "Methods for population-adjusted indirect comparisons in submissions to NICE". However AbbVie went further in performing exploratory anchored analyses vs comparators not used in UK Clinical practice.



3. HRs for OS and PFS for VEN+R vs Idela+BR were not presented in the submission due to the fact that there is no published evidence suggesting that idela+R and idela+BR have similar efficacy (whereas for ibrutinib+BR vs ibrutinib the Hillmen at el 2015 poster provides evidence of similar efficacy, to validate the results of the unanchored comparison of VEN+R vs ibrutinib).

4. Finally, even though Idela+R is listed as a comparator in the NICE Final scope and has been included in the economic model to satisfy the requirements of the final scope, Idela+R is not considered an appropriate comparator by clinicians since its use has been superseded by ibrutinib as the BCRi of choice due to the less favourable toxicity and effectiveness profile of idela+R relative to ibrutinib.

A10

Please clarify why the base case HRs for PFS and OS (table 56, page 137) were taken from the unanchored MAIC analysis (table 20 page 68) instead of the anchored MAIC estimates (table 21 page 68) as recommended in NICE decision support unit (DSU) technical support document (TSD) 18 page 7 *"When connected evidence with a common comparator is available, only "anchored" forms of population adjustment may be used."*

Company response:

The response to question A9 above provides the context.

AbbVie appreciate the guidance in the DSU document 18 and have followed all the recommendations whenever this was possible when conducting anchored comparisons. AbbVie have used the unanchored MAIC HRs for OS and PFS in the base case because the relevant comparators for the submission as stated in the NICE final scope are ibrutinib monotherapy and idelalisib+R.

In the network diagram presented in Figure 14 page 62 (and re-presented in the response to A9), it is evident that there is no common comparator in order to help compare VEN+R with ibrutinib monotherapy and idelalisib+R indirectly using an anchored approach. Therefore, an unanchored MAIC needed to be performed. The anchored MAIC vs ibrutinib+BR (please note that ibrutinib+BR is not a relevant comparator in the UK) was conducted as a scenario analysis based on the Hillmen et al poster which showed that ibrutinib monotherapy has similar efficacy to ibrutinib+BR. Hence, the anchored MAIC was performed to validate the unanchored MAIC results and included in a scenario analysis rather than the base case.

Moreover, AbbVie would like to highlight that the direction of cost-effectiveness results do not change when anchored HRs of VEN+R vs ibrutinib+BR (both adjusted and unadjusted) are used.

A11

Please provide the number of patients on VEN+R who achieved MRD negative status, broken down by age group (aged 50 and younger, aged over 50).

Company response:

These are provided below, based on the MURANO trial, May 2017 data cut

	≤ 50 Years Old (11%)	>50 Years Old (89%)	Total
Best Bone Marrow MRD by FLOW in VEN+R arm			
Negative	3 (14%, 95% CI 0.03-0.36)	50 (29%, 95% CI 0.22-0.36)	53
Positive	2 (10%, 95% CI 0.01-0.30)	15 (9%, 95% CI 0.05-0.14)	17
Undetermined	0	4	4
Missing	16	104	120
Total	21	173	194
Best Peripheral Blood MRD by FLOW in VEN+R arm			
Negative	17 (81%, 95% CI 0.58-0.94)	145 (83%, 95% CI 0.77-0.89)	162
Positive	4 (19%, 95% CI 0.05-0.42)	20 (12%, 95% CI 0.07-0.17)	24
Undetermined	0	1	1
Missing	0	7	7
Total	21	173	194

A12

Please provide the EQ-5D-3L data in the format as shown in table 17 (page 57) and figure 11 (page 60) from the MURANO study comparing by treatment group and for each time point the data was collected.

Company response:

The Table below presents the mean utility values for VEN+R and BR by visit and cycle.

	Mean utility value	
VISIT	**BR**	**VEN+R**
CYCLE 1 DAY 1	[redacted]	[redacted]
CYCLE 2 DAY 1	[redacted]	[redacted]
CYCLE 3 DAY 1	[redacted]	[redacted]
CYCLE 4 DAY 1	[redacted]	[redacted]
CYCLE 4 INTERIM ASSESSMENT	[redacted]	[redacted]
CYCLE 5 DAY 1	[redacted]	[redacted]
CYCLE 6 DAY 1	[redacted]	[redacted]
STUDY TREATMENT COMPLETION/EARLY WITHDRAWAL	[redacted]	[redacted]
END OF COMBINATION TREATMENT RESPONSE VISIT	[redacted]	[redacted]
FOLLOW-UP VISIT 1	[redacted]	[redacted]
FOLLOW-UP VISIT 2	[redacted]	[redacted]
FOLLOW-UP VISIT 3	[redacted]	[redacted]
FOLLOW-UP VISIT 4	[redacted]	[redacted]
FOLLOW-UP VISIT 5	[redacted]	[redacted]
FOLLOW-UP VISIT 6	[redacted]	[redacted]
FOLLOW-UP VISIT 7	[redacted]	[redacted]
FOLLOW-UP VISIT 8	[redacted]	[redacted]
FOLLOW-UP VISIT 9	[redacted]	[redacted]

	FOLLOW-UP VISIT 10	[redacted]	[redacted]
	FOLLOW-UP VISIT 11	[redacted]	[redacted]

For completeness, MURANO EQ-5D-3L reporting by dimension, visit and treatment arm is presented in Appendix 1.

AbbVie would like to highlight that the health state utility values used in the economic model base case analysis are taken from literature sources that were used in the NICE appraisal committees' preferred models for the TA487 (venetoclax monotherapy) and TA359 (idela+R) appraisals.

In conclusion, AbbVie has taken a conservative approach in using health state utility values from the literature as per previous CLL NICE appraisals, rather than the higher utility values reported in the MURANO trial.

A13

Please supply a list of the 181 included studies in the clinical effectiveness systematic review. Please also highlight and provide PDFs of the 49 studies considered eligible for the MAIC.

Company response:

A list of the 181 included studies in the clinical effectiveness systematic review is provided in Appendix 2 below, with the 49 studies considered eligible for the MAIC highlighted yellow.

PDFs of the 49 studies considered eligible for the MAIC have also been provided.

B1

Survival analyses

Please provide graphs demonstrating the implausibility of the non-jointly fitted parametric time-to-event curves. Please show both treatment groups of the MURANO trial on each of the following graphs:

1: PFS with no relationship between treatment or PFS/OS.
2: OS with no relationship between treatment or PFS/OS.
3: PFS with relationship between treatment but not PFS/OS.
4: OS with relationship between treatment but not PFS/OS.
5: PFS with relationship between PFS/OS but not treatment
6: OS with relationship between PFS/OFS but not treatment

Company response:

These are provided below.

1: PFS with no relationship between treatment or PFS/OS.

[redacted]

2: OS with no relationship between treatment or PFS/OS

[redacted]

3: PFS with relationship between treatment but not PFS/OS

4: OS with relationship between treatment but not PFS/OS

5: PFS with relationship between PFS/OS but not treatment

Please note that maximum likelihood estimates for the spline model did not converge, so this model has been excluded.

6: OS with relationship between PFS/OFS but not treatment

B2

A rationale was provided for why model fit statistics was not presented for parameterisation used to generate survival curves in the base-case economic model. Nevertheless, the ERG would like the option to be able to assess appropriateness of alternative parametric fits to the data based on the AIC and BIC values. Please provide the Akaike information criterion (AIC) and Bayesian information criterion (BIC) values for the OS and PFS curves for VEN+R as shown in figure 20 (page 113) and figure 21 (page 116).

Company response:

These are provided below

AIC and BIC fit statistics for parametric extrapolations for VEN+R

Distributions	Overall survival		Progression free survival	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gen gamma	[redacted]	[redacted]	[redacted]	[redacted]
3 knot spline	[redacted]	[redacted]	[redacted]	[redacted]

AIC and BIC fit statistics for the joint OS/PFS model

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Gen gamma	[redacted]	[redacted]
3 knot spline	[redacted]	[redacted]

B3

In section B.3.3.3, the third paragraph on page 114 states the following about the joint model used to estimate the OS and PFS curves for the economic model: *"The alternative approach taken was to make use of the data available by making assumptions of proportionality between endpoints (PFS and OS) and treatment (VEN+R and BR), although there is no precedence of this approach in previous NICE appraisals."* Please provide the option to implement non-joint survival models (i.e. fit separate models for PFS and OS) within the economic model in order to investigate the effect of relaxing the proportionality assumptions between endpoints (OS and FPS) and treatments (VEN+R and BR) underlying the joint model on the cost-effectiveness results.

	Company response: AbbVie has now provided this option within the updated economic model. Please refer to VEN+R excel sheet, columns N-T and AC-AI, with accompanying coefficients in column AT. These can be selected for analysis using GEN SETTINGS C112 and C113. Please note that the new curves are not linked to subgroups and hence tests can be conducted for the R/R CLL population only.
B4	Please provide log cumulative hazard (log(−log(S(t))) plots demonstrating the proportionality between PFS, OS and the treatment groups of MURANO. **Company response:** These are provided below **Figure 1: Log cumulative hazard plots for VEN+R OS/PFS and BR OS/PFS**  **Figure 2: Log cumulative hazard plots for VEN+R/BR OS and VEN+R/BR PFS** 

Figure 3: Log cumulative hazard plots for VEN+R and BR treatment arms for OS and PFS endpoints

B5

Please provide the plausible range of 20-year PFS and OS extrapolations as suggested by your clinical experts.

Company response:

A UK CLL advisory board was organised in January 2018 to elicit clinical expert and economic expert feedback on the economic modelling approach, including the parametrisation of the survival curves and subsequent outcomes. Five UK clinical experts (all members of the UK CLL Forum) and four UK economic experts attended the advisory board.

One of the primary objectives of the meeting was to understand which models were most reasonable to position as plausible scenarios in the model (including the base case). Therefore, validation was sought on the plausibility of the various modelled survival probabilities at long term time horizons. Expert responses are provided below

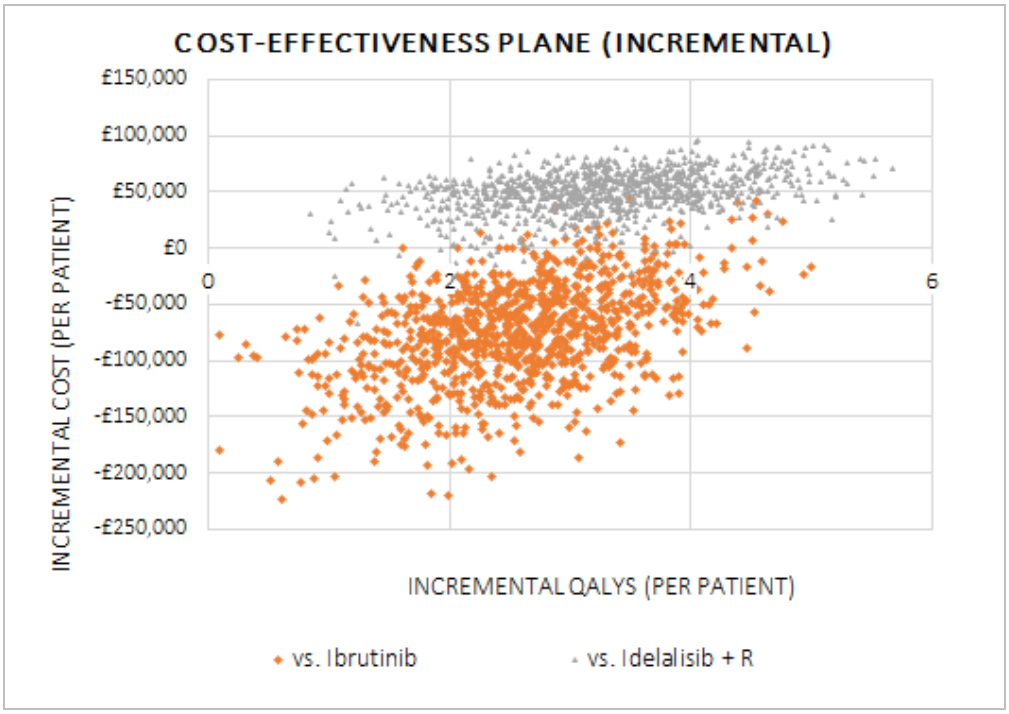
Clinical Expert 1	10% of patients alive at 20 years
Clinical Expert 2	7% to 25% of patients alive at 20 years
Clinical Expert 3	As high as 30% of patients alive at 20 years is reasonable, depending on the population
Clinical Expert 4	Agreed with the more optimistic estimate
Clinical Expert 5	Agreed with the views of colleagues

In addition to clinical expert opinion, alternative modelling approaches and external evidence were used to guide the selection of models that were considered plausible. As described in Appendix L of the company submission, external data included 4-year RESONATE data, FCR data with 10-year follow up and 10-year registry data collected by The Haematological Malignancy Research Network (HMRN) from the Yorkshire and Humber & Yorkshire Coast Cancer networks.

The base case model selection for the extrapolation of VEN+R PFS and OS is the Weibull. The VEN+R 20-year overall survival outcomes for this model ([redacted]) fall within the conservative end of the range of outcomes considered reasonable by clinical expert opinion. The outcomes also compare reasonably well with longer-term external data, and may be considered conservative due to the high undetectable MRD rates associated with VEN+R treatment.

B6	Please provide hazard plots of fitted parametric curves, corresponding with those included in the economic model, compared to the observed data from MURANO (like figure 76, page 174 in appendix L, with smoothed Kaplan–Meier data overlayed). 1: PFS of VEN+R 2: OS of VEN+R 3: PFS of BR 4: OS of BR **Company response:** To make comparison with observed hazards easier, AbbVie has presented these curves over a 5-year time horizon, in addition to the 20-year time horizon featured in the submission. Please see below. Please note, because of the data immaturity, the smoothed observed hazard functions are quite sensitive to the parameters fed to the smoothing function (particularly VEN+R OS). AbbVie have just used the default/global settings from the R function *muhaz*. Agreement is quite strong across all curves apart from VEN+R OS, which is to be expected. The reason why the joint modeling approach was selected was to be able to perform extrapolations which although underestimating the actual observed patterns, however represent more plausible realistic outcomes. The joint modelling approach was fully endorsed by clinical experts at the UK CLL advisory board **Joint model hazard plots (20-year)** 

	Joint model hazard plots (5-year) 
B7	**Priority question**: Figure 24 (page 142) suggests that the model predicts no patients were alive in post-progression state of the ibrutinib group, thus implying that all patients in the ibrutinib group died without disease progression. This seems like an implausible assumption that is unlikely to reflect clinical practice in the UK. Please clarify whether this is due to error in the model or provide rationale to justify appropriateness of this structural assumption. **Company response:** As stated in the submission (section B.3.7.1 page 210), the hazard ratios applied to Ibrutinib lead to PFS exceeding OS (which is restricted in the model to be equal or lower than OS). This results in a zero post-progression period which lacks face validity and it can be considered an implausible outcome. This occurs predominantly due to large uncertainty margins surrounding the MAIC estimates rather than due to a model error. When MAIC estimates are not taken into account and therefore survival for VEN+R and ibrutinib is modelled independently then PPS of ibrutinib is 1.154 years. This can be considered an indicator of the uncertainty surrounding the unanchored MAIC estimates.
B8	Please clarify whether cycle 7 in table 49 for VEN+R and idelalisib+R includes costs of rituximab? **Company response:** AbbVie can confirm that the cost of rituximab is not included in the 7th cycle onwards for the total treatment costs of VEN+R and idelalisib+R. The dosing regimen of rituximab used in the model is 375 mg/m^2 administered on day 1 of cycle 1 and 500 mg/m^2 on day 1 of cycles 2-6 for a total of 6 cycles.

B9	Please provide the cost-effectiveness planes plotted as incremental costs and incremental effectiveness, in addition to those provided in figures 29-30 (page 153/154), which looked at total costs and total effectiveness. **Company response:** These are provided below **Incremental cost-effectiveness plane (list price)**  **Incremental cost-effectiveness plane (net price)** 

C1

Do reference numbers 149 to 183 relate to a section in document B that was removed? If not, please state where in the document these references are cited and provide PDFs of the full papers.

Company response:

References 149 to 168 were inconsistently reported. This happened because the Appendix to Document B was originally part of Document B when submitted to NICE, but was later separated out into two documents as requested by NICE.

Reference numbers 168 to 182 relate to a section in document B that was removed. Please review this answer alongside question C2.

C2

Some reference numbers cited in the appendices, which appear to refer to the bibliography in submission document B, are inconsistent. For example:

a. 115 in the bibliography (Badoux et al. (2011)) is cited as 114 in the appendices.
b. 147 and 148 in the bibliography are cited in the appendices as 146 and 147.

Please review the referencing to ensure that citations in the submission and appendices correspond to the correct references in the bibliography.

Company response:

AbbVie have listed the inconsistent references in the table below. This happened because the Appendix to Document B was originally part of Document B when submitted to NICE, but was later separated out into two documents as requested by NICE.

References	As numbered in **Appendix** document and **Document B main body**	As numbered in **Document B bibliography**
Hillmen et al 2015	68	69
Signorovitch et al 2013	69	70
Signorovitch et al 2011	70	71
Cairo et al 2018	71	72
Killock 2018	72	73
MURANO CSR	73	74
Furman et al 2014	77	78
Tam et al 2015	78	79
Thompson et al 2016	79	80
Sullivan et al 2016	80	81
Sullivan et al 2015	81	82
Silva et al 2015	82	83
Gouveia et al 2015	83	84
Marchetti et al 2015	84	85
Leleu et al 2015	85	86
Yu et al 2015	86	87
Dretzke et al 2010	87	88
Adena et al 2014	88	89
Mandrik et al. 2015	89	90
Pan et al 2014	90	91
Welten et al 2016	91	92
Hoyle et al 2011	92	93
Hatswell et al 2017	93	94
Davies et al 2016	94	95
Dervaux et al 2007	95	96
Scott et al 2007	96	97
Mittmann et al 2012	97	98
Plommet et al 2016	98	99
Ho et al 2017	99	100

Hassan et al 2017	100	101
Djambazov et al 2017	101	102
Sail et al 2017	102	103
Alsaid et al 2017	103	104
Alsaid et al 2017	104	105
Vreman et al 2017	105	106
Yang et al 2018	106	107
Kousoulakou et al	107	108
Casado et al 2017	108	109
Du Bois 1916	109	110
Wallington et al 2013	110	111
ONS 2017	111	112
Latimer 2013	112	113
Royston and Parmar 2002	113	114
Badoux et al 2011	114	115
HMRN 2017	115	116
Munir et al 2015	116	117
Sullivan et al 2016	117	118
Ghia et al 2014	118	119
Cramer et al 2018	119	120
Traina et al 2015	120	121
Robak et al 2015	121	122
Robak et al 2017	122	123
Jain et al 2017	123	124
Shingler et al 2014	124	125
Kosmas et al 2015	125	126
Wierda et al 2016	126	127
Wierda et al 2017	127	128
Ara et al 2011	128	129
NICE 2015	129	130
Beusterien et al 2010	130	131
Tolley et al 2013	131	132
NICE 2014	132	133
Kind 1999	133	134
NICE 2014	134	135
Millar et al 2008	135	136
Curtis and Burns 2017	136	137
Tuthill et al 2009	137	138
Round et al 2015	138	139
NICE 2013	139	140
Naveršnik and Rojnik 2012	140	141
Vemer et al 2016	141	142
Signorovitch et al 2010	142	143
Di Lorenzo et al 2011	143	144
Phillippo et al 2017	144	145
Hosmer and Lemeshow 2008	145	146
Pula et al 2017	146	147
Xenakis et al 2014	148	183
Paiva et al 2016	149	184
Pribylova et al 2016	150	185
Lachaine et al 2016	151	186
Reyes et al 2017	152	187
Hassan et al 2017	153	188
Mittmann et al 2014	154	189
Chen et al 2017	155	190
Parrondo et al 2014	156	191
Ondrusova et al 2017	157	192

	Mahlich et al 2017	158	193
	Jackson 2016	159	194
	Guyot et al 2012	160	195
	Dimier et al 2018	164	196
	Moreton et al 2005	165	197
	Varghese et al 2017	166	198
	Rohatgi 2017	167	199
	Furman et al 2014	168	200

C3	Throughout the appendices PSS is used when referring to patient survival. Please confirm that this should instead be post-progression survival (PPS). **Company response:** AbbVie can confirm that PSS was incorrectly used in the appendices when referring to post-progression survival.

abbvie

APPENDICES

APPENDIX 1 MURANO EQ-5D-3L reporting by dimension, visit and treatment arm

		Dimension									
		Mobility		Self-care		Usual Activities		Pain / Discomfort		Anxiety Depression	
Visit identifier	Level	BR	VEN+R	BR	VEN+R	BR	VEN+R	BR	VEN+R	BR	VEN+R
CYCLE 1 DAY 1	[redacted]										
CYCLE 1 DAY 1	[redacted]										
CYCLE 1 DAY 1	[redacted]										
CYCLE 2 DAY 1	[redacted]										
CYCLE 2 DAY 1	[redacted]										
CYCLE 2 DAY 1	[redacted]										
CYCLE 3 DAY 1	[redacted]										
CYCLE 3 DAY 1	[redacted]										
CYCLE 3 DAY 1	[redacted]										
CYCLE 4 DAY 1	[redacted]										
CYCLE 4 DAY 1	[redacted]										
CYCLE 4 DAY 1	[redacted]										
CYCLE 4 INTERIM ASSESSMENT	[redacted]										
CYCLE 4 INTERIM ASSESSMENT	[redacted]										
CYCLE 4 INTERIM ASSESSMENT	[redacted]										
CYCLE 5 DAY 1	[redacted]										
CYCLE 5 DAY 1	[redacted]										
CYCLE 5 DAY 1	[redacted]										
CYCLE 6 DAY 1	[redacted]										
CYCLE 6 DAY 1	[redacted]										
CYCLE 6 DAY 1	[redacted]										
DAY 1	[redacted]										
DAY 1	[redacted]										
DAY 1	[redacted]										
END OF COMBINATION TREATMENT	[redacted]										

RESPONSE VISIT											
END OF COMBINATION TREATMENT RESPONSE VISIT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
END OF COMBINATION TREATMENT RESPONSE VISIT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

FOLLOW-UP VISIT 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP VISIT 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
STUDY TREATMENT COMPLETION/EARLY WITHDRAWAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
STUDY TREATMENT COMPLETION/EARLY WITHDRAWAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
STUDY TREATMENT COMPLETION/EARLY WITHDRAWAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UNSCHEDULED	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UNSCHEDULED	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UNSCHEDULED	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

APPENDIX 2 - List of 181 included studies in the clinical effectiveness systematic review (49 studies considered eligible for the MAIC are highlighted yellow)

	Highlighted articles were eligible for MAIC
Study Code	**Study Reference**
ADD1 Chanan-Khan 2006	Chanan-Khan A, Miller KC, Musial L, Lawrence D, Padmanabhan S, Takeshita K, Porter CW, Goodrich DW, Bernstein ZP, Wallace P, Spaner D. Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase II study. Journal of Clinical Oncology. 2006 Dec 1;24(34):5343-9.
ASH1 Pollyea 2014	Pollyea DA, Coutre S, Gore L, Adler N, Harris P, Phelps MA, Johnson AJ, Ling Y, Li H, Gutman JA, Byrd JC. A dose escalation study of ibrutinib with lenalidomide for relapsed and refractory chronic lymphocytic leukemia/small lymphocytic lymphoma.2014.
ASH004 Wieda 2017	Wierda WG, Seymour JF, Roberts AW, Kim SY, Lash-Fleming LL, Maher J, Busman T, Zhou L, Nielsen J, Stilgenbauer S. Impact of Number of Prior Therapies and Bulk of Disease on Outcomes with Venetoclax (VEN) Monotherapy for Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL).2017.
ASH026 Del Poeta 2017	Del Poeta G, Del Principe MI, Postorino M, Bomben R, Iannella E, Buccisano F, Rossi MF, Venditti A, Santinelli E, de Fabritiis P, Cantonetti M. Apoptosis Resistance and NOTCH1 Mutations Impair Clinical Outcome in Chronic Lymphocytic Leukemia (CLL) Patients Treated with Ibrutinib.2017.
ASH038 Seymour 2017	Seymour JF, Kipps TJ, Eichhorst BF, Hillmen P, D'Rozario JM, Assouline S, Owen CJ, Gerecitano J, Robak T, De la Serna J, Jaeger U. Venetoclax plus rituximab is superior to bendamustine plus rituximab in patients with relapsed/refractory chronic lymphocytic leukemia-results from pre-planned interim analysis of the randomized phase 3 murano study.2017.
BSH021 Follows 2018	Follows G. UK CLL Forum analysis of patients treated with ibrutinib at first relapse confirms duration of ibrutinib therapy and overall survival has no correlation with the type of first line therapy, and depth or duration of first remission. InBRITISH JOURNAL OF HAEMATOLOGY 2018 Apr 1 (Vol. 181, pp. 70-71). 111 RIVER ST, HOBOKEN 07030-5774, NJ USA: WILEY.
BSH024 Munir 2018	Munir T, Howard D, McParland L, Hockaday A, Oughton J, Messina F, Phillips D, Neilson J, Pemberton N, Paneesha S, Kennedy B. Obinutuzumab as consolidation after chemo-immunotherapy is highly effective in achieving MRD clearance from bone marrow and peripheral blood-Initial results of UK NCRI Phase II/III GALACTIC trial. InBritish Journal of Haematology 2018 Apr 16 (Vol. 181, No. S1, pp. 79-79). Wiley.
COC006 Ghia 2017	Ghia P, Scarfò L, Perez S, Pathiraja K, Derosier M, Small K, Sisk CM, Patton N. Efficacy and safety of dinaciclib vs ofatumumab in patients with relapsed/refractory chronic lymphocytic leukemia. Blood. 2017 Mar 30;129(13):1876-8.
COC037 Sharman 2017	Sharman JP, Brander DM, Mato A, Kambhampati S, Burke JM, Lansigan F, Schreeder MT, Lunin SD, Ghosh N, Zweibach A, Shtivelband MI. Ublituximab And Ibrutinib For Previously Treated Genetically High-Risk Chronic Lymphocytic Leukemia: Results Of The Genuine Phase 3 Study. Hematological Oncology. 2017 Jun;35:111-2.
COC048 Montillo 2017	Montillo M, Byrd JC, Hillmen P, O'Brien S, Barrientos JC, Reddy NM, Coutre S, Tam CS, Mulligan SP, Jaeger U, Barr PM. LONG-TERM EFFICACY AND SAFETY IN THE RESONATE STUDY: IBRUTINIB IN PATIENTS WITH PREVIOUSLY TREATED CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) WITH UP TO FOUR YEARS FOLLOW-UP. Hematological Oncology. 2017 Jun;35:235-6.
COC064 Burger 2017	Burger JA, Sivina M, Ferrajoli A, Jain N, Kim E, Kadia T, Estrov Z, González GN, Huang X, Ohanian M, Andreeff M. Randomized trial of ibrutinib versus ibrutinib plus rituximab (Ib+ R) in patients with chronic lymphocytic leukemia (CLL).2017.
COC256 Zelenetz 2017	Zelenetz AD, Barrientos JC, Brown JR, Coiffier B, Delgado J, Egyed M, Ghia P, Illés Á, Jurczak W, Marlton P, Montillo M. Idelalisib or placebo in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia: interim results from a phase 3, randomised, double-blind, placebo-controlled trial. The Lancet Oncology. 2017 Mar 1;18(3):297-311.
COC277 Dungarwalla 2008	Dungarwalla M, Evans SO, Riley U, Catovsky D, Dearden CE, Matutes E. High dose methylprednisolone and rituximab is an effective therapy in advanced refractory chronic lymphocytic leukemia resistant to fludarabine therapy. Haematologica. 2008 Mar 1;93(3):475-6.

COC389 Tresckow 2016	von Tresckow J, Cramer P, Bahlo J, Robrecht S, Engelke A, Langerbeins P, Fink AM, Illmer T, Klaproth H, Estenfelder S, Ritgen M. CLL2-BIG-a novel treatment regimen of bendamustine followed by GA101 and ibrutinib followed by ibrutinib and GA101 maintenance in patients with chronic lymphocytic leukemia (CLL): Results of a phase II-trial.2016.
EHA202 Michallet 2016	Michallet AS, Campidelli A, Lequeu H, Dilhuydy MS, Tournilhac O, Fornecker L, Cymbalista F, Bene MC, Leblond V, Delmer A, Feugier P. IBRUTINIB FOR RELAPSED CLL PATIENTS OLDER THAN 75 YEARS: PROVEN EFFICACY, TOXICITIES TO KNOW. Hypertension. 2016 Jun 11;23:33-8.
EHA234 Hillmen 2016	Hillmen P, Ferrá C, García-Marco J, Jacob A, Jurczak W, Lamanna N, MacDonald D, Marlton P, Mayer J, Morchauser F, Nathwani A. Idelalisib in combination with bendamustine/rituximab improves overall survival in patients with relapsed/refractory cll: Interim results of a phase 3 randomized double-blind placebo-controlled study. InHaematologica 2016 Jun 1 (Vol. 101, pp. 433-433).
EHA295 Jäger 2015	Jaeger U, Barr PM, Brown JR, Hillmen P, O'Brien S, Barrientos JC, Reddy NM, Coutre S, Mulligan SP, Furman RR, Cymbalista F. Adherence and dose intensity following administration of the ibrutinib 420 mg dose in patients with previously treated CLL. InHaematologica 2015 Jun 1 (Vol. 100, pp. 155-155). VIA GIUSEPPE BELLI 4, 27100 PAVIA, ITALY: FERRATA STORTI FOUNDATION.
PQC6 OBrien 2016	O'Brien S, Jones JA, Coutre SE, Mato AR, Hillmen P, Tam C, Österborg A, Siddiqi T, Thirman MJ, Furman RR, Ilhan O. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. The Lancet Oncology. 2016 Oct 1;17(10):1409-18.
PQC14 Ma 2016	Ma, S., Brander, D. M., Seymour, J. F., Kipps, T. J., Barrientos, J. C., Davids, M. S., Anderson, M. A., Choi, M. Y., Tam, C. S., Mason-Bright, T., Prine, B., Munasinghe, W., Zhu, M., Kim, S. Y., Humerickhouse, R. A., & Roberts, A. W. (2015). Deep and Durable Responses Following Venetoclax (ABT-199 / GDC-0199) Combined with Rituximab in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia: Results from a Phase 1b Study. Blood, 126(23), 830.
PQC29 Stilgenbauer 2016	Stilgenbauer S, Eichhorst B, Schetelig J, Coutre S, Seymour JF, Munir T, Puvvada SD, Wendtner CM, Roberts AW, Jurczak W, Mulligan SP. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. The Lancet Oncology. 2016 Jun 1;17(6):768-78.
PQC32 Ishizawa 2017	Ishizawa K, Fukuhara N, Nakaseko C, Chiba S, Ogura M, Okamoto A, Sunaga Y, Tobinai K. Safety, efficacy and pharmacokinetics of humanized anti-CD52 monoclonal antibody alemtuzumab in Japanese patients with relapsed or refractory B-cell chronic lymphocytic leukemia. Japanese journal of clinical oncology. 2017 Jan 1;47(1):54-60.
PQC38 Perz 2002	Perz J, Topaly J, Fruehauf S, Hensel M, Ho AD. Level of CD 20-expression and efficacy of rituximab treatment in patients with resistant or relapsing B-cell prolymphocytic leukemia and B-cell chronic lymphocytic leukemia. Leukemia & lymphoma. 2002 Jan 1;43(1):149-51.
PQC43 Keating 2002	Keating MJ, Flinn I, Jain V, Binet JL, Hillmen P, Byrd J, Albitar M, Brettman L, Santabarbara P, Wacker B, Rai KR. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. Blood. 2002 May 15;99(10):3554-61.
PQC48 Iskierka-Jazdzewska 2016	Iskierka-Jaidiewska E, Hus M, Giannopaulos K, Madro E, Holojda J, Piotrowska M, Zaucha JM, Piszczeklo W, Szeremet A, Wojciechowska M, Steckiewicz P. RESULTS OF PROSPECTIVE OBSERVATIONAL TRIAL OF POLISH ADULT LEUKEMIA GROUP (PALG) ON IBRUTINIB COMPASSIONATE USE IN RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL) IN POLAND. InHAEMATOLOGICA 2016 Jun 1 (Vol. 101, pp. 439-440). VIA GIUSEPPE BELLI 4, 27100 PAVIA, ITALY: FERRATA STORTI FOUNDATION.
PQC54 Coiffier 2008	Coiffier B, Lepretre S, Pedersen LM, Gadeberg O, Fredriksen H, van Oers MH, Wooldridge J, Kloczko J, Holowiecki J, Hellmann A, Walewski J. Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a phase 1-2 study. Blood. 2008 Feb 1;111(3):1094-100.
PQC78 Byrd 2013	Byrd JC, Furman RR, Coutre SE, Flinn IW, Burger JA, Blum KA, Grant B, Sharman JP, Coleman M, Wierda WG, Jones JA. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. New England Journal of Medicine. 2013 Jul 4;369(1):32-42.
PQC122 Angelopoulou 1996	Angelopoulou MA, Poziopoulos C, Boussiotis VA, Kontopidou F, Pangalis GA. Fludarabine monophosphate in refractory B-chronic lymphocytic leukemia: maintenance may be significant to sustain response. Leukemia & lymphoma. 1996 Jan 1;21(3-4):321-4.

PQC138 Jones 2017	Jones JA, Robak T, Brown JR, Awan FT, Badoux X, Coutre S, Loscertales J, Taylor K, Vandenberghe E, Wach M, Wagner-Johnston N. Efficacy and safety of idelalisib in combination with ofatumumab for previously treated chronic lymphocytic leukaemia: an open-label, randomised phase 3 trial. The Lancet Haematology. 2017 Mar 1;4(3):e114-26.
PQC139 Badoux 2011	Badoux XC, Keating MJ, Wang X, O'Brien SM, Ferrajoli A, Faderl S, Burger J, Koller C, Lerner S, Kantarjian H, Wierda WG. Fludarabine, cyclophosphamide and rituximab chemoimmunotherapy is highly effective treatment for relapsed patients with CLL. Blood. 2011 Jan 1:blood-2010.
PQC140 Chanan_Khan 2016	Chanan-Khan A, Cramer P, Demirkan F, Fraser G, Silva RS, Grosicki S, Pristupa A, Janssens A, Mayer J, Bartlett NL, Dilhuydy MS. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. The Lancet Oncology. 2016 Feb 1;17(2):200-11.
PQC145 Robak 2016	Robak T, Jones JA, Wach M, Brown JR, Menter AR, Vandenberghe E, Ysebaert L, Wagner-Johnston ND, Polikoff J, Awan FT, Badoux XC. Updated results of a phase III randomized, controlled study of idelalisib in combination with ofatumumab for previously treated chronic lymphocytic leukemia (CLL). InHaematologica 2016 Jun 10
PQC156 Fraser 2016	Fraser G, Cramer P, Demirkan F, Santucci Silva R, Pylypenko H, Grosicki S, Janssens A, Pristupa A, Mayer J, Dilhuydy MS, Loscertales J. Ibrutinib (I) plus bendamustine and rituximab (BR) in previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): a 2-year follow-up of the HELIOS study.
PQC157 Moreno 2017	Moreno C, Byrd JC, Hillmen P, O'Brien S, Barrientos JC, Reddy NM, Coutre S, Tam CS, Mulligan SP, Jaeger U, Barr PM. Ibrutinib in previously treated chronic lymphocytic leukemia: updated efficacy and safety of the resonate study with up to four years of follow-up. InHaematologica 2017 Jun 26 (Vol. 102, pp. 311-311). VIA GIUSEPPE BELLI 4, 27100 PAVIA, ITALY: FERRATA STORTI FOUNDATION.
PQC159 Flinn 2005	Flinn IW, Byrd JC, Bartlett N, Kipps T, Gribben J, Thomas D, Larson RA, Rai K, Petric R, Ramon-Suerez J, Gabrilove J. Flavopiridol administered as a 24-hour continuous infusion in chronic lymphocytic leukemia lacks clinical activity. Leukemia research. 2005 Nov 1;29(11):1253-7.
PQC161 Byrd 2005	Byrd JC, Peterson BL, Gabrilove J, Odenike OM, Grever MR, Rai K, Larson RA, Cancer and Leukemia Group B. Treatment of relapsed chronic lymphocytic leukemia by 72-hour continuous infusion or 1-hour bolus infusion of flavopiridol: results from Cancer and Leukemia Group B study 19805. Clinical Cancer Research. 2005 Jun 1;11(11):4176-81.
PQC171 Jain 2016	Jain P, Keating MJ, Wierda W, Sivina M, Thompson PA, Ferrajoli A, Estrov Z, Kantarjian H, O'Brien S, Burger J. Long term follow up of treatment with ibrutinib and rituximab (IR) in patients with high-risk Chronic Lymphocytic Leukemia (CLL). Clinical Cancer Research. 2016 Jan 1:clincanres-1948.
PQC175 Boogaerts 2001	Boogaerts MA, Van Hoof A, Catovsky D, Kovacs M, Montillo M, Zinzani PL, Binet JL, Feremans W, Marcus R, Bosch F, Verhoef G. Activity of oral fludarabine phosphate in previously treated chronic lymphocytic leukemia. Journal of Clinical Oncology. 2001 Nov 15;19(22):4252-8.
PQC176 Rai 2002	Rai KR, Freter CE, Mercier RJ, Cooper MR, Mitchell BS, Stadtmauer EA, Santabarbara P, Wacker B, Brettman L. Alemtuzumab in previously treated chronic lymphocytic leukemia patients who also had received fludarabine. Journal of Clinical Oncology. 2002 Sep 15;20(18):3891-7.
PQC177 Bosanque 1995	Bosanquet AG, McCann SR, Crotty GM, Mills MJ, Catovsky D. Methylprednisolone in advanced chronic lymphocytic leukaemia: rationale for, and effectiveness of treatment suggested by DiSC assay. Acta haematologica. 1995;93(2-4):73-9.
PQC202 Jones 2015	Jones JA, Wach M, Robak T, Brown JR, Menter AR, Vandenberghe E, Ysebaert L, Wagner-Johnston ND, Polikoff J, Salman HS, Taylor KM. Results of a phase III randomized, controlled study evaluating the efficacy and safety of idelalisib (IDELA) in combination with ofatumumab (OFA) for previously treated chronic lymphocytic leukemia (CLL).
PQC205 Elter 2011	Elter T, Gercheva-Kyuchukova L, Pylylpenko H, Robak T, Jaksic B, Rekhtman G, Kyrcz-Krzemień S, Vatutin M, Wu J, Sirard C, Hallek M. Fludarabine plus alemtuzumab versus fludarabine alone in patients with previously treated chronic lymphocytic leukaemia: a randomised phase 3 trial. The lancet oncology. 2011 Dec 1;12(13):1204-13.
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NICE National Institute for Health and Care Excellence

Patient organisation submission

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Bloodwise
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Bloodwise's mission is to beat all blood cancers – stopping people from dying, improving the lives of everyone affected by blood cancer, and where possible preventing people getting blood cancer in the first place. We do this by funding world leading research, supporting all those affected by blood cancer, and campaigning for improvements in care and services. We are entirely funded by voluntary donations and have approximately 100 members of staff and 140 patient ambassadors plus many more volunteers and supporters.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	We sent an email to our database of patient ambassadors asking them to contact us to share their experiences of chronic lymphocytic leukaemia and treatment with venetoclax in combination with rituximab . We were able to speak to two CLL patients about their experiences of taking venetoclax, one of whom is based in the US. However, neither of them have taken venetoclax in combination with rituximab Our submission is based on these responses and we have used direct quotes where possible. We also consulted our medical advisory panel, an expert group of clinicians, to gain further insight into the condition and patients' experiences using this treatment from a clinical perspective. In addition, we liaised with other patient groups, notably leukaemia care and CLLSA for further insight into the condition and treatment options. We are grateful to CLLSA who shared the results of the patient survey they carried out to assess patient experience of the treatment being appraised.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	CLL usually develops slowly and most people won't have any significant symptoms before they are diagnosed. However symptoms can include extreme fatigue and/or weakness, swollen lymph nodes, night sweats, rapid weight loss, fever and repeated infections. If treatment is not required initially, patients are placed on 'watch and wait' so that they can be monitored until treatment is required. This can place patients under significant psychological strain as they are living with the knowledge that they have cancer and that their condition is likely to deteriorate but can do nothing about it. The patients we spoke to were diagnosed as part of routine blood tests when the test results showed that they had high white blood cell counts. One of the patients (Patient A, male, from USA) did not require treatment initially and was on 'watch and wait' for approximately 2 years. During this period, his blood count slowly increased and he started suffering from fatigue and picked up infections easily. It was at this point that he started treatment and was initially treated with rituximab and then ibrutinib before being offered venetoclax. The other patient (Patient B, 75 year old male, from UK) required treatment straight away as it was found that he had had CLL for several years without being aware of this and the condition had developed during this period. He went to see his GP as he was feeling unusually tired, although he was very fit at the time. His symptoms were not initially severe but he had significant problems once treatment started. He initially underwent 2 courses of FCR treatment (fludarabine, cyclophosphamide and rituximab), a combination of chemotherapy and monoclonal antibodies and the standard treatment in the UK for CLL. He became neutropenic and was too unwell to continue with the chemotherapy so moved onto ibrutinib which also caused significant problems at which point his treating haematologist suggested venetoclax. Further information about the patients' experiences on previous treatments and venetoclax are outlined in the sections below.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	As outlined above, the patients we spoke to did not have good experiences with the treatment they had before taking venetoclax. Patient A started with rituximab which was not effective (he later found that his treating haematologist had very limited experience of CLL and was treating him as if he had follicular lymphoma). He started treatment in 2010 and had 6 rounds of rituximab and by 2012 he needed further treatment as his white blood cell count had increased. He was offered the chance to participate in an ibrutinib clinical trial but had to stop after 6 months as he developed a severe skin rash. He was then offered a different trial of idelalisib and rituximab which he took for 30 months. However, his white cell blood count started to rise again at a very fast rate, doubling every two months and his symptoms including swollen lymph nodes, became more apparent, so a new treatment plan was required. He also suffered from gastric problems in response to the treatment causing severe diarrhoea. At this point he was offered venetoclax (off licence rather than as part of a trial). Treatment started in June 2016 and within 4 weeks the swollen nodes had gone and a few weeks later his bloods were back to normal (MRD negative). Patient A became neutropenic as a result of the chemotherapy he initially had and after 2 cycles, could not tolerate treatment. He was then offered ibrutinib which he took for 21 months. He suffered from severe side effects during treatment. These included excessive fluid on the lungs, which required constant chest drains, blurred vision and hearing loss. For some of this time, he had to use a wheelchair and stair lifts and relied completely on his wife as his main carer. His treating consultant advised that he stop treatment when his kidney function started to deteriorate at an alarming rate. He was then offered venetoclax under a compassionate access scheme and has responded amazingly well to it. Both patients have been advised that the next step should they stop responding to venetoclax as well as they currently are, would be to combine the venetoclax with rituximab as this is considered by their clinicians to be even more effective than venetoclax alone.

8. Is there an unmet need for patients with this condition?	Yes, where the current standard treatments have failed or caused severe side effects, there is a need for a more innovative treatment with less significant side effects. Feedback from other patient groups and clinicians is that this is a much needed and wanted treatment option in the CLL community
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Both patients we spoke to had significant problems when treated with chemotherapy (FCR), ibrutinib and idealisib with rituxamib and were unable to function normally as a result. They did not respond well to these treatments or relapsed relatively quickly. Venetoclax has had a hugely positive impact on them. Patient B reports that having been wheelchair bound and frequently admitted to hospital with infections while on earlier treatment regimes, since taking venetoclax, he has experienced a dramatic improvement in his quality of life, stating that "I feel well all the time, my weight is back and I have muscle strength back in my legs…I am able to go on holiday again and my wife has started to enjoy herself again after caring for me for the last few years." Neither of them have suffered any side effects while taking it and their bloods were back in normal range within weeks of starting treatment. The patients also reported that it is very easy to take once they have gone through the initial 5 week ramp up period as involves 4 daily tablets taken at home at the same time. Now that they are both stable, they have monthly blood tests and see the clinician every 2 or 3 months. 28 patients responded to CLLSA's survey asking about their quality of life after taking venetoclax in combination with rituximab and the survey results support these accounts. 32% of respondents had taken venetoclax for 6-12 months and 21% for more than 12 months. 57% reported that they have no problems doing their usual activities and 54% reported having no pain or discomfort at all. High health scores were associated with a longer time on venetoclax. Trial data (MURANO trial) shows high numbers of MRD negativity following treatment with venetoclax in combination with rituximab and improvement in PFS in all the subgroups at 2 years.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The therapy can be intense in the early stages during the ramp up period, when the dose is increased in 5 stages. Patients have to be admitted to hospital during the early stages of this process as there is a risk of cardiac problems when the dose is increased. Although the patients we spoke to did not experience any side effects, side effects can include an increased propensity to neutropenia, although trial data suggested patients were less likely to develop febrile neutropenia than patients on chemotherapy. There is a lack of overall survival data as the trial data does not go beyond 2 years.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Unmutated CLL patients would particularly benefit from the treatment as they relapse very quickly and chemotherapy rarely works for them so they need treatment frequently as well as access to a variety of different treatment options.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	

15. In up to 5 bullet points, please summarise the key messages of your submission:

- CLL patients who have failed to respond to other treatment options need access to venetoclax with rituximab as an alternative treatment plan.
- After the initial ramp up period, side effects are not as severe as those caused by chemotherapy and venetoclax can be tolerated better than ibrutinib and idelalisib.

• The treatment is easy to take and accessible as after the early stages, patients can take the tablets at home and only need to return to the hospital for check ups and blood tests every few weeks. • Trial data shows a significant increase in PFS and MRD negativity in patients who are treated with venetoclax in combination with rituximab. The qualitative evidence from patients indicates a remarkable improvement in quality of life following treatment.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**St James's Hospital Leeds UK**
3. Job title or position	[redacted]

4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**British Society of Haematology** **Royal College of Pathology**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	Chronic lymphocyctic leukaemia is an incurable haematological malignancy where the main goal of treatment is achieving deep clinical remissions with either chemo-immunotherapy or newer targeted therapies in the form of B-cell receptor antagonists or BCL-2 antagonist like Venetoclax. The goal of treatment is also dictated by the fitness status of the patient at the time of requirement of therapy e.g. concomitant medical conditions can also influence the choice of therapy and goal of treatment.

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Clinically significant response would be dependent of the choice of therapy. However, achievement of complete remission (100% reduction) and minimal residual disease negative remission (MRD negative) are the ultimate goals of treatment in patients who are able to tolerate intensive treatment. However, certain therapies like B-cell receptor antagonists such as ibrutinib or idelalisib will achieve partial response in majority of patients due to the unique mechanism of action. This is an acceptable response in majority of patients where this class of drug is used.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is definitely an unmet need for the patients and healthcare professionals in this disease. Majority will relapse even with current therapies and it becomes more important to get the disease into deeper clinical remission. We know that patients relapsing after B-cell receptor antagonist therapy (Ibrutinib and idelalisib) have very unfavourable outcome. These patients can be treated with Venetoclax monotherapy but the complete response rate is around 1-5% which can only be improved with combination therapies. A lot of trials are being performed to look at this cohort of patient to improve the depth of response at this stage as there is no licensed salvage therapy available.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the	- https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.12067 BCSH guidance 2015 (Being updated) - ESMO Guideline: Ann Oncol (2015) 26 (suppl 5): v78-v84. Authors: *B. Eichhorst, T. Robak, E. Montserrat, P. Ghia, P. Hillmen, M. Hallek, C. Buske*

condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is reasonably well defined at present. First line treatment is usually chemo-immunotherapy (FCR for fit patients and Chlorambucil with immunotherapy for unfit patients) in intact TP53 group of patients. B-cell receptor antagonists are available for use in TP53 deleted patients and patient relapsing after one line of chemo-immunotherapy. Patients relapsing after B-cell receptor antagonists are allowed to be treated with Venetoclax monotherapy. This is pretty standard course of action at present.
• What impact would the technology have on the current pathway of care?	Combination of Venetoclax and rituximab is compared to Bendamustine and rituximab in the MURANO trial. The group of patients allowed in the trial had 1-3 previous lines of therapies and majority of the patients had no exposure to B-cell receptor antagonists. This combination will therefore fall into the group of patients relapsing after initial therapy for CLL. Ibrutinib or idelalisib with rituximab is the standard of care in this group of patients as funding for Bendamustine with rituximab has been withdrawn based on the data from RESONATE and GILEAD 116/117 trial.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	This combination therapy is different from B-cell receptor antagonist therapy which is the standard of care in this setting. There are two main differences: 1. The combination of Venetoclax and rituximab achieves deep MRD negative remissions in two thirds of patients.

	2. There is a definite duration of therapy i.e. 2 years of fixed therapy. However, this must be counter balanced by the requirement for close monitoring at the initiation of therapy, requirement of hospitalisation for a small number of patients with this combination.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It will be specialist clinics i.e. Haematology teams
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The main risk with the drug is tumour lysis syndrome so there are certain precautions that need to be taken within the hospital sites using the drug. For example: 1. Following the protocol for assessments of tumour lysis in real time. 2. Availability of haemofiltration/dialysis services on site in order to manage tumour lysis in small number of patients. 3. The need for hospitalisation and assessment of risk of tumour lysis syndrome.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	It is very difficult to answer this question. One has to compare the data from three different trials namely MURANO, RESONATE and GILEAD 116/117. The trial recruitment populations are different and the data cannot be compared. Also, the data for all the trials is maturing but we are awaiting further updates. It is quite clear that Venetoclax with rituximab achieves very deep remission and would theoretically improve the PFS and OS as compared to Bendamustine and rituximab. When compared to ibrutinib or idelalisib with rituximab, the data looks extremely promising but it is virtually impossible to draw further conclusions.

• Do you expect the technology to increase health-related quality of life more than current care?	Yes. This would be primarily related to effectiveness of treatment and duration of therapy.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients intending to have allogeneic bone marrow transplant will benefit from this therapy as the burden of disease will substantially reduce prior to transplant. This is a small cohort of patient as majority of the CLL patients will not be able to tolerate the toxicity of allogeneic transplant.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	The main change in monitoring would be in the escalation phase of the treatment. Some patients will need hospitalisation for monitoring but majority of patients can be monitored as outpatient. After escalation of therapy, the requirements are pretty much the same.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Ability of this combination to achieve deep MRD negative remission should be included.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial	

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes, because all the upcoming data suggests that treatment duration could be defined by the achievement of MRD negativity with combination therapy. This trial was not MRD driven trial but the concept is being used in multiple upcoming front line and relapsed trials.
• Does the use of the technology address any particular unmet need of the patient population?	As above
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Apart from tumour lysis syndrome which is a risk in the escalation phase, the treatment is extremely well tolerated.
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	The concept of MRD negativity is explored with chemo-immunotherapy such as FCR. There is clear data that patient achieving deep MRD negative remission have better progression free survival and overall survival. **Minimal residual disease is an independent predictor for 10-year survival in CLL** Marwan Kwok, Andy C. Rawstron, Abraham Varghese, Paul A. S. Evans, Sheila J. M. O'Connor, Chi Doughty, Darren J. Newton, Paul Moreton and Peter Hillmen Blood 2016 128:2770-2773; doi: https://doi.org/10.1182/blood-2016-05-714162 However, ibrutinib and idelalisib alone will not achieve MRD negativity due to the unique mechanism of action. Venetoclax on the other hand does achieve MRD negative remission so one cannot compare this end point between the trials due to different mechanism of action.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Progression free survival, Overall survival and MRD negativity. All were measured in this trial.
• If surrogate outcome measures were used, do	Yes

they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No, all adverse effects were expected.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. How do data on real-world experience compare with the trial data?	Real world experience appears to be similar with Venetoclax monotherapy trials including M13982 trial. The data in UK is being collected for real world patients and will be likely presented at ASH this year. There is very little real world data available for combination of Venetoclax with rituximab but one would expect it to be similar to Venetoclax monotherapy real world data.
Equality	
22a. Are there any potential equality issues that should be	No

taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	Nil

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Venetoclax with rituximab is a very effective combination in relapsed CLL.
- The combination achieves deep remissions and improves progression free survival and overall survival as compared to Bendamustine and rituximab.
- It is very difficult to compare clinical outcome data to current standard of therapy which is B-cell receptor antagonists. There is no available data for comparison at present.
- The strength of combination is the finite duration of therapy and depth of response. The data will hopefully mature in time to reflect whether the improved depth in response translates into improved clinical outcomes. However, the follow up on trial is short at present to reflect that desired outcome.
- In short, this therapy offers very good and comparable treatment option to relapsing CLL patients and should be available as a choice of therapy in this cohort of patients.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Chronic Lymphocytic Leukaemia Support Association (CLLSA) Lymphoma Action are supporting this submission.
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The purpose of the CLLSA is to provide support to CLL patients and their carers by keeping them informed of recent and relevant developments in CLL treatment and research and to provide opportunities for awareness raising and mutual support through regular meetings and newsletters. Membership of CLLSA is free and there is no charge made for publications or for attendance at our patient meetings. We are reliant on obtaining funds from several areas. These include: Donations, legacies and grants from trusts and pharmaceutical companies. The CLLSA currently has 2476 members and the CLLSA on line HU membership is in excess of 8000.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The responses for this submission are from two patient surveys and quoted references. The first survey was of 248 CLL patients and included a separate survey of 29 carers. These surveys were carried out by The UK CLL Support Association (CLLSA) and the Canadian CLL Patient Advocacy Group (CLLPAG). The surveys invited members and the CLLSA online community (of CLL patients and carers) to answer questions about their experiences. For the second survey information was gathered using an on line tool as a 'real world survey' of CLLSA HU patients who have received Venetoclax + Rituximab (V+R) treatment. The tool used the EQ-5D

	Quality of Life questions with some supplementary questions regarding previous Ibrutinib treatment and length of Venetoclax treatment. In addition to the surveys, information was collected from The Murano study results reported in New England Journal of Medicine March 22nd 2018 ref N Engl J Med 2018; 378:1107-1120, The Lancet Oncology Volume 19, Issue 1, January 2018, Pages 65-75 – Venetoclax for Chronic Lymphocytic Laukaemia progressing after Ibrutinib: an interim analysis of a multicentre, open label, phase 2 trial and The AbbVie press release NORTH CHICAGO, Ill., June 15, 2018 /PRNewswire/
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	CLL, whilst still a rare condition, is the commonest of the leukaemias and is currently an incurable condition for the majority of patients. From our survey, common symptoms reported at diagnosis include fatigue (51.6%), increased lymphocyte count (48%), enlarged lymph nodes (39.1%), frequent infections (21%), night sweats (19.4%), enlarged spleen or discomfort on upper left side of stomach (15.7%), shortness of breath (15.3%), anaemia (13.7%), thrombocytopenia (10.5%), pain (8.1%), fever (5.6%) and neutropenia (5.2%). Being diagnosed with CLL can cause “stress” (75.8%), “anxiety” (59.3%), “difficulty sleeping” (38.7%) and “depression” (30.6%). As such, a diagnosis of CLL can have a profound impact on both physical and psychological wellbeing for both patient and carers/family. Following diagnosis, many patients will live on “watch and wait” for a significant amount of time with a varying symptom burden. In the CLLSA/CLLPAG survey, the average time since diagnosis was 3.65 years and 41.9% of respondents were on watch and wait. This ranges from asymptomatic patients to patients living with significant symptom burden (including fatigue, night sweats, pain and weight loss). In particular 59.3% of patients surveyed said that they were currently suffering from fatigue (compared to 51.6% at diagnosis). Additionally, only 14.5% said that they weren’t currently experiencing any of the

	symptoms listed (down from 22.6% at diagnosis). Treatment is only initiated when the CLL has progressed to the point that it has to be treated. As such, patients can be left living with a significant symptom burden and poor quality of life, uncertain as to what will happen next, waiting until there is a decline in their wellbeing and clinical assessments, before treatment is started. Any treatment usually ends in eventual relapse. Patients live in a cycle of 'waiting, treatment then relapse', which is then repeated and continues until death. With 85% of patients diagnosed aged 65 or older, the more toxic current treatments are often not well tolerated by the majority of patients, who may also have comorbidities. CLL tends to respond less well to each line of therapy, with shorter subsequent remissions. Patients live in fear of relapse, knowing further toxic treatment is likely to impact negatively on their quality of life. As CLL is an evolving disease, many patients also live in fear that their disease could evolve through a Richter's transformation to an acute form of lymphoma, which is a rapidly progressing and generally 'end of life' event. This occurs in approximately 10-15% of patients. Patients with CLL also have a higher risk of infection, as their immune system is severely compromised by the disease. These frequent and persistent infections can impact hugely on quality of life, as well as being a leading cause of death for CLL patients. During the winter, many patients (and their families) experience long periods of isolation to try to reduce the risk of infection. As outlined above, living with CLL is difficult and does not affect a patient in isolation, but instead creates a "ripple effect", impacting on the whole family. Family, and even friends and colleagues of a patient may all be affected by the diagnosis. Family members/carers can be challenged with exhausting caretaking duties when someone they know is diagnosed with CLL. In the survey, 18 out of 20 carers cited having to wholly take on previously shared household duties like meal preparation, shopping and upkeep of the household. This had led to many having to abandon their own jobs to be able to cope with this increased burden, ultimately adding to the financial impact that living with CLL can cause.

	For some, caregiving was also cited as having direct physical health implications on the carer themselves and, for a few, marital relations with their partners had ceased. Patients' compromised immune systems and treatment side effects were cited by 20% of carers as a reason for reduced social contact with family and friends for both caregivers and patients and that they sacrificed holidays and non-essential social events because of it. With the stress of diagnosis and probable relapse in the future, many patients continue to live with depression (22.6%), anxiety (40.3%) and have difficulty sleeping (34.7%). Patients live with significant emotional, psychological and physical issues that impact negatively on quality of life and their ability to carry out day to day tasks, making personal or family relationships difficult and preventing patients from enjoying a normal life. Improvements in effective, less toxic treatments and consequently, quality of life will have a wider impact on the lives of their carers, perhaps allowing a return to work for both patient and carer, and a resumption of normal activities. Living with CLL is living with uncertainty for both the patient and carer -uncertainty about disease progression, length of life, quality of life, possible infections and an inability to live a 'normal' life.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	From the CLLSA HU on line survey of V+R patients, of the 248 patients surveyed, 58.1% had received treatment for their CLL (1- 6 lines of treatment). Due to internet discussion forums, patients are increasingly aware of the need for personalised medicine which is tailored to their particular 'type' of genetic mutation in their CLL. Outside clinical trials, the majority of younger patients will be treated with FCR or BR first line unless they have 17p del or are TP53 mutated (in which case they should receive Ibrutinib). Patients who are more frail may have Chloramubil/Obintuzumab or other treatments. Unfortunately, some patients are still being offered further chemoimmunotherapy on relapse, a situation

	which they know will offer them a shorter subsequent remission and will further damage their bone marrow. This is not acceptable to them when there are effective targeted treatments with fewer side effects such as Venetoclax+Rituximab available. Patients with relapsed or refractory CLL want the following and do not feel that further chemoimmunotherapy offers them these things – • tolerable side effects and safety profile, • an effective treatment with high response rates and the potential for Minimal Residual Disease (MRD) negativity to give them the longest possible remission, • symptom control leading to a better quality of life, effective for high risk patients, • an oral treatment • preferably treatment for a limited time period.
8. Is there an unmet need for patients with this condition?	For relapsed/refractory CLL patients, irrespective of the length of the first remission, more chemoimmunotherapy has the potential to irreparably damage the bone marrow leading to on going cytopenias and a very restricted lifestyle. In addition, many patients experience clonal evolution of their CLL which then leads to relapse and makes re-treatment with the same treatment less effective. Due to the heterogeneous nature of the disease and the age range of patients, there is a need for access to multiple treatment options for relapsed/refractory patients with CLL. For patients unsuitable for treatment with idelalisib/ibrutinib or who have stopped treatment with idelalisib/ ibrutinib due to intolerance or disease progression, further treatment options are extremely limited. The most likely option in this setting would be BSC (best supportive care), which usually leads to further progression of the disease and ultimately death. V+R in this scenario meets the end of life criteria. As such, additional treatment options are needed in this setting, with Venetoclax+Rituximab offering

	excellent response rates and an acceptable safety profile.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients are aware of the V+R Murano data and see the advantages of this technology to be that Venetoclax is an oral treatment that is time limited, with high rates of response and the potential for MRD negativity, which hopefully will lead to longer remissions. Patients worry about infections and the NEJM reported that in the MURANO study, the rate of grade 3 or 4 neutropenia was higher in the V+R group than in the Bendamustine–Rituximab (B+R) comparator group, BUT the rates of grade 3 or 4 febrile neutropenia and infections or infestations were lower with V+R than with B+R. CLLSA asked members who have received V+R to complete an on line QOL survey in preparation for this STA. 92% of patients reported no problems with washing or dressing themselves. 79% said they had no problem or only slight problems undertaking their usual activities, and 96.4% reported none or only sight difficulty with mobility. With regard to their Health Score, 71% reported a score of 65 or more out of 100 and it was noted that higher health scores were associated with a longer time on Venetoclax. Regarding anxiety and depression, which is a significant comorbidity for relapsed CLL patients, only 1 patient (3.57%) reported being moderately anxious/depressed with the rest reporting no anxiety/depression (57.14%) or only slight anxiety/depression (39.29%). This reflects their confidence in the efficacy of this treatment and the potential for a long remission. By comparison the CLLSA/CLLPAG survey reported 22.6% patients were depressed and 40.3% were anxious. Patients from the survey said – “improved so much”, “put on weight, now very active and independent again”, “no side effects whatsoever”, “hardly any side effects”, “I have my life back”, ““Very benign experience”, “Some fatigue from step-wise dose increases”, “Some slight nausea early-on, indigestion/gas/diarrhoea which has improved significantly.”

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The initial risk of tumour lysis syndrome and the potential need for an overnight stay for the first treatment are possible disadvantages. Treatment with Venetoclax is ramped up from an initial 20mg to full dose over many weeks to overcome this possible complication. Treatment with Rituximab by iv or sc means attending as a hospital day case which may be a disadvantage to some patients. Some patients report ongoing fatigue but commented that they cannot be sure if this is due to Venetoclax.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	There is a small population of patients who received Ibrutinib first line because they have participated in a clinical trial and are now relapsing and for whom there is a desperate need for an effective treatment as their survival can be only months. A report in the Lancet (Ref *The Lancet Oncology Volume 19, Issue 1, January 2018, Pages 65-75 Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial*) showed Venetoclax+Rituximab to be an effective treatment for these patients. Assessment at 24 weeks after starting treatment in the main cohort and 36 weeks in the expansion cohort showed a response rate of between 60-70%. Median progression-free survival was 24·7 months and median overall survival was not reached.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and	In the UK there is now a small population of patients who have commenced treatment with Idelalisib or ibrutinib over the past few years. This may be either after NICE guidance has been issued, via clinical trials, compassionate or early access schemes or via the Cancer Drugs Fund. Some of those patients are now failing these treatments and are in desperate need of a next line of effective treatment, as an alternative to best supportive care. These patients may not be covered by

the technology?	TA487 – Venetoclax monotherapy for treating CLL because they may not have also had previous chemoimmunotherapy, particularly if they were participants of the FLAIR study or if they were 17pdel or mutated TP53 when needing first line treatment. It is important that patients who have received Ibrutinib as first line treatment are considered a part of this TA for V+R treatment
Other issues	
13. Are there any other issues that you would like the committee to consider?	We consider V+R to be a step change for relapsed/refractory patients who have had at least one prior therapy. This treatment gives patients the potential to achieve MRD negativity and provides significant psychological benefits by reducing anxiety regarding possible early relapse. The MURANO study has shown that the rate of MRD negativity and progression free survival (PFS) is very significantly higher in the V+R group The rates of minimal residual disease (MRD) negativity should also be considered as a surrogate marker of benefit as this will differentiate the comparators and the subject technology. For patients with relapsed CLL, V+R will provide an alternative to Ibrutinib and Idelalisib, both of which have significant side effects. For some patients it will also the offer the potential benefit of MRD negativity and consequent stopping of treatment. For patients who relapse after Ibrutinib or Idelalisib therapy, the combination V+R offers significant improvement in progression free survival compared with current alternatives and is very likely to significantly improve overall survival. This combination of V+R should therefore lead to an increase in quality of life however, that may not be reflected in the QUALY calculation.

Key messages
15. In up to 5 bullet points, please summarise the key messages of your submission: • V+R is an effective treatment across all subgroups of CLL. including TP53 mutated, 17p del and unmutated IgVH • V+R is a time limited and mainly oral therapy with a tolerable side effect profile and no increase in grade 3/4 infections • V+R treatment results in a high level of responses and MRD negativity – a surrogate marker for length of remission • V+R appears to be effective in the small group of patients that have received prior treatment with a bcl-2 inhibitor • V+R is a treatment option for patients with cardiac and anticoagulant comorbidity issues that are unsuitable for Ibruitnib.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Leukaemia Care
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Leukaemia Care is a national blood cancer charity, founded in 1969. We are dedicated to ensuring that anyone affected by blood cancer receives the right information, advice and support. Approximately 85-90% of our income comes from fundraising activities – such as legacies, community events, marathons etc. Leukaemia Care also received funding from a wide range of pharmaceutical companies, but in total those funds are less than 15% of our annual income. Leukaemia Care has undertaken a voluntary commitment to adhere to specific policies that regulate our involvement with the pharmaceutical industry set out at: http://www.leukaemiacare.org.uk/wp-content/uploads/2018/02/CODE-OF-PRACTICE.pdf
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO
5. How did you gather information about the experiences of patients and carers to include in your submission?	Patient/carer responses and experiences in this submission have been gathered from researching the following sources: • 2018 Leukaemia Care "Watch Wait Worry" report https://www.leukaemiacare.org.uk/wp-content/uploads/2018/04/FINAL-Watch-and-Wait-report-Leukaemia-Care-EMBARGOED-16-APRIL.pdf • 2016 Leukaemia Care patient experience survey of 1007 CLL patients • 2016 CLLPAG/CLLSA & Lymphoma Canada survey 248 CLL patients and a separate survey of 29 carers

	• 2017 CLLPAG and Lymphoma Canada survey Of the 320 CLL/SLL patients: 279 (87.19%) were diagnosed with CLL, 11 (3.44%) were diagnosed with SLL and 30 (9.38%) were diagnosed with CLL & SLL. 21 with venetoclax experience. • 2017 CLLPAG and Lymphoma Canada survey of 41 caregivers • 2018 survey of 28 CLLSA and on-line community members, experiences of venenetoclax treatment using EQ-5D Quality of Life questions • 2014 CLLSA survey of Quality of life issues of 282 People living with CLL • CLL on-line peer to peer support community at HealthUnlocked https://healthunlocked.com/cllsupport • Interviews of patients
Living with the condition	

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**Diagnosis:** Chronic lymphocytic leukaemia is rare condition and currently incurable for the majority. The disease is extremely heterogonous, and is diagnosed within a predominantly older population, *"Age-specific incidence rates rise steeply from around age 40-44. The highest rates are in the 90+ age group for males and females"* (Cancer Research UK).
	
	Common symptoms reported at diagnosis include: fatigue, increased lymphocyte count, enlarged lymph nodes, frequent infections, night sweats, enlarged spleen or discomfort, shortness of breath, anaemia, thrombocytopenia, neutropenia, pain and fever.
	
	The Leukaemia Care survey of 1,007 CLL patients indicates:
	
	• Most common symptoms reported before diagnosis were:
	  • fatigue (43%)
	  • swollen lymph nodes (31%)

- weakness/breathlessness (24%)
- night sweats (24%)

- 28% of CLL patients are asymptomatic at diagnosis
- 77% of presenting CLL patients are placed on W&W at diagnosis
- 43% of patients had concerns about W&W
- 23% of patients required treatment upon presentation
- Only 24% of those who have now relapsed since treatment were asymptomatic at presentation,

Emotional impact

Patient reports and surveys show that a diagnosis of CLL causes: shock, distress, anxiety, difficulty sleeping and depression. A diagnosis of CLL may profoundly impact on the physical and psychological wellbeing for the patient, carer and family.

"I was by myself for my appointment and told 'you have leukemia' which immediately scared me to death, I thought, this is it, I am going to die, soon." [Diane]

The Leukaemia Care survey of 1,007 patients asked; 'how has your emotional and wellbeing changed since diagnosis?'

- 37% of all patients felt depressed or anxious more often.
- 41% of relapsed patients felt depressed or anxious more often.

Limited retreatment choice may further impact negatively on a CLL patient's quality of life and survival.

Relapsed patients live with uncertainty, an increasing tumour and symptom burden, and an impaired quality of life due to long term side effects of disease development and previous therapies. This negatively impacts on emotional wellbeing, a reduced quality of life may be experienced continuously over a long period of time; as CLL may not be treated or retreated for some time following diagnosis, progression or relapse. Treatment may often not be given until CLL has progressed to a stage it is seriously impacting a patient. During this "wait" patients are monitored and face constant uncertainly and emotional strain, and often describe this as *"watch and worry*".

'Watch and Wait' is a process of regularly monitoring the progression of CLL and only initiating treatment once intervention is required. This is done because traditional treatments are very intensive and can cause greater issues for patients than the CLL.

For many patients there is a substantial emotional and physical burden that comes with Watching and Waiting, or rather, worrying.

"Watch and Wait or "Watch and Worry"? How long would this go on? I resigned myself to trying to put W&W to the back of my mind and get on with my life despite the restrictions that my condition were putting on me." [Ian, 69]

In the 2018 Leukaemia Care report; over half of CLL patients on "Watch and Wait" are feeling more depressed or anxious following diagnosis. https://www.leukaemiacare.org.uk/wp-content/uploads/2018/04/FINAL-Watch-and-Wait-report-Leukaemia-Care-EMBARGOED-16-APRIL.pdf

Infection

Immunity complications are a major issue for CLL patients. Multiple lines of therapy and relapse add short and long-term treatment related immunity complications to an already damaged immune

	system caused by CLL. Treatment toxicities and side effects can cause patients considerable distress, put them at risk, isolate them and add a burden to friends, family and the health service.
	
	CLL patients are at increased risk from opportune infection pre, during and post treatment; this can have a major impact on carrying out normal activities and become a serious problem during winter for patients and their families trying to avoid seasonal outbreaks of respiratory infections. The greatest number of CLL patients lives end due to infectious complications. CLL patients spend long spells in isolation with difficulties associating with work colleagues, family and friends. As part of day to day survival and coping strategies, CLL patients may have to rely on prophylactic antimicrobials and IVIG supplementation to reduce serious infection and maintain a quality of life.
	
	Day to day living: Leukaemia Care Patient experience survey of 1,007 CLL patients
	• 46% of CLL patients are experiencing **pain** to some degree as a direct result of their condition
	• 37% of CLL patients have **difficulty moving around**
	• 40% of CLL patients have difficulty performing some of their **daily routines**, such as cooking or cleaning
	• 60% of CLL patients report it has impacted on their ability to **travel**
	  • 17% physically,
	  • 35% due to practical difficulties, e.g. insurance
	  • 13% have chosen not to
	Financial Impact:
	• 50% were not in work at diagnosis.

- Of those in **work or education** before their diagnosis:
  - 51% have been impacted
    - 21% reduced hours
    - 30% no longer able to work or continue education
- Consequently, 32% of patients reported a **negative financial impact** because of having CLL, due to increased costs or reduced income

Living with a CLL diagnosis can be challenging for the whole family, as uncertainties are shared and family members may be required to take on care taking duties; this reduces their own ability to maintain employment and contribute to society. Stress and the physiological impact of increased challenges can also impact on a family member/carer's health and ultimately the marital and family relationship. Patients living with CLL can struggle with the invisible burden of their disease and the impact this can have on all: day to day relationships, recreation and social activity.

Patients and their treating clinicians need treatment choices and access to therapies that may provide a real chance of achieving Minimal Residual Disease (MRD) negativity and a durable remission. The CLL patient population is varied and many are not fit enough or have comorbidities that prevent the use of existing options. Access to an effective therapy after relapse should be given regardless of length of first remission, this may break the cycle and consequences of repeated treatment and relapse. The average age of a CLL patient is 72, fitness and comorbidities can make currently available NICE approved therapies unsuitable due to toxicities or treatment side effects. Many patients we interviewed, or who are active in on on-line communities, are aware and often share the cumulative effect of their retreatments and repeated use of chemoimmunotherapy and the damage to bone marrow this has caused.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Of the 1,007 patients in the LC patient experience survey, 210 Total reported they had relapsed from treatment • 108 relapsed once • 40 relapsed twice • 28 relapsed three times • 29 relapsed four times or more In an era of developing personalised medicine CLL patients are becoming increasingly aware of current limitations and the need for an appropriate tailored approach to their own treatment rather than a one bucket fits all approach. Patients also see the need for treatment options to fit with the increasingly complicated treatment landscape and emerging cytogenic markers that will further stratify patients and treatment. Patients relapsing from a prior therapy require access to tolerable therapies that offer a chance of reaching MRD negativity early, followed by a treatment free period and improved quality of life. Patients are still being treated today second line with a chemotherapy as a matter of routine due to limited access to appropriate novel therapies, remissions from repeated chemotherapy reduce and are accompanied with cumulative toxicity issues. Patients are aware of complexities being caused by restricted access to ibrutinib through NHSE for those relapsing after 3 years, therefor patients are being forced down a pathway of being retreated with chemo immunotherapies and to the cumulative long-term toxicity issues this can create. This is also the case for adaptive first line trials that offer the chance of first line access to non - chemo based regimens. Patients failing non-chemo arms often do not have a choice other than a chemoimmunotherapy. Patients worry they will not achieve enduring remissions or about effects of toxicities. Ibrutinib and Idelallisib plus rituximab are alternatives to a chemotherapeutic approach in the relapsed setting, but are often not suitable, or available to all in a subgroup.

	Patients are becoming increasingly informed and proactive in their healthcare discussions and require access to the most appropriate therapies. An example of a connected and aware patient population is CLLsupport@healthunlocked where over 8,000 CLL patients share experiences and challenges daily about living with CLL, relapse and retreatment. Patients are very aware of the significance of MRD negativity as a surrogate for measuring potential enduring remission and OS. Patient experience surveys clearly show a wish by patients for a treatment free period. The MURANO trial data and recent release of MRD follow up at ASCO and EHA this year emphasise the remarkable response and MRD negative states being achieved by most of trial participants using the venetoclax rituximab breakthrough therapy. The defined two-year treatment this therapy offers, is an alternative to continuous treatment and risks associated with repeated chemo use. Patients understand that alternative novel therapies available in this setting do not come without risk and treatment choice is required to avoid: infectious complications, cardiac, arthralgia, anti-coagulation, and colitis issues associated with the BCR therapies which can make them unsuitable for comorbid patients.
8. Is there an unmet need for patients with this condition?	• Effective treatment options are required to enable patients to achieve MRD negativity early in the relapsed setting to break the re-treatment relapse cycle seen in CLL. • Less toxic treatment options are needed as an alternative to chemotherapy use in this setting to achieve MRD negativity without repeated use of chemotherapies and increased risks of long term damage to bone marrow, chance of clonal evolution, immune complications and reductions in quality of life. • Effective treatments with reduced and different toxicity profiles are required as alternatives to currently available BCRi based therapies, Ibrutinb or Idelalisib plus rituximab • CLL is a heterogeneous disease, and the patient population is varied so there is an unmet need for patients and treating physicians to have access to several options when considering long term treatment plans that consider cytogenetic and disease characteristics

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?

Excerpts: Leukaemia Care Patient experience survey of 1,007 CLL patients

1. What treatment methods would you prefer?	2. Overall 3. CLL Percentage (%)	4. Relapse	5. Not Relapsed	6. Relapse N/A
7. Oral – tablet	8. 50	9. 69	10. 48	11. 43
12. Intravenous infusion (given through a drip)	13. 39	14. 42	15. 49	16. 20
17. Don't know	18. 24	19. 8	20. 21	21. 42
22. Oral – suspension	23. 13	24. 17	25. 11	26. 16
27. Subcutaneous injection (injection under the skin)	28. 8	29. 12	30. 7	31. 6
32. Intramuscular injection (injection into the muscle)	33. 5	34. 10	35. 4	36. 3

Would you consider it positive if a treatment plan contained a treatment-free period or included stopping treatment altogether?	Overall CLL Percentage (%)	Relapse	Not Relapsed	Relapse N/A
Yes	59	54	56	76
No	41	46	44	24
Don't Know	51%	40%	48%	66%

- See patient preferences above, 'Would you consider it positive if a treatment plan contained a treatment-free period or included stopping treatment altogether?'– Patients prefer a treatment-free period or being able to stop treatment altogether Venetoclax plus rituximab provides a treatment free interval after a defined 2-year treatment period, the vast majority are achieving MRD negativity and are still in remission .

	• See patient preferences above, 'What treatment methods would you prefer**?'** – Patients prefer oral tablet and IV administration - Venetoclax plus rituximab is administered by both oral tablet and intravenously • Pharmacoeconomics – Venetoclax plus rituximab will reduce long term costs to NHS with the treatment free interval and reduced need for NHS management of adverse events and negative quality of life issues. • Venetoclax plus rituximab has gentler toxicity profile compared to a 2nd line immunochemotherapeutic approach. • The reduced number of adverse events experienced by venetoclax trial participants offers patients an alternative therapy to those who are currently limited by comorbid issues. • Venetoclax plus rituximab will provide potential clinical choice to aid with planning long term treatment strategies. • Venetoclax plus rituximab offers patients a high chance of achieving MRD negativity, a recognised surrogate for depth of remission. • Very high numbers of patients treated with venetoclax plus rituximab are achieving undetectable MRD regardless of the risk features. **Quality of Life CLLSA EQ5D type patient venetoclax+ rituximab survey** • 92% of patients reported no problems with washing or dressing themselves. • 79% said they had no problem or only slight problems undertaking their usual activities, • 96.4% reported none or only slight difficulty with mobility. **Health Score** • 71% reported a score of 65 or more out of 100, higher health scores were associated with a longer time on Venetoclax. • Regarding anxiety and depression only 1 patient (3.57%) reported being moderately anxious/depressed with all others reporting no anxiety/depression (57.14%) or only slight anxiety/depression (39.29%). Several patients' comments:

	• "*it's been a bit of a life saver*" • *"Even my kids understood MRD to mean mummy didn't have cancer"* • *"I realise how fortunate I have been to participate in a trial with such an outcome, REMISSION." John describes venetoclax as, "quite miraculous"* • *"no side effects whatsoever"* • *"I have my life back"* • *"Very benign experience"* • *"Some fatigue from step-wise dose increases",* • *"This treatment has given me my life back and allowed me to contribute to society in a meaningful way"*
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	• IV administration of rituximab, however this is also standard with bendumustine plus rituximab and other current chemoimmunotherapy options as well as idelalisib plus rituximab in this setting. • The initial dose escalation requires a hospital administration phase to reduce tumour lysis risk, this could be a disadvantage, however patients are prepared to undergo this to gain the outcome benefits. • Long term patient experiences of general side effects seem to be suggesting some fatigue, but this may not be the venetoclax as this is a symptom very commonly experienced in all settings

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	• Venetoclax rituximab is demonstrating it is an effective treatment option for those in the relapsed refractory setting, including those who have17p TP53 aberrations and those relapsing from both chemoimmunotherapy and BCR inhibitors. The very high numbers achieving undetectable MRD in the peripheral blood at the end of treatment assessment did so regardless of the risk features. This group should not be subdivided to exclude venetoclax plus rituximab for subgroups. • There is a therapeutic void developing that is forcing treating clinicians to put patients on chemo therapeutics against their clinical judgement and undo long term individual treatment plans that have set out to avoid the risks and cumulative effects of chemotherapeutics use in an era of personalized medicine and breakthrough technologies. • It is important that patients who relapse having received non-chemo agents as a first line or second line therapy via a clinical trial or due to compassionate access programs are not forced to receive a chemoimmunotherapy against the clinical judgement of their treating physician. The NICE guidance issued for venetoclax single agent use license currently prevents those relapsing from BCRs alone from access to treatment with single agent venetoclax, these patients require effective therapy very soon after relapse and if unsuitable for chemoimmunotherapy, may only have best supportive care as an option. • First line patients who have relapsed after three years or those younger than 65 are currently restricted from accessing Ibrutinib as a 2nd line treatment, this again is pushing clinicians to retreat with chemotherapeutics if a trial is not available. This a group who would benefit from access to a tolerable therapy that has a high chance of inducing MRD negativity.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	There is a developing therapeutic void in the relapsed refractory setting and a need for options for patients and their treating physicians to be able to navigate the increasing complex net of treatments to ensure a long term strategy and order plan can be mapped out in the event of a treatment failure. The high levels of negative emotional and psychological well being experienced by this community is caused by limited option and uncertainty. This is compounded by reducing options or ability to follow on with a potential treatment due to comorbidities, fitness or capacity.

	MRD negativity is becoming increasingly important as an outcome measure when measuring benefit of a novel experimental therapy. It becomes especially relevant when median trial end points cannot be reached due to high PFS responses and survival of patients in a trial. The high level of Minimal Residual Disease (MRD) negativity achieved in MURANO is evidencing MRD should be considered an effective measurement against comparators and prevent delay in getting a much-needed therapy to patients. There has been a great difficulty in measuring effectiveness of therapies going through appraisal recently because of the inability of trials to meet median survival endpoints and thus by definition create uncertainties. We hope NICE accept MRD negativity as a key measurement of benefit and a treatments promise to aid with much needed accelerated access for patients and their treating doctors. The venetoclax plus rituximab treatment is a breakthrough therapy offering a step change for relapsed patients who have received at least one prior therapy. This treatment offers patients a good chance of achieving an enduring remission and MRD negative status without the associated risks of repeated lines of chemotherapy or other agents that do not offer a chance of MRD negativity. Relapsing first line patients may be relapsing from established chemoimmunotherapy or first line trials of novel non-chemo approaches. The few available therapies for this group mean many are having to be retreated with chemoimmunotherapy or are further restricted due to comorbid issues. The relapsed refractory group is diverse and the disease very heterogenous. Venetoclax plus rituximab and MURANO offers an effective solution to bridge treatments and give patients their lives back. Ref: The primary analysis of the MURANO trial (NCT02005471) https://ash.confex.com/ash/2017/webprogram/Paper109076.html Ref : *The Lancet Oncology January 2018, Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial*) showed

	Venetoclax+Rituximab to be an effective treatment for these patients. https://www.sciencedirect.com/journal/the-lancet-oncology/vol/19/issue/1 Ref: MIRANO study paper published in NEJM https://www.nejm.org/doi/full/10.1056/NEJMoa1713976 Ref: ASCO review - http://www.ascopost.com/News/58679 Ref: Cancer Network review http://www.cancernetwork.com/chronic-lymphocytic-leukemia/venetoclaxrituximab-found-superior-chemotherapy-cll Ref: The Oncologist review http://www.cancernetwork.com/chronic-lymphocytic-leukemia/venetoclaxrituximab-found-superior-chemotherapy-cll Ref: Nature review https://www.nature.com/articles/s41571-018-0017-z Ref: AbbVie press release NORTH CHICAGO, Ill., June 15, 2018 /PRNewswire https://news.abbvie.com/news/abbvie-announces-new-undetectable-minimal-residual-disease-data-from-phase-3-relapsedrefractory-chronic-lymphocytic-leukemia-murano-trial-venetoclax-in-combination-with-rituximab-at-23rd-european-hematology-association-annual-congress.htm

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Venetoclax + rituximab is an effective treatment in the relapsed refractory setting, regardless of high risk features,17p TP53 aberrations and unmutated IGVH, this group should not be subdivided.
- Venetoclax + rituximab offers patients potential of a treatment free interval - a defined 2-year treatment period
- Venetoclax + rituximab is achieving high levels of response and MRD negativity (a surrogate for remission durability), this is seen in those pre-treated with BCRis or chemoimmunotherapeutic combinations.
- Venetoclax + rituximab gives patients with comorbid, cardiac, anticoagulation and bowel issues an alternative to treatment with a BCRi,
- Venetoclax + rituximab offers patients a chance of achieving an enduring remission without the risks associated with repeated chemotherapeutic use, enabling an appropriate personalised long term treatment approach.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Submitting on behalf of NCRI/RCP/ACP**
3. Job title or position	[redacted]

4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**NCRI/RCP/ACP**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**None**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	The main aim of therapy of relapsed or refractory chronic lymphocytic leukaemia is to achieve remission (complete or partial remission) resulting in disease control with prolonged survival and improved quality of life. Use of Venetoclax in combination with rituximab in relapsed or refractory chronic lymphocytic leukaemia has shown greater achievement of minimal residual disease as compared to chemo- immunotherapy and other novel agents.

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Progression Free Survival (PFS) Overall Survival (OS) Absence of detectable Minimal Residual Disease (MRD) in the Bone Marrow by sensitive flow Cytometry-termed MRD negativity.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Even though in the last few years novel agents have offered therapy options for patients with relapsed or refractory chronic lymphocytic leukaemia there are still unmet needs. These would include greater achievement of MRD negativity and a fixed duration of therapy, as compared to using therapy until progression. Patients with 17p deletion or TP53 mutation remain in a poorer prognostic group.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Relapsed chronic lymphocytic leukaemia in patients treated with at least one prior chemoImmunotherapy is eligible for B Cell Receptor Inhibitor (BCRi) therapy. In the majority of cases this is Ibrutinib monotherapy (NICE TA 429) Although many such patients are also eligible for Idelalisib and Rituximab (TA359), in practise Ibrutinib has been the drug of choice in the vast majority, due to decreased toxicity and comparable efficacy. Many patients develop resistance to Ibrutinib and eventually fail BCRi therapy. Currently such patients can be treated with Venetoclax single agent (NICE TA487). Patients with relapsed refractory CLL who are

	managed with supportive care have a very poor outlook and this group as a whole is considered to be at the 'end of life'.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	British Society for Haematology's Investigation and Management of Chronic Lymphocytic Leukemia clinical guideline is followed in the UK for the management of CLL. The published guideline from 2012 has now been rewritten and has been accepted for publication in British Journal of Haematology, and will be available online and in print very shortly
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care in CLL is well defined. The NCRI FLAIR trial is widely available as front line therapy for fit and younger patients and first line chemo Immunotherapy is used outside of clinical trials stratified by risk/benefit BCRi and Venetoclax are used within NICE guidance There is broadly uniform management across the UK based on access to NCRI clinical trials and NICE guidance.
• What impact would the technology have on the current pathway of care?	Addition of this for the therapy of CLL will increase the choice of agents for the management of relapsed or refractory chronic lymphocytic leukaemia and allow for greater achievement MRD negativity and therefore may provide an opportunity for a finite duration of treatment guided by MRD assay in the bone marrow
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Venetoclax and Rituximab should be available as an option in relapsed /refractory CLL or in patients with 17p Deletion or TP53 mutation unsuitable for BCRi This is unchanged from current guidance on single agent Venetoclax

• How does healthcare resource use differ between the technology and current care?	The additional cost of Rituximab to Venetoclax is likely to be outweighed by the possibility of discontinuation of therapy in patients who attain an MRD undetectable complete remission.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This will be used in secondary care setting and it is possible treatment may be initiated in the BCSH Level 2 or higher centre and once the dose escalation is carried out (week 5 onwards) patient may be treated in the BCSH Level 1 unit due to risk of tumour lysis during the escalation phase
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment or training is required as Rituximab is widely prescribed and is well tolerated. Rituximab dosage schedule mirrors standard chemoImmunotherapy and is therefore not an additional pressure on day case facilities
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. There will be a higher proportion of patients who attain an MRD undetectable Complete Remission who
• Do you expect the technology to increase length of life more than current care?	Yes. Better PFS improvement and higher MRD negativity due to this technology is likely to led to increase in the length of life as use of Venetoclax in combination with rituximab has shown longer time for next therapy (median not reached as compared to 28 months in the chemo immunotherapy arm

• Do you expect the technology to increase health-related quality of life more than current care?	Better PFS improvement, higher MRD negativity & finite duration of therapy is likely to increase the health related quality of life
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	None. The technology is effective in CLL characterised by 17p deletion and TP53 mutation
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	There is no significant difference in the initial process of drug delivery compared with current care (Single agent Venetoclax) Once the ramp up dose escalation has completed, the addition of Rituximab will necessitate a day case facility once each 4 weeks for 6 months. Rituximab is well tolerated in all patient groups with good acceptability in the context of improved response rates No additional tests are required.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	In the pivotal trial, venetoclax was administered for 2 years and rituximab 375 mg per square meter of body-surface area intravenously was administered from week 5 for the first dose [day 1 of cycle 1] and 500 mg per square meter intravenously thereafter [day 1 of cycles 2 through 6]. In future therapy may be stopped sooner based on MRD negativity.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes. Deeper remission is often associated with improved Quality of Life. Finite duration of therapy may improve quality of life in the event of adverse effects while on therapy
16. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes. This group of patients with Relapsed/Refractory CLL is generally considered to be at the “end of Life” and therefore the impact of high remission rates and prolonged survival is a substantial shift in prognosis compared with either supportive care or ChemoImmunotherapy such as Bendamustine and Rituximab

impact on health-related benefits and how might it improve the way that current need is met?	Patients on supportive care have a poor prognosis and require frequent or prolonged remissions for management of palliative care needs such as infections or transfusion requirement. Alternative chemoimmunotherapy is unsuitable in most cases in an elderly population or those with 17p or TP53 mutation. Chemoimmunotherapy (eg Bendamustine Rituximab) is associated with a higher risk of febrile neutropoenia , lower overall response rates and shorter Progression free survival.
• Is the technology a 'step-change' in the management of the condition?	Yes.
• Does the use of the technology address any particular unmet need of the patient population?	Greater and an earlier opportunity for possible discontinuation of therapy based on MRD assessment and achievement of MRD undetectable responses.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	During the dose escalation process there is an increased risk of Tumour Lysis syndrome Venetoclax is associated with well described, generally mild adverse reactions once the patient is taking a steady state dose. Rituximab is associated with first dose infusional related reactions which are well described and manageable.

Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	The NCRI Flair Trial randomises previously untreated patients to either Chemoimmunotherapy, Ibrutinib or combination Ibrutinib and Venetoclax.
• If not, how could the results be extrapolated to the UK setting?	The Flair trial is testing the hypothesis that patients who attain an MRD undetectable remission can safely discontinue therapy. These results may inform treatment discontinuation outwith clinical trials in the context of MRD undetectable responses to Venetoclax and Rituximab.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Progression free survival, time for next therapy and percentage achievement of MRD negativity were the important outcomes and were measured in the trial
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	none

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	none
21. How do data on real-world experience compare with the trial data?	The pivotal trial compared Venetoclax and Rituximab to Bendamustine and Rituximab. In the real world, patients with 17p deletion or TP53 mutation would be eligible for BCRi.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None
22b. Consider whether these issues are different from issues with current care and why.	Not applicable
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Prolonged progression free survival
- Higher MRD negativity
- Longer time for next therapy
- Better overall response rate
- Prolonged Event-free survival

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NHS England submission in September 2018 for the 1st meeting on the NICE appraisal of the combination of venetoclax and rituximab in patients previously treated for chronic lymphatic leukaemia (CLL)

1. NHS England notes the positive CHMP opinion granted in September 2018 for venetoclax in combination with rituximab being indicated for the treatment of adult CLL patients who have received at least one prior therapy. NHS England hopes (and expects) that the SPC will make it clear that the treatment duration should be for a maximum of 2 years as this is line with the key phase III trial (the Murano trial) which used a maximum of 2 years treatment duration with venetoclax plus rituximab.
2. NHS England notes that the company has positioned venetoclax plus rituximab as a alternative to ibrutinib in the population treated with 1 prior systemic therapy. NHS England considers this to be reasonable now that the CHMP opinion is known and that the majority of patients in the Murano trial (59%) had only 1-prior treatment.
3. NHS England welcomes both the design of the Murano trial in having a fixed duration of venetoclax plus rituximab and the intent of patients, clinicians and AbbVie to use this fixed duration in clinical practice. NHS England has been in extensive recent dialogue with CLL charities and CLL clinicians and is aware of the great interest and attraction of patients having the option of a fixed duration of treatment of venetoclax plus rituximab versus ibrutinib, a drug which is given continuously until disease progression. A significant proportion of patients (10-15%) cannot tolerate continuing on ibrutinib and many others suffer low grade ibrutinib toxicities for very extensive durations with consequent diminution of quality of life.
4. NHS England considers the population of patients in the Muarano trials to be generalizable to the population of patients who would potentially receive venetoclax plus rituximab in England.
5. For a disease such as CLL in the 1-prior therapy setting, a median duration of follow-up of 23.8 months is still relatively short. The rate of progression free survival (PFS) of 85% at 2 years with venetoclax plus rituximab is impressive though there are few patients at risk after 24 months. The results of the Murano trial are therefore immature in terms of the PFS achieved with venetoclax plus rituximab but the uncertainty is also compounded because little is currently known as to the durability of response once treatment has been discontinued at 2 years. Further follow up information is therefore vital to help guide patients and clinicians to be able to set this treatment in context of the treatment pathway. This issue also applies to the need to know how active ibrutinib is after venetoclax plus rituximab and also how active re-treatment is with venetoclax plus rituximab. There are clearly biologically plausible reasons for expecting non-cross resistance but actions always speak louder than words in treatment pathways which have increasing numbers of therapy options arriving within a relatively short time.
6. The Murano data for venetoclax plus rituximab is also exciting given that the rates of minimimal resisdual disease are high eg 60% at 18 months. Minimal residual disease status correlates with with both PFS and overall survival and also with the hope that such responses will be durable enough to give patients a significant time without both the symptoms of the disease and the side-effects of active therapy. This high rate of minimal residual disease is most unusual at the 2nd line setting in the CLL treatment pathway.

7. NHS England notes that in the matched adjusted indirect comparison (MAIC) of venetoclax plus rituximab versus ibrutinib using the Murano and Resonate trials, venetoclax plus rituximab has a similar PFS to ibrutinib but is superior in OS. This is counterintuitive. It is important to note that the Murano and Resonate trial poulations were very different. NHS England also notes the MAIC done using the Murano and Helios trials and that both PFS and OS of venetoclax plus rituximab versus ibrutinib are not statistically significantly different (in the Helios trial it is widely considered that the addition of bendamaustine plus rituximab to ibrutinib added toxicity but not benefit). NHS England therefore regards the outcome of the MAIC comparing Murano and Resonate data with considerable caution.
8. NHS England notes that the company does not appear to have included any post-progression costs in the economic model of venetoclax plus rituximab versus ibrutinib. If this is the case, then this is inappropriate as ibrutunib will potentially be used after venetoclax plus rituximab. Venetoclax monotherapy is currently available via the CDF for those who fail ibrutinib.
9. The life years gained (LYG) in the company's economic analysis for ventoclax plus rituximab (10.8 years) is very greatly in excess of that for ibrutinib (4.6 years). Yet the QALYs gained for venetoclax plus rituximab are much reduced at 5.7 wherease the QALYs achieved with ibrutinib reduce by a lesser factor to 3.1. NHS England doubts the accuracy of these estimations when an apparent increase in life of 6 years only brings 2.6 QALYs.
10. NHS England notes that the company has used a price of £786 per 500mg vial of rituximab. This is not likely to be the price of rituximab in use in NHS England: a price of [redacted] per 500mg vial is much more likely since biosimilar rituximabs are in widespread use.
11. NHS England notes that the wording of the CHMP conclusion potentially allows use of venetoclax plus rituximab after 1st line ibrutinib in the 17p deleted or TP53 mutated patients. The SPC may make this issue clearer but NHS England notes that such patients could access venetoclax monotherapy via the CDF on failing ibrutinib. Since rituximab does not appear to be very active (at least when combined with cytotoxic chemotherapy) in 17p deleted or TP53 mutated patients, it may be that the question of access of venetoclax plus rituximab to 17p deleted or TP53 mutated CLL patients is not a very important one.
12. NHS England confirms that the clinically relevant comparator to venetoclax plus rituximab in clinical practice is ibrutinib. Idelalisib plus rituximab is not used very ofeten as it is perceived to be less active than ibrutinib yet more toxic.
13. NHS England notes that all the patients in the Murabo trial were fit as 57% were of ECOG performance status 0 ad 42% of PS 1 and would recommend that if NICE approves use of venetoclax plus rituximab that this combination should be used in patients of PS 0 or 1.
14. NHS England also notes that only 77% in the Murano trial had previously received an anti-CD-20 antibody and only 2% had previously received ibrutinib/idelalisib.
15. NHS England would only wish to commission 2 years of treatment with venetoclax and rituximab as that is evidence base for the use of venetoclax plus rituximab in CLL patients with at least 1-prior therapy. NHS England is onfident that the commissioning mechanism to achieve this are present but also knows how keen patients and clinicians are for the fixed duration of therapy given how active ventoclax plus rituximab appears to be.
16. NHS England regards venetoclax plus rituximab as offering very promising but uncertain benefits at the expense of modest toxicity. There are many uncertainties as to the duration of PFS, duration of OS and subsequent treatments (esp the benefits of ibrutinib and re-

treatments with venetoclaxplus rituximab). NHS England therefore regards venetoclax plus rituximab as being a good candidate for the CDF on the basis of its clinical uncertainties.

Prof Peter Clark

Chair NHS England Chemotherapy Clinical Reference Group and CDF National Clinical Lead for the Cancer Drug Fund

September 2018

NICE National Institute for Health and Care Excellence

Clinical expert statement

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Peter Hillmen**
2. Name of organisation	**University of Leeds**

3. Job title or position	**Professor of Experimental Haematology and Honorary Consultant Haematologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☒ other (please specify): I am the Chair of the NCRI Haematological Oncology Clinical Study Group and currently of the NCRI CLL sub-group
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the	☐ yes

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim for the treatment of chronic lymphocytic leukaemia (CLL) is to achieve as deeper remission as possible which will then translate into a longer time to progression resulting in a prolongation of overall survival. Better remissions, including complete remissions and the eradication of detectable minimal residual disease, are associated with better outcomes and improved quality of life in CLL.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A clinically significant treatment response is the achievement of an objective response by International Workshop on CLL (IWCLL) criteria which equates to a partial remission or better. Such responses are expected to translate into more prolonged remissions. A partial remission by IWCLL criteria is in effect at least a 50% improvement in bulk of disease (lymphadenopathy and/or splenomegaly) as well as a significant improvement in cytopenias (if present).
9. In your view, is there an unmet need for patients and	In my opinion there is definitely an unmet need for patients with relapsed CLL. The majority of patients with relapsed CLL still die as a result of resistant disease. Patients with uncontrolled disease have a considerable both shortening of their life expectancy as well as a poor quality of life with heavy use of healthcare resources.

healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Patients with CLL who have failed to respond to, or have relapsed after, chemoimmunotherapy (CIT) are currently offered ibrutinib monotherapy which is supported by previous NICE Guidance and NHSE funding. Patients receive ibrutinib continuously until disease progression or intolerance of therapy. In this population of patients the median duration of treatment with ibrutinib is approximately 4 years with disease progression being the most common reason for treatment failure.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE Guidance from January 2017 (TA 429) Schuh *et al.* Guideline for the treatment of chronic lymphocytic leukaemia: A British Society for Haematology Guideline. *Br J Haematol.* 2018 Jul 15. doi: 10.1111/bjh.15460. [Epub ahead of print]
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is well defined after recent agreement with NHSE to implement the NICE Technology Appraisal (TA429). I believe that this pathway of care is widely agreed open by specialists in CLL.

• What impact would the technology have on the current pathway of care?	The major advantages of venetoclax plus rituximab compared to ibrutinib monotherapy in relapse after chemoimmunotherapy is that the majority of patients achieve the eradication of detectable CLL (minimal residual disease [MRD] negativity) and patients stop venetoclax after 24 months of therapy (unlike ibrutinib which is given continuously). There are some patients in whom there is a relative contraindication to ibrutinib, such as those on long-term anticoagulation and those with a history of significant cardiac disease, in whom venetoclax plus rituximab would definitely be preferred. In the remainder the choice between ventoclax plus rituximab and ibrutinib monotherapy would be patient and clinician choice. It is important to emphasize that the effect of the availability of venetoclax plus rituximab on the pathway will depend on the availability of ibrutinib for patients who progress after therapy. It is important to state that the two therapies, venetoclax plus rituximab and ibrutinib monotherapy, are both important treatments for CLL with different modes of action which both have a positive impact on the treatment and outcome for patients with CLL.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	At present venetoclax is being used as monotherapy in the NHS within the Cancer Drug Fund for patients who have either (1) failed CIT and ibrutinib; or (2) who have a 17p deletion or TP53 mutation (in whom CIT is ineffective) who have failed ibrutinib. When combined with rituximab the rate of MRD negativity increases from 15% to over 50% and this will lead to a change in practice from continuous single agent venetoclax to a fixed duration of 24 months of venetoclax. If the technology is implemented then as it is written then patients who present with 17p deletion or TP53 mutation and therefore receive ibrutinib as their first treatment will be treated with venetoclax monotherapy whereas those who develop 17p deletion or TP53 mutation after chemoimmunotherapy will be treated with venetoclax plus rituximab. This doesn't make sense as the former group would also experience better response to venetoclax plus rituximab. I believe that the combination therapy should be available to both groups of patients.
• How does healthcare resource use differ between the technology and current care?	There will be the addition of 6 doses of intravenous rituximab in the new technology which will have some cost (biosimilar rituximab is now widely used in the NHS) and an impact on day case activity. There will be a significant reduction in the duration of venetoclax therapy from continuous monotherapy until disease progression at present to a fixed duration of 2 years of venetoclax.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology should only by specialist haematologists or oncologists with experience of treating patients with CLL.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	To address the day case workload derived from the additional rituximab infusions. I anticipate this will be relatively minimal.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes the adoption of venetoclax plus rituximab will lead to improved survival for patients with CLL, limit the duration of therapy given from indefinite to a fixed duration of 2 years and improve patients' quality of life.
• Do you expect the technology to increase length of life more than current care?	Yes. This has been demonstrated in the MURANO Trial.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. This is because patients will spend more time in remission and off therapy.

13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I think that the technology is a significant advance for the general population of patients with relapsed CLL. The decision of whether to use ibrutinib monotherapy or venetoclax plus rituximab is difficult and will depend on individual patient's perspectives. There are some patients in whom ibrutinib monotherapy has a relative contra-indication, for example those on long-term anticoagulation or those with significant cardiac disease, in whom venetoclax plus rituximab is likely to be preferable to ibrutinib. In contract patients with significant renal dysfunction are probably better treated with ibrutinib.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Venetoclax is generally well tolerated by patients. The main issue is the initiation of therapy and the necessity to manage tumour lysis syndrome (TLS) in the first month of therapy. This requires regular hospital visits in the first 5 weeks of treatment with more intense monitoring. Approximately 3% of patients will experience laboratory tumour lysis and may need overnight admission as a result. The risk of TLS is no longer present after the patient has escalated to the full dose of venetoclax (after 5 weeks of therapy). As mentioned in Section 11 I believe that venetoclax plus rituximab should be also available for patients who present with 17p deletion or TP53 mutation and therefore receive ibrutinib as their first treatment who will at the moment only be treated with venetoclax monotherapy. There is no logical reason why this group of patients should receive less effective therapy (I,e monotherapy rather than combination therapy) than similar patients who have previously been treated with chemoimmunotherapy.

15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	There will be major benefits for the QALY due to the fixed duration of therapy compared to the standard of care at present. In addition patients tend to tolerate venetoclax well which will improve their compliance and outcome.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes the combination of venetoclax plus rituximab is innovative in that it leads to a high proportion of patients achieving the best possible remissions (the eradication of minimal residual disease) and is the first targeted therapy for CLL with a fixed duration of treatment.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes due to the fixed duration of therapy and eradication of MRD.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. The majority of patients with relapsed CLL will die as a result of resistant CLL to conventional therapies and this technology promises to have a major impact on this.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The expected side effects are of limited duration and are manageable.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. The UK was involved in the venetoclax trials and is now testing venetoclax combinations in our large front-line Phase III trial, the FLAIR trial. Over 100 hospitals in the UK are currently entering patients in the FLAIR trial.

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Improvement in progression free survival and overall survival. These were assessed in the trials.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator	No

treatment(s) since the publication of NICE technology appraisal guidance [TA429] and [TA359]?	
22. How do data on real-world experience compare with the trial data?	They are limited but similar
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
23b. Consider whether these issues are different from issues with current care and why.	No

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Venetoclax plus rituximab is more effective than venetoclax monotherapy
- Venetoclax plus rituximab offers the advantage of a defined duration of therapy in relapsed CLL
- The majority of patients achieve the eradication of detectable minimal residual disease in relapsed CLL which is not seen with other targeted therapies
- Venetoclax plus rituximab is well tolerated
- Venetoclax plus rituximab is an important new option for patients with CLL

Thank you for your time.

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Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]

Produced by: Warwick Evidence

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None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows

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Contributions of authors

Chidozie Nduka (Research Fellow) helped co-ordinate the report, and reviewed and critiqued the clinical effectiveness evidence; Felix Achana (Senior Research Fellow) reviewed and critiqued the indirect and matched adjusted indirect comparisons, and the cost-effectiveness evidence and undertook additional analyses; Daniel Gallacher (Research Associate) reviewed and critiqued the statistical and the survival analysis and undertook additional analyses; Xavier Armoiry (Senior Research Fellow) reviewed and critiqued the clinical effectiveness evidence and the indirect and matched adjusted indirect comparisons; Rachel Court (Information Specialist) critiqued the company searches and undertook additional searches; Kate Evans (Research Project Administrator) reviewed and critiqued the background section; Renata Walewska (Consultant Haematologist) provided expert clinical advice; Hema Mistry (Assistant Professor) co-ordinated the project and the report, and reviewed and critiqued the cost-effectiveness evidence.

Word count: 33,220 (including references and appendices)

Please note that: Sections highlighted in yellow and underlined are [redacted] Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.

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DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

Del(17p)	Deletion of the short arm of chromosome 17
AIC	Akaike information criteria
ALC	Absolute lymphocyte count
AEs	Adverse events
ALT	Alanine aminotransferase
AST	Aspartate Transaminase
BCRi	B-cell receptor inhibitor
BCSH	British Committee for Standards in Haematology
BR	Bendamustine plus rituximab
BSC	Best supportive care
BSA	Body surface area
CEAC	Cost-effectiveness acceptability curves
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
CIRS	Cumulative Illness Rating Scale
CIT	Chemo-immunotherapy treatment
CRCL	Creatinine Clearance
CR	Complete response rate
CRi	CR with incomplete hematologic recovery
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
CT	Computerised tomography
CTCAE	Common terminology criteria for adverse events
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EMA	European Medicines Agency

ERG	Evidence Review Group
EQ-5D-3L	EuroQoL five-dimension 3-level version
FCR	Fludarabine, cyclophosphamide, rituximab
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
IC	Indirect comparison
ICER	Incremental cost-effectiveness ratio
IDELA+R	Idelalisib in combination with rituximab
IGHV	Immunoglobulin heavy-chain variable
IPD	Individual patient data
IRC	Independent review committee
IV	Intravenous
iwCLL	International Workshop on Chronic Lymphocytic Leukaemia
KM	Kaplan-Meier
LCI	Lower confidence interval
LDH	Lactate dehydrogenase
LY	Life years
MAIC	Matched adjusted indirect comparison
MRD	Minimal residue disease
NCI	National Cancer Institute
NMA	Network meta-analysis
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PFS	Progression free survival
PH	Proportional hazards
PICOS	Population, intervention, comparator, outcome
PPS	Post-progression survival

PR	Partial response/remission
PSS	Personal social services
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
R/R	Relapsed or refractory
SAEs	Serious adverse events (SAEs)
SC	Subcutaneous
SLL	Small lymphocytic lymphoma
SUCRA	Surface under the cumulative ranking curve
TA	Technology appraisal
TLS	Tumour Lysis Syndrome
ToT	Time to treatment
TP53	Mutation in the TP53 gene
UCI	Upper confidence interval
VEN+R	Venetoclax in combination with rituximab

1 SUMMARY

Chronic lymphocytic leukaemia (CLL) is a cancer that starts in the blood stem cells. Stem cells are basic cells that develop into different types of cells that have different functions. As the stem cells of the blood develop, they become blast cells, which are immature blood cells. In leukaemia, there is an overproduction of blast cells. These blast cells do not develop into mature blood cells. Over time, the blast cells crowd out normal blood cells so that these normal cells are unable to perform their functions. When leukaemia is diagnosed, these blast cells may be called leukaemia cells. In lymphocytic leukaemias, these leukaemia cells develop from abnormal lymphoid stem cells.

Treatments for CLL include: watchful waiting, chemotherapy, targeted therapy, surgery, stem cell transplant, and supportive therapy. The type(s) of treatment offered is based on a number of factors including: stage, age, overall health, and personal preferences. The objective of the final scope to appraise the clinical and cost-effectiveness of targeted therapy (venetoclax in combination with rituximab) within its marketing authorisation for treating relapsed or refractory chronic lymphocytic leukaemia.

1.1 Critique of the decision problem in the company's submission

The company specifies that patients with relapsed or refractory (R/R) CLL were eligible to be included as part of the submission only if they previously received chemo-immunotherapy (CIT). While the final scope also describes patients with R/R CLL as the target population for the technology appraisal, the ERG clinical advisor considers that CLL patients with deletion of the short arm of chromosome 17 (del(17p)) / mutation in the TP53 gene (TP53 mutation) may never receive CIT, given that these patients receive ibrutinib as first-line in clinical practice. The intervention in the submission is venetoclax in combination with rituximab (VEN+R), which is the same as the final scope. Venetoclax is given until disease progression or unacceptable toxicity, or for a maximum duration of two years, whichever occurs first. While the two-year stopping rule seems arbitrary and not based on any empirical evidence comparing different stopping rules (e.g. 18 months versus 24 months), the ERG's clinical advisor agrees with the two-year stopping rule of venetoclax as it is anticipated that most patients would have achieved negative minimal residual disease (MRD) status by this time, otherwise a different line of therapy

must be considered. Single-agent ibrutinib or idelalisib-rituximab combination (IDELA+R) were the main comparators presented in the decision problem and final scope, with ibrutinib considered more clinically relevant by the ERG's clinical advisor: ibrutinib is more effective and less toxic compared to IDELA+R. The outcomes of interest (progression-free survival, overall survival, response rates, minimal residual disease status, adverse events, and health-related quality of life) were also clinically relevant and consistent with the final scope and trial evidence submitted (MURANO, RESONATE, and Study 116). Given that data from the key trial evidence (MURANO) was not mature enough to estimate the overall survival (OS), the ERG also agrees that progression free survival (PFS) was a reasonable primary endpoint. However, the ERG maintains that OS is a much more reliable outcome than PFS.

1.2 Summary of clinical effectiveness evidence submitted by the company

The MURANO trial of VEN+R compared against Bendamustine-Rituximab (BR) combination showed that the risk of progression or death (PFS) was reported to be significantly lower in the VEN+R group compared to the BR group after a median follow-up duration of 23.8 months, as assessed by the investigators (hazard ratio (HR), 0.17; 95% confidence interval (CI) 0.11 to 0.25) and by an independent review committee (HR 0.19; 95% CI 0.13 to 0.28). VEN+R was also superior to BR in terms of OS (HR 0.48; 95% CI 0.25 to 0.90) and MRD clearance rates in blood (absolute difference at any time during the trial 60.4%; 95% CI 52.3% to 68.6%) and bone marrow (absolute difference at any time during the trial 25.8%; 95% CI 19.0% to 32.6%). In the absence of a head-to-head trial comparing VEN+R to ibrutinib (or IDELA+R) and RCT evidence providing a comparator common to VEN+R and ibrutinib (or IDELA+R), the company also identified from the literature search other trials (RESONATE and Study 116) suitable for performing an unanchored matched adjusted indirect treatment comparison (MAIC). Respectively, the RESONATE and Study 116 trials showed ibrutinib and IDELA+R to be significantly more effective than their comparators (ofatumumab and rituximab-placebo).

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG had no major concerns over the statistical methods in MURANO, RESONATE and Study 116 trials. The ERG acknowledges that patients in MURANO who would not have been eligible for these comparator trials (RESONATE or Study 116) were appropriately excluded from

the MAIC. To adjust for any residual cross-trial differences in the MAIC, patients in the MURANO trial were weighted such that their weighted mean baseline characteristics matched those reported for the RESONATE and Study 116 trials.

The ERG reviewed the results of the unanchored MAIC with emphasis on the comparison of VEN+R with ibrutinib. These results showed that VEN+R has a [redacted] progression or death (PFS) events, however, this treatment effect remains statistically not significant given the wide confidence intervals in the hazard ratio ([redacted] For OS, the MAIC results showed that VEN+R lowered the rate of death events overall by [redacted] compared to ibrutinib ([redacted] Given this degree of contrast between the PFS and OS benefits, the ERG considers that the magnitude of the latter may not be realistic. Sensitivity analysis undertaken by the ERG indirectly comparing estimates of the treatment effect of VEN+R (from the MURANO trial) against single-agent ibrutinib (from a previously published indirect treatment comparison of ibrutinib vs BR vs ibrutinib+BR) validated the ERG's concerns: HRs = [redacted] and [redacted] for PFS and OS respectively.

1.4 Summary of cost-effectiveness submitted evidence by the company

The company conducted a systematic literature search to identify published cost-effectiveness studies and economic models, but found none comparing the cost-effectiveness VEN+R with ibrutinib or IDELA+R as treatment options for R/R CLL. Thus, the company developed a *de novo* partitioned survival model (consistent with the NICE reference case) to simulate lifetime economic costs and outcomes associated with the comparator interventions from the UK NHS and personal social services (PSS) perspective. The base-case model simulated survival outcomes for patients on VEN+R based on evidence from the MURANO trial with extrapolation over a lifetime horizon. In the model, this was assumed to be 30-years for an R/R CLL cohort with a mean age of 64 years. Survival outcomes for comparator interventions were generated by applying hazard ratios derived from unanchored MAIC comparisons to model predictions of outcomes for patients on VEN+R. The CS base-case applied a discount rate of 3.5% per annum to both costs and outcomes over the modelled time-horizon. The model suggested that VEN+R dominated ibrutinib (i.e. VEN+R was cheaper and generated more quality-adjusted life years

(QALYs) compared with ibrutinib). For the comparison with IDELA+R, the model generated an incremental cost-effectiveness ratio (ICER) of [redacted] per QALY gained for VEN+R. Based on list price comparisons, probabilistic sensitivity analysis suggested that VEN+R was close to [redacted] probability of being cost-effective at £20,000 per QALY compared to ibrutinib and over [redacted] probability of being cost-effective at £20,000 per QALY compared to IDELA+R. Sensitivity analyses suggest the ICER was mainly sensitive to the hazard ratio for overall survival, the modelled time horizon and the methods used to extrapolate survival outcomes over longer time horizon.

1.5 Summary of the ERG's critique of cost-effectiveness evidence submitted

The ERG found the company's approach to economic modelling appropriate and consistent with NICE reference case. The model structure is similar to economic models that informed two previous appraisals in CLL (TA359 and TA587). The ERG is satisfied with the approach used to estimate health-state utilities and adverse events disutilities. Costs relevant to the decision problem appears to have been appropriately accounted for in the model, although a minor error in calculation of intervention costs had meant that rituximab costs were included during (rather than after) the dose escalation stage of the VEN+R treatment regimen. As stated above, for the comparison with ibrutinib, the ERG had major reservations about robustness of the company's MAIC analyses, and believes any uncertainty in the hazard ratio would translate into uncertainties in cost-effectiveness that would be difficult to quantify. For the comparison with IDELA+R, the ERG does not believe evidence was presented to estimate efficacy of VEN+R vs. IDELA+R with a degree of confidence. Overall, the key drivers of cost-effectiveness were the OS hazard ratio, the methods used to extrapolate survival outcomes and the 2-year fixed treatment duration which considerably lowered treatment costs for VEN+R. The ERG believes these parameters are highly uncertain, the former because of the uncertainty emanating from the MAIC analysis mentioned above and the latter two, because the immaturity of the MURANO data meant no robust data is currently available to validate the 2-year fixed treatment duration.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The key strength of the company's submission relies on the appropriateness and good methodological quality of the trials included in the MAIC.

The ERG also confirms that no eligible study was missing from the MAIC.

The structure of the economic model is similar to economic models used in previous NICE technology appraisals of interventions in CLL. Health-state utility values were taken from previous NICE appraisal committees' most preferred base-case model in CLL (TA487) and a similar approach to estimation of disutility associated with adverse events was applied. Extensive sensitivity analyses suggests results were mostly robust to alternative parameter inputs and model assumptions considered in the CS.

1.6.2 Weaknesses and areas of uncertainty

The absence of head-to-head trials comparing VEN+R against single-agent ibrutinib is perhaps the most obvious weakness in the company's submission.

The ERG also considers that the immaturity of OS data from the MURANO trial is a major weakness in the company's submission as it contributes significantly to the implausible OS results in the MAIC, with OS reduced by [redacted] and PFS by [redacted]

The wide confidence intervals for the primary endpoint (PFS) HRs suggest that the treatment effect of VEN+R may be somewhat biased.

The ERG has major reservations about robustness of the companies MAIC analyses, and believes any uncertainty in the hazard ratio would translate into uncertainties in the cost-effectiveness analyses that are difficult to quantify.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG focused its exploratory analyses around HRs for PFS and OS for VEN+R vs. ibrutinib or IDELA+R and the methods used to extrapolate survival over a lifetime horizon. These are the main components of the company's economic model where ERG believed the evidence base was weakest, and the ERG identified these as the key drivers of cost-effectiveness in the CS sensitivity analyses. For the comparison with ibrutinib, the ERGs preferred a base-case model that used HRs generated from indirect comparison analysis, and joint-Gamma model to extrapolate survival outcomes, to suggest VEN+R was considerably cheaper (incremental costs of [redacted]) but also generated fewer QALYs (incremental QALYs of -0.39) compared with ibrutinib with an ICER of [redacted] per QALY lost based on list price comparisons. The ERG's exploratory base-case analyses were not conducted for the comparison with IDELA+R due to lack of robust evidence on the relative effectiveness of the two interventions.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The company submission (CS) provides an overview of chronic lymphocytic leukaemia (CLL) (CS section B 1.3.1). The CS correctly states that 'CLL is the most common of the chronic leukaemias'.[1] The CS describes CLL as a disease of unknown aetiology characterised by the accumulation of mature B lymphocytes in blood, lymph nodes, spleen, liver, and bone marrow. This description is broadly consistent with the final scope provided by the National Institute of Health and Care Excellence (NICE). According to the CS, this accumulation of B lymphocytes can lead to a wide variety of symptoms that manifest as fatigue, loss of appetite, weight loss, night sweats and shortness of breath on exertion. However, it should be noted that CLL is often asymptomatic and diagnosed by chance. The clinical pattern ranges from no treatment needed to rapid progression. These symptoms are also consistent with those described by the British Committee for Standards in Haematology (BCSH).[2] The CS identifies recurrent genetic abnormalities (deletions or mutations) as the main cause of CLL. The disease is subject to clonal variation during the disease course (due to mutation of the tumour suppressor gene TP53) which mediates resistance to chemotherapy. TP53 dysregulation is observed in 5-10% of untreated CLL patients and present in 40-50% of patients with refractory disease. The ERG finds research to support these statements.[3]

There were 3,709 new diagnoses of CLL in 2015 which is slightly higher than reported in the CS.[4] The ERG agrees that the age-standardised incidence of CLL is 6.5 per 100,000.[4] Based on a study by Shanafelt et al (2010), the company states that survival of CLL patients is observed to be significantly shorter than that of the age-matched general population ($p < 0.001$).[5] However, this study was conducted in Minnesota, USA. The company does not provide incidence statistics by age or survival rates. According to Cancer Research UK, CLL incidence is strongly related to age, with the highest incidence rates being in older people. In the UK in 2013-2015, on average each year more than 4 in 10 (43%) of new cases were in people aged 75 and over'.[6] More so, the five-year survival rate for men in the UK is 51% - 72% and 73% - 81% for women.[7]

The company provides an overview of the disease burden (CS section B.1.3.2) for symptomatic CLL patients. They discuss reduction of health-related quality of life (HRQoL) and attribute it primarily to disease progression and fatigue, which the ERG verifies to be accurate.

2.2 Critique of company's overview of current service provision

The current treatment of CLL is outlined in section B.1.3.4 and is consistent with the final scope. The CS makes reference to NICE guidance and guidelines published by the BCSH. Key recommendations are summarised in CS Table 3 and pathways shown in Table 3 and Figure 1. The current treatment pathway depends on diagnosis and previous treatments. Venetoclax monotherapy is recommended by NICE technology appraisal (TA) guidance TA487 as a second line treatment for patients with del(17p) and/or TP53 mutation experiencing disease progression after receiving B-cell receptor inhibitor (BCRi) treatment.[8] NICE TA429 recommends ibrutinib for patients who have had at least 1 prior chemo-immunotherapy treatment (CIT).[9] This is in alignment with the final scope. Additionally, NICE TA359 recommends idelalisib in combination with rituximab for adults with relapsed or refractory (R/R) CLL disease.[10] However, the CS states that ibrutinib is the more commonly used BCRi therapy due to toxicity concerns associated with idelalisib and ibrutinib being more effective than idelalisib in combination with rituximab (IDELA+R). The ERG clinical advisor agrees that this treatment strategy reflects the current position of the National Health Service (NHS).

Unmet need

The CS considers the high unmet need for the treatment of CLL patients with relapsed or refractory disease and high risk genetic subtypes (including TP53 dysregulation). They describe a need to identify effective therapies with alternative mechanisms of action and acceptable side effect profiles (CS section B.1.3.1). The CS states that early intervention with chemotherapy does not improve the natural history of the disease, may drive clonal evolution and later treatment resistance and hence, therapy is only recommended for patients with rapidly progressive or symptomatic disease. The company suggests that once treatments are stopped, due to disease progression and no other treatment options available, survival is poor (CS section B.1.3.2). The company also details that there is increased negative impact on both the patients' and their carers' HRQoL as the disease progresses. They highlight an increased economic burden reporting that

R/R CLL patients have the highest resource use among CLL patients (CS section B.1.3.2),), which the ERG clinical advisor suggests is plausible.

Furthermore according to the CS (section B.1.3.5) patients post CIT with deletion of the short arm of chromosome 17 (del(17p)) / mutation in the TP53 gene (TP53) have fewer treatment options than non-del(17p)/TP53 patients. BCRi therapies (e.g. ibrutinib) are highly effective in this subgroup, but are associated with an indefinite treatment period and do not result in high rates of undetectable minimal residue disease (MRD). Therefore, the CS finds there is an unmet need for therapies demonstrating improved survival outcomes in both del(17p)/TP53 and non-del(17p)/TP53 sub-populations and that demonstrate potential to achieve MRD-negative status.

Treatment pathway of VEN+R

The company anticipates venetoclax in combination with rituximab (VEN+R) is likely to be used for patients with CLL who have received at least one prior therapy (CS section B.1.3.5, figure 1) within the UK NHS, specifically post-CIT. However, the ERG clinical advisor disagrees with the positioning of VEN+R in the treatment pathway for patients with del(17p) and/or TP53 mutation because CIT is generally not considered a treatment option in these patients.

3 Critique of company's definition of decision problem

The company described the decision problem in Table 1 of the submission (CS, pg 15-17).

3.1 Population

In their decision problem, the company describes adults with R/R CLL as the target population for the technology appraisal, which is broadly consistent with the final scope and the trial populations in the key evidence submitted.[11-13]

Following consultations with their clinical experts, the company further specify that patients were eligible to be included as part of the submission only if they previously received chemo-immunotherapy – in line with the anticipated position of the technology (VEN+R) in the treatment pathway for R/R CLL in the UK (CS, Figure 1). However, the ERG is concerned that restricting the target population to patients post CIT potentially excludes CLL patients with del(17p) and/or TP53 mutation. In this high-risk subgroup, the ERG clinical advisor questions the position of VEN+R as illustrated in the proposed treatment pathway in the CS (CS Figure 1). The ERG clinical advisor considers that patients with del(17p)/TP53 mutation CLL may never receive CIT, given that these patients receive BCRi therapy (ibrutinib) as first-line in clinical practice.

Although the company recognises ibrutinib as the mainstay for the first-line treatment of del(17p)/TP53 mutation CLL as recommended in NICE TA429, they maintain that a small number of these patients receive CIT as first-line treatment (CS pg 26). The ERG considers this evidence to be largely anecdotal, and should not have informed the population selection in the decision problem.

3.2 Intervention

The intervention in the submission is venetoclax in combination with rituximab, which is the same as the final scope. The company provides a description of the technology and the mechanism of action of venetoclax (CS Table 2, pg 18) which the ERG's clinical advisor confirms to be accurate. According to the summary of product characteristics, VEN+R is indicated for the treatment of adult patients with CLL who have received at least one prior

therapy. Venetoclax is initially administered (orally) in weekly dose increments up to 400 mg at week 5. At this time, rituximab is commenced simultaneously as a monthly injection up to a total of six months/cycles (375 mg/m^2 in the first cycle and 500 mg/m^2 in cycles 2 to 6). From week 5 onwards, venetoclax is given at a dose of 400 mg daily up to a maximum of two years. The ERG clinical advisor agrees with this two-year stopping rule, irrespective of the treatment outcome, as time limited treatment would increase compliance, would be a more acceptable option to some patients and reduce the cost of the treatment. However, it is anticipated that most patients would have achieved negative MRD status by this time.

3.3 Comparators

Ibrutinib and IDELA+R were listed comparators in the decision problem and final scope. The CS stated that in the absence of head-to-head trials comparing VEN+R with ibrutinib or IDELA+R, together with the absence of randomised controlled trial (RCT) evidence that could have enabled an indirect treatment comparison using network meta-analysis, the company carried out a matched adjusted indirect comparison (MAIC) of VEN+R versus single-agent ibrutinib.

In contrast to the final scope, the company deemed best supportive care (BSC) inappropriate as a comparator in the appraisal, while asserting that BSC is only reserved for later lines of therapy after all treatment options have failed. The ERG clinical advisor agrees that BSC is the last course of action given for palliation as opposed to disease modification.

Although venetoclax monotherapy was not included in the NICE scope and therefore was not discussed by the company, the ERG's clinical advisor has emphasized that venetoclax monotherapy appears to have a more favourable safety profile compared to ibrutinib, and is the mainstay of treatment in CLL patients who do not tolerate ibrutinib irrespective of TP53 mutation status.

3.4 Outcomes

The outcomes of interest in the final scope match those specified in the decision problem as well as trial evidence submitted.

The ERG has noted that its clinical advisor considered MRD to be the single most important clinical indicator to assess in trials in patients with CLL, emphasising strongly that a MRD negative status is the closest a patient gets to a cure. However, the company did not provide MAIC analyses of the MRD status, when the ERG requested this at the clarification stage.

The ERG also agrees that progression free survival (PFS) was a reasonable primary endpoint considering that data from the MURANO trial was not mature enough to estimate the overall survival (OS) and that PFS is a valid surrogate outcome for OS.[14]

3.5 Other relevant factors

The CS reports that there are no equality issues presented by VEN+R. The company also anticipates that the European Medicines Agency (EMA) license for VEN+R will be issued in [redacted].

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The company undertook a broad systematic review aimed at identifying randomised and non-randomised clinical trials investigating the clinical effectiveness of VEN+R and comparator interventions for treating patients with R/R CLL. Comparator interventions include those defined in the company decision problem for this submission and many others as reported in CS Table 5, pg 29. One trial of VEN+R (MURANO) was identified and considered relevant to the decision problem.[11] Overall the ERG found the company's systematic review to be of reasonable quality. Table 1 summarises the ERG's quality assessment of the company's systematic review.

Table 1: Quality assessment of the CS systematic review of clinical effectiveness

CRD Quality Item	Yes/No/Uncertain with comments
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all relevant research?	Yes
3. Is the validity of included studies adequately assessed?	The validity of the MURANO trial alone was assessed, including issues pertaining to the external validity of the study outcomes (CS Table 10, pg 39).
4. Is sufficient detail of the individual studies presented?	Sufficient details were presented for the MURANO trial alone
5. Are the primary studies summarised appropriately?	The MURANO trial alone was summarised appropriately.

4.1.1 Searches (Description of company's search strategy)

Although the company did not search trial registers and Health Technology Assessment (HTA) agencies for studies eligible for their systematic review, the ERG considers the literature searches to be comprehensive using a number of relevant bibliographic databases (such as MEDLINE and Embase via the ProQuest interface). The searches ─ undertaken on 21 July 2017 and updated on 30 April 2018 ─ were conducted using appropriate search terms; without any restriction on publication date (except for the 2014 publication date limit applied to the search for conference proceedings); and excluded published letters, notes, errata and editorials. While restricting the searches to studies published in English language may have introduced some language bias, the ERG has found no missing relevant studies published in a different language. The ERG also

reviewed the list of studies excluded from the MAIC and deemed them irrelevant to the company's decision problem and final scope. However, of the 49 studies potentially eligible for the MAIC (CS Figure 1, pg 32), the ERG could only review 48 full-texts provided by the company at the ERG's request (Clarification Response C1). Nonetheless, additional searches undertaken by the ERG identified no missing studies that were relevant to the decision problem.

4.1.2 Inclusion/exclusion criteria used in the study selection

Eligibility criteria for the CS systematic review are summarised in CS Table 5, pg 29. Adults with established R/R CLL were eligible for the company's systematic review, which matches the NICE final scope. However, the inclusion criteria for the target population is broader than the company's decision problem, which specifies that the target population must include patients who have received prior chemo-immunotherapy. The ERG critiqued the rationale for this distinction in section 3.1. The interventions (VEN+R), comparators (ibrutinib and IDELA+R) and study outcomes listed in the final scope and decision problem were also specified as part of the inclusion criteria.

4.1.3 Critique of data extraction

The ERG considers that the company conducted the study selection (two independent reviewers with third reviewer/strategic advisor resolving discrepancies) and data extraction (two independent reviewers with third reviewer/strategic advisor resolving discrepancies) appropriately. However, no information is provided on the method of data extraction.

4.1.4 Quality assessment of key trials

The company provided a quality assessment of its own MURANO trial using the minimum criteria for assessing risk of bias in RCTs as set out in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the NICE single technology appraisal user guide (CS Table 13, pg 46). In addition, the company addresses issues about the generalisability of the trial findings to clinical practice in England. The ERG conclude that these are sufficient, however, the company has not presented quality assessments of the RESONATE[12]

and Study 116[13] trials in the main submission. Table 2 summarises the ERG's critique of the company's quality appraisal for MURANO.

Although the MURANO trial was open-label using two different routes of administration for VEN+R (oral venetoclax + intravenous rituximab) and one route for BR (intravenous), the ERG considers that this trial need not have been open-label as oral placebos could have been administered in the BR arm.

The company suggests that the MURANO trial is reflective of clinical practice in England because BR was considered the most effective treatment for managing R/R CLL patients with del(17p) at the time the trial was initiated.

Table 2: Quality assessment of the MURANO trial

Question	Company's response	ERG's response	Rationale for ERG's response	ERG's rationale for discrepancy
Was randomisation carried out appropriately?	Yes.	Yes	Participants were randomised 1:1 using a web-based randomisation system	N/A
Was the concealment of treatment allocation adequate?	The MURANO trial was open label, using two different methods of administration (oral or intravenous (IV))	Unclear	Protecting the allocation sequence before and until assignment is not described, but an Interactive Voice/Web Response System is used to randomize patients, which may also serve this purpose.	Allocation concealment was not reported in the submission or MURANO protocol or report
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Baseline characteristics were similar between treatment arms	N/A
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	No	This was an open label trial which suggests that the participants and investigators were not blind to treatment allocation. However, the ERG maintains that the outcome assessors could have been blinded.	N/A
Were there any unexpected imbalances in drop-outs between groups?	No	No	Although there was a significant difference in withdrawal rates between	N/A

			VEN+R and BR (4% vs 10%, $p < 0.02$), the ERG is not surprised about this given the open-label nature of the trial. The ERG would be more concerned if withdrawal rates were much higher in the VEN+R arm compared to BR, especially considering that BR is administered for a total of six 28-day cycles and VEN+R is given for two years.	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	All efficacy outcomes reported in the results were pre-specified in the protocol	N/A
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Although seven patients in the BR arm withdrew from the trial just after randomisation, these patients were accounted for in the efficacy analyses	

4.1.5 Evidence Synthesis

In the absence of a head-to-head trial comparing VEN+R to any of the comparators listed in the final scope, the company sought to perform a matched adjusted indirect comparison of VEN+R against these comparators by screening the search records for relevant comparator trials. Two trials (RESONATE and Study 116) were identified for this purpose and deemed relevant to the decision problem.

The ERG considers that the criteria for including studies in the MAIC as stated in CS section B.2.9.3 (pg 43 and 44) are not exhaustive. For instance, while the company states that study outcomes and follow-up duration of survival data had to be similar between MURANO and its comparator trials, it is not stated that trial populations had to be comparable across these trials. Nonetheless, the ERG also considers that the aim of MAIC is to create comparable groups by using the IPD of one to remove people till the remaining group matches the recruits in the other trial.

Although no formal quality appraisal was presented for the MAIC, the ERG considers that inclusion/exclusion criteria were fairly matched across the MURANO, RESONATE and Study 116 trials. For instance, all included patients must have been treated previously for CLL and have an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1. Patients in the MURANO trial who would not have been eligible for the RESONATE and Study 116 trials, were appropriately excluded from the MAIC.[15] Only quantitative effect-modifiers (prior to matching) were selected as baseline matching characteristics for the MAIC, the ERG considers this method of variable selection to be sufficiently rigorous. However, the ERG is unable to determine how the RESONATE and Study 116 trials were assessed for availability of individual patient-level data as implied in the CS (Section B.2.9.4, pg 67).

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

Evidence for the clinical effectiveness on VEN+R comes from a single pivotal RCT. The MURANO trial (ClinicalTrials.gov Identifier: NCT02005471) was a phase III open-label, multicentre, active treatment controlled RCT sponsored by the company. The results are currently being reviewed by the EMA as part of the process aimed to extend marketing authorisation of venetoclax, which is already licensed for treating CLL as a single agent. The trial was designed to investigate the use of venetoclax in combination with rituximab (VEN+R) in patients with R/R CLL.

The dosing schedule for VEN+R is described in section 3. Interestingly, unlike single agent ibrutinib which is licensed for the same indication as VEN+R (patients with R/R CLL), venetoclax is given for a maximum of two years. The comparator in the MURANO trial was bendamustine plus rituximab (BR) where bendamustine was given intravenously (70mg/ m^2 on days one and two of each 28-day cycle) and rituximab was administered as described for VEN+R in section 3.

The MURANO trial was commenced in March 2014 and all participants were randomised by September 2015. The clinical cut-off date was May 2017. The randomisation ratio was 1:1 between treatment arms and stratified according to del(17p) status, responsiveness to previous

therapy, and geographic region. Cross-over to the VEN+R arm in the event of disease progression was not allowed, however, treatment post-progression was at the investigators' discretion. Key inclusion criteria are reported in CS Table 7 (pg 33) including age ≥18 years, CLL with R/R status, no more than three previous treatments, and an ECOG performance status score of 0 or 1. Key exclusion criteria were: (a) receiving warfarin or any strong inhibitor of the cytochrome P450 family of enzymes responsible for metabolising most prescribed drugs; b) aggressive forms of CLL with central nervous system involvement; c) previous allogeneic or autologous stem-cell transplant. The ERG considers that these inclusion/exclusion criteria are appropriate.

A flow-chart of the participants in the MURANO trial was presented in CS pg 41. Of the 389 randomised patients in the trial, 382 (98%) received at least one dose of the assigned treatment, including 194 in the VEN+R arm and 188 in the BR arm. Twenty-eight patients withdrew from the trial: eight in the VEN+R group and 20 who were randomised to the BR group. The difference in withdrawal rates was significant (4% vs 10%, $p < 0.02$). However, the ERG would be more concerned if withdrawal rates were much higher in the VEN+R arm compared to BR, especially considering that BR is administered for a total of six 28-day cycles and VEN+R is given for two years.

After a median follow-up duration of 24.8 months, 78 of the 194 patients who received at least one dose of either venetoclax or rituximab remained on treatment, however, 68 participants already completed the two-year venetoclax treatment. Forty-eight patients in the VEN+R arm discontinued venetoclax with or without rituximab, including 10 patients who stopped following disease progression or relapse and 24 patients who discontinued treatment as a result of adverse events (AEs) (clarification response A7). Patients in the BR arm were also assessed and followed similarly as patients in the VEN+R arm. After a median follow-up duration of 22.1 months in the BR group, 154 of 188 patients who received at least one dose of either bendamustine or rituximab completed the treatment schedule. Expectedly, there were fewer discontinuations in the BR arm (n = 27) given the relatively shorter course of treatment. However, the main reasons for BR discontinuations were also disease progression or relapse (n = 6) and AEs (n = 11).

The baseline characteristics of patients enrolled in MURANO are reported in Table 3. Although it would appear that patients were seemingly healthy (as determined by CLL staging and ECOG

scores) entering into the trial, the ERG notes that there were no meaningful differences in demographic or disease characteristics between VEN+R or BR groups at baseline. The ERG requested clarification for Rai staging at diagnosis for 64 patients in the VEN+R group and 55 patients in the BR group who had not been accounted for. The company responded by providing Binet staging for these missing patients instead (clarification response A2). Although the degree of concordance between these staging systems remains uncertain, the ERG notes that the distribution of patients across the Binet stages are roughly comparable to patient distribution across the Rai stages, and are similar between VEN+R and BR groups. The ERG also requested a breakdown of the patients by country and geographical region in order to determine how applicable the findings were to the UK population. Although there were only 10 patients from the UK (six in VEN+R and four in BR), about two-thirds of the trial population were of European descent (130 in VEN+R and 131 in BR), which eased the ERG's concerns (clarification response A5). The ERG clinical expert also considers that the population of the MURANO trial was generalisable to UK population.

Table 3: Summary of baseline characteristics of MURANO patients

Period of enrolment	March 2014 to Sept 2015	
Characteristic	**VEN+R (n=194)**	**BR (n=195)**
Male n (%)	136 (70.1)	151 (77.4)
Age Median (min–max)	64.5 (28–83)	66.0 (22–85)
ECOG score of 0 / 1	111 (57.2) / 82 (42.3)	108 (55.7) /84 (43.3)
ECOG score of 1		
Rai staging Stage 0–II / Stage III–IV	88 (67.7) / 30 (23.1)	103 (73.6) / 18 (12.9)
Del(17p) status present	46 (26.6)	46 (27.2)
TP53 mutation status, n (%)		
N	192	184
Mutated	48 (25.0)	51 (27.7)
Unmutated	144 (75.0)	133 (72.3)
Del(17p) vs. TP53 mutation status, n/N (%)	171	158
Only del(17p)	24 (14.0)	18 (11.4)

TP53 mutation only	19 (11.1)	23 (14.6)
Del(17p) and TP53 mutated	22 (12.9)	22 (13.9)
Immunoglobulin heavy-chain variable (IGHV) Mutated	53 (29.4)	51 (28.3)
Risk status with regards to responsiveness to prior therapy, n (%)		
High	109 (56.2)	118 (60.5)
Low	84 (43.3)	75 (38.5)
Number of prior CLL therapy, n (%)		
1 previous line	111 (57.2)	117 (60.0)
2 previous lines	57 (29.4)	43 (22.1)
3 previous lines	22 (11.3)	34 (17.4)
>3 previous lines	4 (2.1)	1 (0.5)
Type of prior CLL therapies, n (%)		
Alkylating agent	182 (93.3)	185 (95.4)
Purine analogue	157 (80.5)	158 (81.4)
Anti-CD20 antibody	153 (78.5)	148 (76.3)
B-cell receptor inhibitors	3 (1.5)	5 (2.6)

4.3 Description and critique of company's outcome selection

The NICE scope lists the specified outcomes as:

- progression-free survival (PFS)
- overall survival (OS)
- response rates
- minimal residual disease (MRD) negative rate assessed in blood and bone marrow
- adverse effects of treatment
- health-related quality of life (HRQoL).

In the MURANO RCT, PFS was assessed by investigators (investigator-assessed PFS), which was the primary endpoint, and by an independent review committee (IRC-assessed PFS) and this was a secondary endpoint. In both cases, PFS was defined as the time from randomisation to the first occurrence of progression or relapse using the International Workshop on Chronic Lymphocytic Leukaemia (iwCLL) guidelines[16, 17] or death from any cause, whichever occurs first.

On Table 9 of the CS, the company has reported the protocol criteria for response based on 2008 iwCLL guidelines. These guidelines include parameters related to tumour load (lymphadenopathy, hepatomegaly, blood lymphocytes count, marrow infiltration) and to function of hematopoietic system or marrow (platelets and neutrophils counts, haemoglobin level).

On page 38 of the CS, the company has acknowledged that PFS can be affected by timing of assessments and can be prone to investigator bias but has stated that the use of strict criteria for response evaluation was implemented in the MURANO RCT. To evaluate disease status, patients were evaluated through computerised tomography (CT) scans of target lesions, blood counts and physical examinations of indicator lesions in up to six of the largest dominant nodes or tumour masses as well as in six extra-nodal lesions. The same was done for non-target lesions.

While the ERG agree that there was a strict protocol in place to assess disease status by investigators and that investigator-assessed PFS is a more relevant to the clinical practice, the ERG believe that IRC-assessed PFS was more preferable to investigator-assessed PFS as the former suggests that the outcome assessors were blinded to treatment allocation, reducing the potential for bias.

OS was defined as the time from randomisation to death from any cause.

To monitor HRQoL, the company used the EuroQoL five-dimension 3-level version (EQ-5D-3L) which was collected at regular intervals before progression, once at progression, and once at the first assessment following progression.

MRD negative rate was assessed through the clearance rate of MRD from blood or marrow samples. However, not all patients had both blood and bone marrow testing. Although the company reports a high level of concordance among patients who had both blood and bone marrow testing, the ERG is concerned that more patients had MRD peripheral blood testing than bone marrow because bone marrow is considered more sensitive than peripheral blood for MRD detection in CLL.[18]

Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.

Overall, the outcomes selected in the CS are consistent with those identified by NICE as relevant to the decision problem.

4.4 Summary and Critique of MURANO Trial Statistics

The company's approach to trial statistics is presented in CS section B.2.4. Generally, statistical analyses entailed the use of stratified log-rank tests or stratified Cochran-Mantel-Haenszel tests, both of which were suitable for the design of the trial. Hazard ratios (HR) were obtained using stratified Cox proportional hazards (PH) models, however, no assessment of the proportional hazards assumption was made within the clinical effectiveness section of the company's submission.

The ERG reproduced a similar sample size calculation to that presented by the company and are satisfied that the trial was suitably powered to detect the specified difference in the primary outcome (HR of 0.66 in PFS). The results presented by the company were based on interim analyses planned after 140 events (75%) had occurred:[11] there were 146 reported events in the MURANO trial. The interim analyses were reviewed by an independent data monitoring committee, who recommended that the primary analysis be performed at this data cut-off. The final analysis was originally planned for the trial after 186 events had occurred. The interim analysis was also originally planned to be implemented 12 months after the final patient was enrolled into the study, however this was amended in version six of the study protocol.

For the primary outcome (investigator-assessed PFS), the company mention adjusting their significance level at 0.05 when performing a stratified log-rank test, however, no further detail was provided on this adjustment in their submission. Upon examining the clinical study report (CSR) provided by the company, the ERG discovered that the significance level at the primary endpoint was actually 0.0498, whereas a significance threshold of 0.002 was set for the interim analysis performed after 140 events had occurred. Nonetheless, as the interim analysis has become the primary analysis, the ERG do not believe this has any major consequence on the type-1 error rate of the trial outcomes.

The log-rank tests were stratified by del(17p) status, CLL risk status, and geographic region. The company also implemented a fixed sequence testing procedure which was not referred to in their submission. The following secondary endpoints were tested in the order presented:

- Complete response rate (CR) based on IRC assessment in all randomised patients (0.05 threshold, 2-sided)
- Overall response rate (ORR) based on IRC assessment in all randomized patients (0.05 threshold, 2-sided)
- OS in all randomized patients (0.0001 threshold, 2-sided)

Formal hypothesis testing would stop when one of the outcomes was not significant. The ERG is unsure why other secondary outcomes were not included in the fixed-sequence procedure, notably the proportion of patients achieving MRD-negativity. The final hypothesis test on OS is planned to be conducted 3 years after the final patient has been enrolled, and will use a 2-sided threshold of 0.0499, however this endpoint has not yet been reached. IRC-assessed PFS of patients with 17p deletion was originally included in the fixed sequence testing procedure, however this secondary outcome was excluded in version 4 of the statistical analysis plan. This secondary outcome, as well as the other secondary outcomes were tested at the 0.05 significance threshold which could have increased the likelihood of a Type 1 error.

Treatment allocation was performed using a block stratified randomisation procedure, which was deemed suitable by the ERG.

The ERG examined the approaches to trial statistics of the RESONATE and Study 116 trials, due to their importance in the indirect treatment comparison.

RESONATE (ibrutinib): This trial was assessed by an ERG during the TA429 appraisal of ibrutinib. The statistical analyses in the submission were based on Cox-models and log-rank tests, similar to the RESONATE study. The ERG for TA429 had no major concerns over the trial statistics.

STUDY 116 (IDELA+R): This trial was assessed by Warwick ERG during the TA359 appraisal of idelalisib in combination with rituximab. The approach to trial statistics was also similar to the RESONATE study, and entailed Cox-PH models and log-rank tests. The ERG of TA359 did not report any major concerns with the approach to trial statistics in Study 116.

Overall, the ERG has no major concerns over the approach to individual trial statistics of MURANO, RESONATE or STUDY 116.

4.5 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

4.5.1 Effectiveness

In this section, the ERG has summarised and critiqued the results from the MURANO trial.

The key results, including survival outcomes (PFS and OS) and response outcomes, are summarised in Table 4 and discussed in the following sections. In the table, the results are reported differently, some as number, some as %. There is little difference between investigators and IRC.

Table 4: Main survival outcomes

	VEN-R	BR
Number of patients	194	195
Median follow-up period	23.8 months	
Progression free survival (PFS): progression assessed by <u>investigators</u> (primary endpoint)		
Number of progressions or deaths	32	114
Median PFS (months)	Not reached	17
HR for progression or death (95% confidence interval (CI)) p-value	0.17 (0.11, 0.25) <0.0001	
Progression-free rates: % (95% CI)		
at 1 year	93 (NR)	73 (NR)
at 2 years	84.9 (79.1, 90.6)	36.3 (28.5, 44.0)
Progression free survival (PFS): progression assessed by <u>IRC</u> (secondary endpoint)		
Number of progressions or deaths	NR	NR
Median PFS (months)	Not reached	18.1
HR for progression or death (95% CI) p-value	0.19 (0.13, 0.28) <0.0001	
Progression-free rates: % (95% CI)		
at 1 year	NR	NR
at 2 years	82.8 (76.6-88.9)	37.4 (29.4-45.4)
Overall survival (OS)		
Number of deaths	NR	NR
Median PFS (months)	Not reached	Not reached
HR for death (95% CI) P value	0.48 (0.25, 0.90) NR	
OS rates: % (95% CI)		
at 1 year	NR	NR
at 2 years	91.9 (NR)	86.6 (NR)

NR: not reported in company submission; VEN-R: venetoclax rituximab; BR: bendamustine rituximab; IRC: independent review committee

4.5.1.1 Progression-free survival

Following a median of 23.8 months of controlled follow-up, the risk of progression or death was significantly lower in the VEN+R group compared to the BR group, irrespective of whether PFS was assessed by investigators (primary endpoint) (HR, 0.17; 95% confidence interval (CI): 0.11 to 0.25; $p < 0.0001$) or by an IRC (secondary endpoint) (HR 0.19; 95% CI: 0.13 to 0.28; $p < 0.0001$). These results were robust to sensitivity analyses conducted by the company.

4.5.1.2 Overall survival

The risk of death was significantly decreased in the VEN+R group compared to the BR group despite the limited duration of follow-up (HR, 0.48; 95% CI: 0.25 to 0.90; p = NA). However, OS results were still immature given that median OS was not reached in both arms.

4.5.1.3 Response outcomes including MRD outcomes

The rate of complete response (CR) or CR with incomplete hematologic recovery (CRi) was 18.6% higher ($p < 0.0001$) in the VEN+R arm compared to BR when assessed by investigators (see Table 5). However, there was no statistically significant difference in CR/CRi rates between VEN+R and BR when assessed by the IRC. On page 50 of the CS, the company has provided a reason for this discrepancy between the investigators and IRC indicating that there was a difference in the interpretation of residual adenopathy on CT especially regarding lesions measuring ≤30mm. The ERG clinical advisor agrees with the company's rationale.

Table 5: Main response outcomes including MRD outcomes

	VEN-R	BR
Response outcomes:		
Assessed by IRC		
CR / CRi: % (95% CI)	8.2 (NR)	3.6 (NR)
Difference on CR / CRi: % (95% CI) ; p-value	4.7 (-0.3 to 9.6); <0.081	
ORR: % (95% CI)	92.3 (87.6 to 95.6)	72.3 (65.5 to 78.5)
Difference on ORR: % (95% CI); p-value	20.0 (12.4 to 27.6); <0.0001	
Assessed by investigators		
CR / CRi	26.8 (NR)	8.2 (NR)
Difference on CR / CRi: % (95% CI) ; p value	18.6 (NR); <0.0001	
ORR: % (95%CI)	93.3 (88.8 to 96.4)	67.7 (60.6 to 74.2)
Difference on ORR: % (95% CI); p-value	25.6 (17.9 to 33.3); <0.0001	
Clearance rates of MRD:		
Based on peripheral blood samples		
At 9-months time point: n (%)	121 (62.4)	26 (13.3)
Absolute difference: % (95% CI) ; p-value	49.0 (40.4 to 57.6); NR	
At any time during the trial: n (%)	162 (83.5)	45 (23.1)
Absolute difference: % (95% CI); p-value	60.4 (52.3 to 68.6); NR	
Based on bone marrow aspirate		
At any time during the trial: n (%)	53 (27.3)	3 (1.5)
Absolute difference: % (95% CI); p-value	25.8 (19.0 to 32.6); <0.0001	

Overall response rate was improved (although non-significantly so) in the VEN+R group compared to the BR group, irrespective of whether ORR was assessed by investigators (absolute difference of 25.6%, 95% CI 17.9 to 33.3) or by an IRC (absolute difference of 20.0%, 95% CI 12.4 to 27.6).

Patients in the VEN+R group achieved higher clearance rates of MRD based on peripheral blood samples (absolute difference of 60.4%, 95% CI 52.3 to 68.6 at any time of the trial) and on bone marrow aspirate (absolute difference of 25.8%, 95% CI 19.0 to 32.6 at any time of the trial).

Although MRD assessments of bone marrow aspirates were only available for 29.6% (n = 115) of patients and peripheral blood MRD assessments available for 94.1% (n = 366), the company asserts that the level of concordance between MRD status in peripheral blood and bone marrow was 84.3% based on 108 pairs of post baseline samples across both treatment groups (82.5% for the VEN+R treatment group matching 85.3% for the BR treatment group). The ERG agrees with this assertion.

4.5.1.4 Health-related quality of life (HRQoL)

In the MURANO trial, HRQoL was measured using the EQ-5D-3L version questionnaire. On page 56 of the CS, it is indicated that only 35% of patients in the VEN+R group completed baseline patient-reported outcomes due to an undetected protocol error. Upon request, the company provides a breakdown of utility data by treatment arm, which revealed that patients in the VEN+R arm did not have a worse HRQoL than patients in the BR arm (Clarification Response A12). However, the ERG considers that this finding may have been influenced by the open-label nature of the MURANO trial. Overall, the ERG believes that the reliability of HRQoL outcomes is questionable.

4.5.1.5 Subgroup analyses

The company has presented a number of analyses by predefined subgroups in CS page 59 for the primary endpoint, investigator-assessed PFS.

These subgroups were:

- Age (<65 vs ≥65 yrs)
- CLL risk status (low vs high)
- Geographical region
- Number of previous therapies (1 vs 2 vs ≥3)
- Effect of most recent therapy
- Del(17p) status
- TP53 mutation status
- Baseline immunoglobulin heavy-chain variable (IGHV) mutation status

Results based on these pre-defined subgroups did not identify any subgroups more or less likely to benefit significantly from VEN+R. For instance, the risk of death or progression as assessed by the investigators was significantly higher in the VEN+R arm than the BR arm among R/R CLL patients with positive (HR 0.13, 95% CI 0.05 to 0.29) and negative (HR 0.19, 95% CI 0.12 to 0.32) 17p deletion status alike. Similarly, R/R CLL patients with TP53 mutation (HR 0.15, 95% CI 0.09 to 0.25) and non-mutation (HR 0.19, 95% CI 0.10 to 0.36) experienced significantly higher rates of death or progression in the VEN+R arm compared to the BR arm. Overall, the treatment benefit of VEN+R over BR was consistent across all subgroups.

4.5.2 Safety

Table 6 compares the safety of VEN+R and BR. Overall, there were more AEs in the VEN+R arm (n = 335) than in the BR arm (n = 255). Discontinuation rates due to AEs were also significantly higher in the VEN+R arm compared to BR (12.4% versus 5.9%, p = 0.03). However, it is not specified in the CS or CSR if AEs were treatment-related. The ERG also notes that the EMA is yet to ascertain the safety of VEN+R.

Grade 3 or 4 adverse events

Although the proportions of all patients with grade 3 or 4 AEs, defined using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) criteria (Protocol, pg 111), were significantly higher in the VEN+R arm compared to BR (82% versus 70.2%, P = 0.007), the only grade 3 or 4 AE with a significantly higher occurrence in VEN+R compared to BR was neutropenia (57.7% versus 38.8%, P = 0.0002). In this condition, the serum concentrations of white blood cells called neutrophils are decreased below the normal range, predisposing the patient to a number of infections. However, the ERG agrees that the low neutrophil count can easily be corrected if treated promptly; this is consistent with previous evidence analysing the safety of VEN+R.[19] The percentages of the other grade 3 or 4 AEs were either comparable between treatment arms (infections, anaemia, thrombocytopaenia, tumour lysis syndrome (TLS) and grade 3 or 4 AEs with less than 2% difference in incidence between VEN+R and BR) or significantly higher in the BR arm (febrile neutropaenia, infusion-related reaction and hypotension).

Serious adverse events (SAEs)

SAEs were broadly described as life-threatening or fatal according to the NCI CTCAE. Again, the proportions of SAEs were either similar between treatment arms or significantly higher in the BR arm. However, the ERG is unsure why the number of patients diagnosed with SAE pneumonia (n = 16) is greater than the number diagnosed with Grade 3 or 4 pneumonia in the VEN+R arm (n = 10). The ERG would expect fewer occurrences of SAEs compared to grade 3/4 AEs as is the pattern with other SAEs listed in CS Table 23.

Safety of VEN+R versus ibrutinib

The company has not compared the safety profile of VEN+R against any of the comparators in the scope. There are also no trials that directly compare AEs between VEN+R and ibrutinib or IDELA+R. However, the ERG clinical advisor suggests that the side effect profile of venetoclax is favourable compared to its key comparator ibrutinib. The ERG clinical advisor also suggests that the two-year stopping rule of VEN+R makes this intervention more attractive than ibrutinib which is administered indefinitely until disease progression.

Table 6: Summary of Adverse Events

Event	VEN+R (n=194)	BR (n = 188)	ERG-calculated p-values
Grade 3 or 4 AE — no. of patients (%)	159 (82.0)	132 (70.2)	0.01
Total no. of events	335	255	
Discontinuations due to AEs	24	11	0.03
Grade 3 or 4 AEs with at least 2% difference in incidence between groups — no. of patients (%)	130 (67.0)	104 (55.3)	0.02
Neutropenia	112 (57.7)	73 (38.8)	<0.001
Infections and infestations	34 (17.5)	41 (21.8)	0.29
Anaemia	21 (10.8)	26 (13.8)	0.37
Thrombocytopenia	11 (5.7)	19 (10.1)	0.11
Febrile neutropenia	7 (3.6)	18 (9.6)	0.02
Pneumonia	10 (5.2)	15 (8.0)	0.26
Infusion-related reaction	3 (1.5)	10 (5.3)	0.04
TLS	6 (3.1)	2 (1.1)	0.17
Hypotension	0	5 (2.7)	0.02
Hyperglycaemia	4 (2.1)	0	0.05
Hypogammaglobulinemia	4 (2.1)	0	0.05
SAEs — no. of patients (%)	90 (46.4)	81 (43.1)	0.52
SAEs with at least 2% incidence in either group — no. of patients (%)	47 (24.2)	76 (40.4)	<0.001
Pneumonia	16 (8.2)	15 (8.0)	0.92
Febrile neutropenia	7 (3.6)	16 (8.5)	0.04
Pyrexia	5 (2.6)	13 (6.9)	0.04
Anaemia	3 (1.5)	5 (2.7)	0.45
Infusion-related reaction	1 (0.5)	6 (3.2)	0.05
Sepsis	1 (0.5)	4 (2.1)	0.17
TLS	4 (2.1)	1 (0.5)	0.19
Hypotension	0	5 (2.7)	0.02
Fatal AEs	10 (5.2)	11 (5.9)	0.76

4.6 Critique of comparator trials identified and included in the indirect comparison and/or multiple treatment comparison

To reiterate, RESONATE and Study 116 were included as comparator trials in the MAIC.

Table 7 compares the study methods between MURANO and the comparator trials. The baseline characteristics of patients in MURANO, RESONATE and Study 116 are compared in Tables 100 (Appendix D1.1.8.2, pg 67) and 103 (Appendix D.1.1.8.3, pg 74) of the company's appendices, and are discussed in section 4.7.

To summarise, the RESONATE trial was a multicentre, open-label, phase 3 study in which 391 patients with R/R CLL or small lymphocytic lymphoma (SLL) were randomly assigned to receive daily oral ibrutinib until disease progression or toxicity occurs, whichever comes first, or weekly (and subsequently monthly) intravenous ofatumumab for up to 24 weeks. At baseline, a significantly higher proportion of patients in the ibrutinib group had bulky disease ≥ 5cm compared to the ofatumumab group (64% versus 52%, $p = 0.04$), and the median time from the last treatment received prior to enrolment in the trial was four months shorter in the ibrutinib arm compared to the ofatumumab arm (8 mo versus 12 mo, $p = 0.02$). However, there were no other significant differences between the two groups at baseline. The primary endpoint was duration of PFS as assessed by an IRC, whereas OS duration and ORR were key secondary endpoints. The results show ibrutinib to be superior to ofatumumab. At a median follow-up of 9.4 months, the median PFS duration had not been reached in the ibrutinib arm, as compared to 8.1 months in the ofatumumab arm (HR 0.22, $p < 0.001$). Similarly, ibrutinib significantly improved OS (HR 0.43, $p = 0.005$) and ORR (42.6% versus 4.1%, $p < 0.001$). The statistical analyses in the trial were based on Cox- proportional hazard models and log-rank tests, which the ERG deems appropriate. The ERG also agrees with the company's quality assessment of RESONATE as presented in Table 110 of CS Appendix D1.3, and judges the trial to be of good quality.

Study 116 was a randomised, double-blind, placebo-controlled, phase 3 trial in which 220 patients with decreased kidney and bone marrow function were randomised to receive rituximab in combination with either idelalisib (IDELA+R) or placebo (placebo + rituximab). Although the baseline characteristics, as presented in the published trial, were comparable between treatment arms, the ERG is unsure how similar at baseline the proportions of patients with kidney and bone marrow diseases (or any other co-existing conditions) are between idelalisib and placebo. The primary endpoint was PFS and the secondary endpoints included OS and ORR. An independent data and safety monitoring board stopped the trial at the first pre-specified interim analysis following results of the overwhelming efficacy of idelalisib: median PFS was 5.5 months in the

placebo group but had not been reached in the idelalisib group (HR 0.15, $p < 0.001$). The statistical analyses in the trial were based on Cox- proportional hazard models and log-rank tests, which the ERG deems appropriate. The ERG also agrees with the company's quality assessment of RESONATE: although Study 116 is a double-blind randomised trial, the risk of selection bias in this study may be high as details of the randomisation procedure and allocation concealment are not reported (CS Appendix D1.3, Table 110).

Table 7: Comparison of study methods across the MAIC trials

	MURANO	**RESONATE**	**STUDY 116**
Comparators and dose	Venetoclax (ramped up to 400 mg per day, oral) + rituximab vs Bendamustine + rituximab	Ibrutinib (420 mg once daily, oral) vs Ofatumumab	Idelalisib (150 mg twice daily, oral) + rituximab vs Placebo + rituximab
Location	109 sites in 20 countries including US, Canada, Australia, New Zealand, and countries in Europe and Asia	67 sites in the United States, Australia, and seven European countries	90 Centres in US and Europe
Trial Design	1:1 multicentre randomised, open-label, phase 3 trial	1:1 multicentre randomised, open-label, phase 3 trial	1:1 multicentre randomised, double blind phase 3 trial
Eligibility Criteria	18 years of age or older Diagnosed with R/R CLL that also required therapy Received one to three previous treatments (including one or more chemotherapy-containing regimens) ECOG score of 0 or 1 Adequate bone marrow, kidney, and liver function Patients who had received previous treatment with bendamustine were eligible provided that the duration of response after the treatment was at least 24 months.	Patients with previously treated CLL or SLL who require therapy were eligible Unsuitable for purine analogue therapy (e.g. patients with short progression-free interval after chemoimmunotherapy, co-existing illnesses, 70 years of age or more, or presence of 17p deletion). ECOG score of 0 or 1 Absolute neutrophil count of at least 750 cells per microliter Platelet count of at least 30,000 cells per microliter	Patients with CLL that had progressed within 24 months after their last treatment Unsuitable for cytotoxic therapy (e.g. severe neutropenia or thrombocytopenia caused by cumulative myelotoxicity from previous therapies, an estimated creatinine clearance of less than 60 ml per minute, or a CIRS score on the Cumulative Illness Rating Scale (CIRS) of 6 or more for coexisting illnesses not related to CLL

		Adequate liver and kidney function Patients requiring warfarin or strong CYP3A4/5 inhibitors were excluded.	Previous treatment must have included either a CD20 antibody-based regimen or at least two previous cytotoxic regimens.
Outcomes of interest	PFS OS IRC PFS ORR CR MRD clearance Event-free survival (EFS) Duration of Response Time to next treatment	PFS OS ORR	PFS OS ORR CR Lymph Node Response HRQoL
Crossover details	Crossover was not permitted in the trial design.	Patients on Ofatumumab were able to switch to ibrutinib following disease progression	Patients on placebo were able to switch to idelalisib following disease progression.
Randomisation strata	Presence or absence of chromosome 17p deletion Responsiveness to previous therapy Geographic region	Resistance to purine analogue therapy (defined as no response or a relapse within 12 months after the last dose of a purine analogue) Presence or absence of chromosome 17p deletion	Presence or absence of 17p deletion and/or TP53 mutation Presence or absence of unmutated IGHV
Subgroups	Age (<65y vs ≥65y) CLL risk (low vs high)[a] Geographic Region (North America vs Asia vs Western Europe vs Central/Eastern Europe vs Australasia) Number of previous therapies (1 vs 2 vs ≥3) Presence or absence of chromosome 17p deletion TP53 mutation status	Age (<65y vs ≥65y) Gender (male vs female) Race (white, non-white) Geography (Europe vs USA) Rai Stage (0-2 vs 3-4) ECOG Score (0 vs 1) Bulky disease (<5cm vs ≥5cm)	IGHV (mutated vs unmutated) Presence or absence of 17p deletion and/or TP53 mutation Presence or absence of 17p deletion Gender (male vs female) Age (≤65y vs >65y)

	IGHV mutation status Effect of most recent therapy (relapse vs refractory)	Number of previous treatments (<3 vs ≥3) Presence or absence of chromosome 17p deletion Presence or absence of 11q22.3 deletion Baseline β_2 microglobulin level (≤ 3.5mg/L vs >3.5mg/L Resistance to purine analogue therapy (yes *vs* no)	

[a] High-risk CLL status was defined as any of the following: presence of 17p deletion, no response to front-line chemotherapy-containing regimen, relapsed disease with 12 months of chemotherapy alone, or relapsed disease within 24 months of chemoimmunotherapy.
CIRS, Cumulative Illness Rating Scale: The CIRS score ranges from 0 to 56, with higher scores indicating an increased number or greater severity of coexisting illnesses.

4.7 Critique of the indirect comparison and/or multiple treatment comparison

Using individual patient data (IPD) from the RESONATE and HELIOS trials, Hillmen and colleagues published an indirect comparison of ibrutinib-BR combination versus BR versus single agent ibrutinib.[20] However, the company states in CS section B.2.9.4 that IPD were neither available for RESONATE nor for Study 116. Hence, the MAIC entailed comparison of aggregate data from RESONATE and Study 116 with IPD from MURANO.

Clinical trial selection

The RESONATE and MURANO trials were both open-label with similar inclusion/exclusion criteria, whereas Study 116 was a double-blind trial with contrasting criteria: while patients with adequate kidney and bone marrow function were eligible for inclusion in MURANO and RESONATE, such patients were excluded from Study 116. Table 8 and Table 9 compare other characteristics between the trials. As shown, there were cross-trial differences in a number of baseline characteristics including age, Rai stage, ECOG score, bulky disease status and Beta-2 Microglobulin concentration. Without IPD from the comparator trials in the MAIC, the ERG is concerned that there may still be residual unobserved differences and potential sources of bias even after matching.[15] Nonetheless, the ERG regards the implementation of the MAIC as reliable.

Identification of outcome measures

The primary end-points in MURANO and RESONATE were assessed differently: investigator-assessed PFS was the primary outcome in the MURANO trial, whereas PFS was assessed by the IRC in the RESONATE trial. In the indirect comparison of these trials, the ERG considers that the IRC-assessed PFS IPD in MURANO (a secondary end-point in the trial) should have been reanalysed to match the IRC-assessed PFS in RESONATE.[15] However, as illustrated in CS Table 20 (pg 70), the outcome measure used was investigator-assessed PFS. The MURANO IPD matched the primary outcome measure used in Study 116 (CS Table 20, pg 70).

Matching trial populations

Fifty-six patients in the MURANO trial (25 in the VEN+R arm versus 31 in the BR arm) who had an ECOG score of > 1 or received prior B-cell receptor inhibitor therapy were excluded from the indirect comparison because these patients would have been ineligible for the published RESONATE trial. Similarly, 54 patients in the MURANO trial (24 in VEN+R versus 30 in BR) who would not have been eligible to be included in Study 116 were excluded from the indirect comparison.

To adjust for residual cross-trial differences, patients in the MURANO trial were weighted such that their weighted mean baseline characteristics matched those reported for the RESONATE and Study 116 trials. While previous evidence supports this approach to matching,[15] the ERG is concerned about the marked deviation of the matched sample characteristics (such as age, Rai stage, bulky disease status, prior therapy status, ECOG score, and Beta-2 microglobulin concentration) and sample size from the original MURANO trial population (N = 194 in VEN+R arm). It is also unclear what informs the arbitrary significance threshold of 0.25 used for selecting variables/effect-modifiers on which trials were matched. However, the ERG acknowledges that the trials were matched on the relevant prognostic factors of R/R CLL.

Network of evidence

A schematic of the evidence network for the relevant comparators in the MAIC is presented in CS Figure 13. The evidence network shows there was no common comparator connecting all the

treatments in the included trials (VEN+R, ibrutinib, IDELA+R). Hence, the evidence network was disconnected and unanchored MAIC analyses were performed to estimate the relative effectiveness of VEN+R over ibrutinib (and IDELA+R) and inform the base-case HRs for PFS and OS (clarification response A10).

However, the company acknowledges that there is a higher risk of residual bias associated with performing an unanchored MAIC, and sought to perform an exploratory anchored MAIC analysis for testing the robustness of the unanchored MAIC results. An anchored MAIC is a standard indirect treatment comparison with a common comparator for the treatments in the network, and the company uses evidence from the MURANO (VEN+R versus BR) and HELIOS (ibrutinib+BR versus placebo+BR)[21] trials to perform this exploratory analysis because BR is the common comparator in both trials. The ERG agrees with this approach to sensitivity analysis, but disagrees that the effect estimates from the unanchored MAIC were consistent with the anchored MAIC results. More so, ibrutinib monotherapy, and not ibrutinib+BR, is the specified comparator in the final scope and decision problem. The company justifies using ibrutinib+BR in the anchored MAIC by citing Hillmen and colleagues who found single agent ibrutinib to be as effective as ibrutinib+BR for treating patients with R/R CLL.[20]

Table 8: Baseline characteristics of the trial populations in the MURANO and RESONATE trials before and after matching

Characteristics	Before matching		After matching	
	VEN+R MURANO	Ibrutinib RESONATE	VEN+R MURANO	Ibrutinib RESONATE
	(N=169)[a]	(N=195)	(N=62)[b]	(N=195)
Age ≥65	50.89%	60.51%	60.51%	60.51%
Rai stage III-IV	27.22%	55.90%	55.90%	55.90%
Bulky disease ≥5cm	43.79%	63.59%	63.59%	63.59%
Prior therapy >1	43.79%	82.05%	82.05%	82.05%
Chromosome 11q del	35.50%	33.16%	33.16%	33.16%
Chromosome 17p del	27.22%	32.31%	32.31%	32.31%
ECOG=1	45.56%	59.49%	59.49%	59.49%

IGVH=Mutated	29.59%	26.87%	26.87%	26.87%
β2-microglobulin>3.5 mg/L	64.50%	83.71%	83.71%	83.71%
Prior Purine Analog	80.47%	85.13%	85.13%	85.13%
Prior AntiCD20	73.96%	93.85%	93.85%	93.85%

[a] 25 patients with prior BCRi therapy, ECOG>1, and no central lab measurement for assessing del(17p) status were excluded from the VEN+R IPD population (N = 194) before matching. [b] About two-thirds of the VEN+R IPD population were unmatched to the ibrutinib arm of RESONATE. The ERG deemed the comparator arms in the trials (BR and ofatumumab) irrelevant to the table.

Table 9: Baseline characteristics of the trial populations in the MURANO and Study 116 trials before and after matching

Characteristics	**Before matching**		**After matching**	
	VEN+R MURANO	**IDELA+R Study 116**	**VEN+R MURANO**	**IDELA+R Study 116**
	(N=170)	**(N=110)**	**(N=53)**	**(N=110)**
Age ≥65	50.59%	80.91%	80.91%	80.91%
Rai stage III-IV	27.06%	67.37%	67.37%	67.37%
Prior therapy >1	56.47%	75.00%	75.00%	75.00%
Chromosome 11q del	35.88%	34.00%	34.00%	34.00%
Chromosome 17p del	27.06%	23.64%	23.64%	23.64%
IGVH=Mutated	29.41%	17.27%	17.27%	17.27%
β2-microglobulin>3.5 mg/L	64.12%	85.45%	85.45%	85.45%

[a] 24 patients with prior BCRi, ECOG>1, and no central lab measurement for assessing del(17p) status were excluded from the VEN+R IPD before matching. [b] About two-thirds of the VEN+R IPD population were unmatched to the IDELA-R arm of Study 116. The ERG deemed the comparator arms in the trials (BR and ofatumumab) irrelevant to the table.

Results from the MAIC analyses

The results from MAIC comparisons undertaken by the company are presented in CS Tables 20 and 21. The ERG has reviewed those regarding the VEN+R vs ibrutinib comparison given that single-agent ibrutinib has been acknowledged as the most relevant comparator to VEN+R: the ERG clinical advisor confirms that ibrutinib is considerably more effective than IDELA+R and is better tolerated. Based on adjusted comparisons, VEN+R is thought to reduce the risk of

progression or death compared to ibrutinib, although the difference is not statistically significant (PFS HR [redacted] 95% CI [redacted]); regarding the OS outcome, VEN+R was found to reduce the risk of death compared to ibrutinib, this reduction reached statistical significance (OS HR [redacted] 95% CI [redacted]).

The ERG was surprised by the magnitude of this result suggesting a [redacted]% reduction for the risk of death with VEN+R relative to ibrutinib. The magnitude of this benefit is in marked contrast to the CS MAIC results for PFS where VEN+R reduces the risk of progression or death by only [redacted]% compared to ibrutinib (this difference is not statistically significant).

For most RCTs conducted on cancer drugs, except those comparing immune checkpoint inhibitors to conventional chemotherapy treatment, there is usually a notable correlation between PFS and OS indicating that a positive benefit in PFS should translate into a positive benefit in OS, in other words, PFS is often thought to be a valid surrogate outcome to OS.[14] This is one of the reasons why in a number of cancer trials undertaken in people with early stage/moderately advanced disease stage, PFS is usually taken as primary endpoint, while OS, is chosen as secondary endpoint. Based on recent RCTs for drugs tested in patients with R/R CLL, one can observe the correlated trend between PFS and OS benefits (Table 10): a large benefit on PFS (low HR) seems to translate into a lower benefit (higher HR) in OS.

Table 10: Comparison of PFS and OS outcomes in R/R CLL

Study	Treatment 1	Treatment 2	PFS HR $_{1 \text{ vs } 2}$	OS HR $_{1 \text{ vs } 2}$
HELIOS[21]	Ibrutinib+BR	BR	0.20	0.63
MURANO[11]	VEN+R	BR	0.19	0.48
RESONATE[12]	Ibrutinib	Ofatumumab	0.22	0.43
Company's MAIC	VEN+R	Ibrutinib	[redacted]	[redacted]

However, these observed relationships between PFS and OS are at odds with the results of the company's MAIC, where a moderate (non-significant) reduction of the risk of progression or death translates into a very high reduction for the risk of death. A similar relationship has

previously not been observed and the ERG believes that nothing in the mechanism of action of VEN+R could explain these apparently incoherent and illogical results.

A crude indirect comparison between ibrutinib and BR using the MAIC results and VEN+R as a common comparator would suggest that the risk of death is reduced by approximately [redacted] with BR compared to ibrutinib (the OS HR for VEN+R vs BR is [redacted] while the MAIC calculated OS HR for VEN-R vs IBRU is [redacted]), which again appears to be implausible and contrasts with ibrutinib becoming the gold standard for treating people with R/R CLL since its recommendation in 2016.[9]

In the cost-effectiveness section, the ERG will further demonstrate the non-plausibility of OS HRs estimates from the MAIC by examining the predicted life expectancy for ibrutinib obtained through the cost-effectiveness model that used results from the MAIC. Given the OS HR from the MAIC which were deemed implausible, the ERG requested at clarification stage the set of data used by the company to undertake the analyses. The ERG used the data and MAIC code provided to reproduce and critique the MAIC performed by the company.

Critique of the MAIC Implementation

To reiterate, a MAIC can be used to compare two treatments when IPD is available for one treatment of interest, and summary data available for another treatment of interest. Either through the use of a common comparator (anchored) or not (unanchored), the MAIC estimates the efficacy of the treatment with IPD available in the population of the treatment with summary data. This is a cause for concern, as the company have estimated that the relative efficacy of VEN+R compared to ibrutinib in the population of the RESONATE trial through estimation of a hazard ratio, and assumed that the relationship will be identical in the MURANO trial population. The company have not discussed this assumption and the potential flaws. As previously demonstrated by AbbVie and Novartis, a MAIC conducted on the same two treatments, but from different perspectives can yield different estimates of relative efficacy (e.g. depending on which treatment you have IPD for, and numbers after matching).[22, 23] Hence, it is important to carefully consider the population of interest, and may not be appropriate to assume generalisability of a relative treatment effect from one trial population to another. It is also evidence that it is unlikely that all prognostic and treatment-effect modifiers are completely accounted for.

In an unanchored MAIC, it is important to include both prognostic and treatment modifiers, in order to allow adjustment for differences in trial population.[24]

In the company's selection of covariates, they specify a threshold of 0.25 for p-values of tests of prognostic factors and of interaction with treatment effect in MURANO. The ERG acknowledges that there is precedence for applying a 0.25 significance threshold when selecting a complete set of potential predictors,[25] however there are concerns that this may lead to the inclusion of variables that are having an interactive effect only by chance, without any true interactive effect with treatment. The additional concern of the ERG is the dichotomisation of several continuous or categorical variables, resulting in a potential large loss of information. The ERG understand that this was likely done to reduce the number of categories matched, thus increasing the sample size; however, this could result in, for example, a participant aged 65 being assumed equal to a participant aged 85, yet they will likely have considerably different life expectancy. With the dichotomised variables containing heterogeneous populations, there is no guarantee that the distribution of these variables is well matched after performing the MAIC.

The ERG scrutinised the MAIC approach conducted by the company, to verify that there were no major mistakes which could explain the implausible HR. The ERG found one error in the data extraction from RESONATE relating to the β2 microglobulin > 3.5mg/litre proportion. The correct proportion is 153/195 and not 298/356[12]. When the unanchored adjusted MAIC is re-run, the impact is minor (sample size of the VEN+R IPD 62 to 61; [redacted]

The covariates that met the prognostic criteria for association can be found in Table 11, alongside covariates that met the treatment interaction threshold.

The company examined other trials which presented data on treatment interactions, also shown in Table 11.

The company then reached the conclusion that the variables which met either of the following criteria would be considered as effect modifiers in their MAIC:

- MURANO variables with association $p<0.25$ when interacted with treatment.
- Some evidence of potential effect modifying status in comparator trial publication.

The ERG are concerned that some relevant prognostic factors may not have been included in the economic model, as they are not specifically considered in these criteria. They would only have been included if they were also a treatment-effect modifier. The ERG are also concerned about the lack of inclusion of modifiers which appear to meet the company's inclusion criteria. These were absolute lymphocyte count (ALC), creatinine clearance (CRCL), response duration of recent therapy, refractory to last anti-leukaemia therapy, BCRi and ZAP70 expression. It is possible that this is down to a lack of corresponding data in the comparator trials, however this is not discussed by the company. The ERG is concerned that despite the matching, there may remain considerable imbalances between excluded variables reported in Table 11 and other unmeasured variables, potentially biasing the analysis and contributing to the implausible estimates of treatment effect. In addition, the criteria have been selected based on their influence on the PFS outcome, yet are used in both PFS and OS MAICs. Whilst the immaturity may have prevented an OS based analysis, the company do not seem to have considered this approach, and assumed a direct relationship between OS and PFS.

Table 11: Comparison of potential MAIC factors from company's search

	MURANO prognostic modifiers	MURANO treatment effect modifiers	External study treatment effect modifiers	Covariates included for matching by company
Variables	• **Age** • Hispanic ethnicity • TLS risk • **bulky disease** • risk status • **central lab measurements for del(17p)** • 12 trisomy • chromosome 13 deletion • CRCL • **TP53 mutation** • **IGHV mutation** • refractory to last chemo-containing therapy • refractory to last anti-leukaemia therapy, • fludarabine refractory • **number of prior CLL treatments** • **prior purine analogue agent** • **prior anti-CD20** • time from first diagnosis • time from last prior therapy to randomization • time to randomization	• **Age** • **ECOG**, • **bulky disease** • ALC • **chromosome 11q deletion** • CRCL • **Beta-2 microglobulin** • **IGHV mutation** • response duration to recent therapy, • refractory to last anti leukaemia therapy • **number of prior CLL therapies**, • **prior purine analogue agent** • prior BCRi.	• **Age**, • **Rai stage** • **ECOG** • **Chromosome 11q deletion** • **IGHV** • ZAP70 expression • **number of prior therapies** • **Beta-2 microglobulin** • **del(17p) or TP53 mutation**.	• Age • Rai Stage • Bulky Disease • Number of prior treatments • Chromosome 11q deletion • Del(17p) or TP53 mutation • ECOG • IGHV Mutation • Beta-2 microglobulin • Prior Purine • Prior Anti CD20

	from relapse since last line of treatment.			
Included in Matching	8/20	8/13	8/9	11/11

Bold indicates variable was included in company's matching.

4.8 Additional work on clinical effectiveness undertaken by the ERG

For the purpose of cost-effectiveness modelling, the ERG has proposed another method to estimate the relative benefit of VEN+R compared to ibrutinib given the implausible OS findings obtained from the MAIC.

The ERG agrees with the company's network of evidence for drugs used in R/R CLL presented in CS Figure 14, which suggests that there is no sufficient evidence to indirectly compare ibrutinib to VEN+R using results from RCTs.

However, the ERG has identified an abstract by Hillmen et al.[20] that compared single-agent ibrutinib to BR. This abstract was cited in the CS but the company did not use the results presented from this abstract for the purpose of comparing ibrutinib to BR. In this study, the authors use IPD data from the RESONATE and HELIOS RCTs to compare the efficacy of ibrutinib against BR after adjusting for a number of covariates, namely age, gender, Rai staging, ECOG score, del(11q) status, refractory status, number of prior lines of therapy, bulky disease, IGVH status. Results from this indirect comparison are reported in Table 12.

Table 12: Indirect comparison of ibrutinib versus BR

Study	**Treatment 1**	**Treatment 2**	**PFS HR** $_{1 \text{ vs } 2}$	**OS HR** $_{1 \text{ vs } 2}$
Hillmen et al. (2015)[20]	BR	Ibrutinib	7.52 (95% CI 4.72- 11.99)	2.24 (95% CI 1.14 -4.4)

Although the Hillmen et al. (2015)[20] results have not been obtained from a direct comparison, the use of IPD and appropriate methods of adjustment was deemed by the ERG to provide reasonable estimates of the ibrutinib vs BR comparison. Therefore, the ERG has decided to undertake

exploratory analyses to provide more robust estimates for the key clinical effectiveness outcome measures between ibrutinib and VEN+R. This was done using BR as common comparator.

The ERG compared hazard ratio (95% CI) estimates for PFS and OS across these two studies. For PFS outcomes, we used estimates obtained from IRC analyses. We used the package '*network*' in Stata 15[26] to conduct a network meta-analysis (NMA). Because this package operates in a frequentist paradigm, there was no need to perform sensitivity analysis on prior distributions. Given that the network was very sparse, we used a fixed-effects model. We used a common heterogeneity model, where the between-studies variance is assumed equal across comparisons. Since there was no mixed (direct + indirect) comparisons between interventions, there was no need to check networks for inconsistency. We did not present any rankograms or surface under the cumulative ranking curve (SUCRA) scores for these interventions.

PFS network meta-analyses

The data we used for the NMA for PFS are presented in Table 13.

Table 13: Data used in the ERG's NMA for PFS

Study	**Year**	**Treatment 1**	**Treatment 2**	**PFS_HR$_{1vs2}$**	**PFS_HR_ LCI$_{1vs2}$**	**PFS_HR_ UCI$_{1vs2}$**
Murano	2018	VEN+R	BR	0.19	0.13	0.28
Hillmen RESONATE+HELIOS	2015	BR Ibrutinib	Ibrutinib BR	7.52 0.13	4.72 0.083	11.99 0.211

LCI – lower confidence interval; UCI – upper confidence interval

The network of interventions is presented in Figure 1.

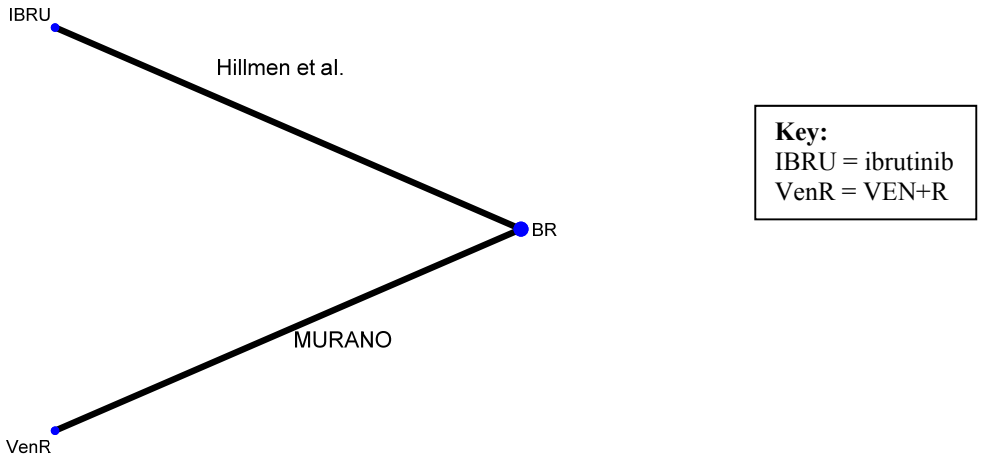


Figure 1: Network of interventions

Following the NMA, the HR for progression or death of VEN+R relative to ibrutinib is 1.43 (95% CI 0.78-2.61).

OS network meta-analyses

The data we used for the NMA for OS are presented in Table 14.

Table 14: Data used in the ERG's NMA for OS

Study	**Year**	**Treatment 1**	**Treatment 2**	**OS_HR$_{1vs2}$**	**OS_HR_ LCI$_{1vs2}$**	**OS_HR_ UCI$_{1vs2}$**
Murano	2018	VEN+R	BR	0.48	0.25	0.9
Hillmen	2015	BR	Ibrutinib	2.24	1.14	4.4
RESONATE+HELIOS		Ibrutinib	BR	0.45	0.23	0.88

LCI – lower confidence interval; UCI – upper confidence interval

The network of interventions for OS NMA is similar to that for PFS. Following the NMA, the HR for death of VEN+R relative to ibrutinib is 1.08 (95% CI 0.42-2.73).

Face-validity check and limitations

In Table 15, the ERG has summarised the PFS and OS estimates for the indirect comparison of VEN+R to ibrutinib using either the MAIC reported in the CS, or the ERG's exploratory NMA.

Table 15: Comparison of PFS and OS outcomes in R/R CLL using the MAIC or the ERG's exploratory NMA

Study	**Treatment 1**	**Treatment 2**	**PFS HR $_{1 \text{ vs } 2}$**	**OS HR $_{1 \text{ vs } 2}$**
Company's MAIC	VEN+R	Ibrutinib	[redacted]	[redacted]
ERG's NMA			1.43 (0.78-2.61)	1.08 (0.42-2.73)

There is a considerable difference between the company's and the ERG's estimates regarding the performance of VEN+R relative to ibrutinib. There is no formal argument to prefer the ERG's estimate for PFS rather than that of the company. However, the ERG believes that the estimates for both PFS and OS appear consistent with the idea that a benefit observed on PFS is associated with a lower benefit on OS. Moreover, when applied to the economic model, the ERG's estimates does not lead to implausible results with PFS exceeding OS for ibrutinib (see CS Figure 24).

We show in the cost-effectiveness section that using the ERG's NMA HR for OS in the model leads to an extrapolated life expectancy which is much more consistent with the predicted mean survival using reconstructed IPD.

The ERG acknowledges the exploratory nature of our analyses since we did not conduct a full systematic review to search for potential sources of additional of information. Furthermore, our NMA may seem simplistic because we cannot assess whether the transitivity assumption does hold.

4.9 Conclusions of the clinical effectiveness section

The ERG recognises the dearth of comparator studies relevant to the final scope and company's decision problem, and acknowledges the RESONATE and Study 116 trials as appropriate sources of aggregate data for comparison against IPD from the MURANO trial. The RESONATE trial investigated the efficacy of the more relevant comparator of VEN+R (single-agent ibrutinib) and matched better with the MURANO trial. The methods used in matching trial populations have been previously validated; however, the ERG is concerned about the imprecise estimates of the treatment effect of VEN+R (confidence intervals of HRs for PFS and OS were wide) as well as the implausible HRs for OS. Additional work undertaken by the ERG indirectly comparing estimates of the treatment effect of VEN+R from the MURANO trial against single-agent ibrutinib from Hillmen and colleagues[20] supports the ERG's position.

5 COST EFFECTIVENESS

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 Objectives and search strategy

The CS states on pg 82 that a systematic literature search was conducted to identify studies that assessed the cost-effectiveness of interventions for VEN+R and its appropriate comparators. The scope of the review was broadened to include all interventions in R/R CLL. Two other systematic reviews, aimed at identifying HRQoL data and relevant cost and resource use data for England and Wales that could be used in the company's economic model, are briefly described on pgs 119 and 130. The company provided an appropriate description of the cost-effectiveness, the HRQoL and the cost and health care resource use systematic reviews and details of the different search strategies were reported in Appendices G, H and I, respectively. In brief, the company searched MEDLINE, EMBASE, Econlit, Cochrane library including the NHS Economic Evaluation Database and HTA databases. Manual searches were also performed on seven conference proceedings websites and these searches were restricted to the last three years. In addition, reference lists of included papers were also consulted and for the HRQoL and cost and resource use reviews, previous NICE submissions in CLL were assessed. Original searches were carried out on 8 July 2017. Although these searches were updated on 30 April 2018, a limit to records with a publication date between 2014 and 2017 was applied. The search strategies were appropriate. The ERG has undertaken targeted searches to check for recent 2018 publications and has not identified any further cost-effectiveness studies, mainly due to the scarcity of evidence in this area.

5.1.2 Inclusion/exclusion criteria used in the study selection

The CS on pg 83-84 (CS table 26) tabulated the inclusion and exclusion criteria for the systematic reviews of economic evaluations which used the population, intervention, comparator, outcome (PICOS) framework and included: population, intervention/comparator, outcomes, study design type, publication type, and language. The selection criteria limited studies to those in adult patients 18 years or older, those with established R/R CLL including del(17p) R/R CLL patients, and studies published in English language. The study selection seemed appropriate. A similar inclusion/exclusion criteria was used for the HRQoL and cost and resource use reviews, however,

there were no restrictions applied on the type of interventions or type of comparators for these two reviews.

5.1.3 Included studies

CS Figures 18, 66 and 67 provided the flow diagrams for the cost-effectiveness, HRQoL, and cost and resource use systematic reviews, respectively. The cost-effectiveness search included 29 studies and 27 studies were excluded with complete references and reasons provided in Appendix G. Likewise, the HRQoL search included 13 studies and 20 studies were excluded with complete references and reasons provided in Appendix H; and the cost and resource use search included 16 studies and 14 studies were excluded with complete references and reasons provided in Appendix I.

The CS did not state whether the studies were independently assessed by two reviewers. Quality assessment for the cost-effectiveness studies was conducted by the company using the Drummond checklist[27] however, a more update checklist such as the CHEERS checklist[28] would have been more appropriate and it would have also been beneficial to have summary of the quality assessment.

To summarise, no cost-effectiveness studies assessing VEN+R for treating patients with relapsed or refractory CLL were identified.

5.1.4 Conclusions

The company did not provide a formal conclusion from the data available of the three systematic reviews: cost-effectiveness, HRQoL and cost and resource use.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist

Attribute	Reference case and TA Methods guidance	Does the de novo economic evaluation match the reference case
Comparator(s)	Therapies routinely used in the NHS. Including technologies regarded as current best practice for the two populations	Ibrutinib as an option for first line treatment of del(17p)/TP53 patients and second line treatment of non-del(17p)/TP53 patients. Idelalisib + rituximab for treatment of R/R CLL.
Patient group	As per NICE final scope	1. Patients with relapsed CLL - a CLL patient who previously achieved a CR or partial response/remission (PR), but after a period of six or more months demonstrates evidence of disease progression; 2. Patients with refractory CLL – a CLL patient who has progression within six months of the last anti-leukemic therapy R/R CLL population is split into two subgroups: a. patients with del(17p) and/or TP53 mutation

Attribute	Reference case and TA Methods guidance	Does the de novo economic evaluation match the reference case
		b. patients with non-del(17p) and/or TP53 mutation
Perspective costs	NHS & Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-effectiveness analysis	Cost-effectiveness analysis (Cost per quality-adjusted life year (QALY))
Time horizon	Sufficient to capture differences in costs and outcomes	Yes (lifetime duration – approximately 30 years)
Synthesis of evidence on outcomes	Systematic review	Data are drawn from one study: MURANO trial
Outcome measure	Quality-adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	Yes. Health states were evaluated using EQ-5D-3L data collected from MURANO trial
Benefit valuation	Time-trade off or standard gamble	The standard UK EQ-5D tariff is used, which is based upon time-trade off
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes
Discount rate	Annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the	Yes

Attribute	Reference case and TA Methods guidance	Does the de novo economic evaluation match the reference case
	individuals receiving the health benefits	
Probabilistic modelling	Probabilistic modelling	Yes
Sensitivity analysis		A range of sensitivity and scenario analyses is presented

The cost-effectiveness evidence submitted by the company appears to satisfy the NICE reference case, and the decision problem defined in the scope.

5.2.2 Model structure

The company presented a *de novo* partitioned survival model with a 28-day cycle length (which matches the typical treatment cycle length of the intervention and the comparators) and a lifetime time horizon. The model consisted of three health states: progression free (or pre-progression), progression (or post-progression), and death (Figure 2). The partitioned survival approach uses an "area under the curve" approach, where the number of patients in each health state at a given time is taken directly from survival curves fitted to the clinical data. This approach allows the survival of the comparator arms to be estimated using PFS and OS hazard ratios applied to the VEN+R survival curves. A half-cycle correction was applied in the base-case analysis.

The model assumes all patients enter the model in the pre-progression health state. Patients in the pre-progression health state, stay in that health state until disease progression. Transitions to the death state could occur from either the pre-progression or post-progression health state. Costs of disease management, utilities and risks of death all differ between the pre-progression and the post-progression health states. We note that many people with CLL may die of other causes.

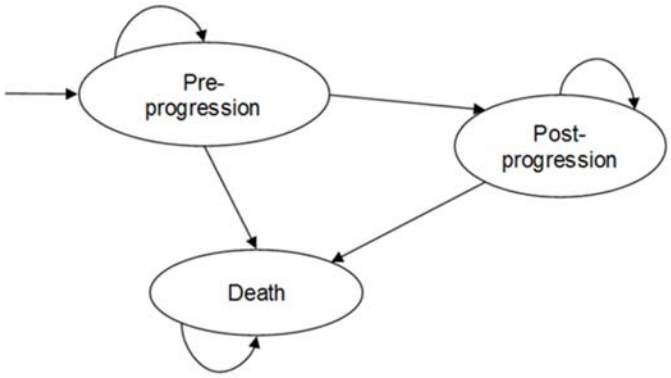


Figure 2: Model structure presented by the company

ERG summary

- The model takes a simple partitioned survival approach with three health states, and is consistent with other models built for patients with R/R CLL, and captures the two important clinical endpoints of OS and PFS.
- The cycle length of the model (28-days) is sufficiently short to capture changes over the relevant time interval.

5.2.3 Population

The population modelled in the company's base case analysis included:

- Patients with relapsed CLL - a CLL patient who previously achieved a CR or PR, but after a period of six or more months demonstrates evidence of disease progression;
- Patients with refractory CLL – a CLL patient who has progression within six months of the last anti-leukaemic therapy.

R/R CLL population is split into two further subgroups:

- patients with del(17p) and/or TP53 mutation
- patients with non-del(17p) and/or TP53 mutation.

Data for the base-case and the subgroup analyses were based on the MURANO study (a pooled dataset of the intervention and the control group). The study population was assumed by the

company to be reasonably similar to the UK population likely to receive treatment. However, out of the 389 patients recruited in the MURANO study, only 10 were from the UK (see section 4.2).

Data for ibrutinib arm came from RESONATE study[12] and data for the IDELA+R arm came from Study 116.[13]

Individuals in the modelled cohort had an average starting age of 64.18 years and 73.82% were male. An average body surface area (BSA) of 1.92m^2 was used to estimate the dosing of BR containing treatment regimens. The majority of patients (58.6%) in MURANO trial had at least one prior therapy, whereas 25.7% had at least two prior therapies. 26.96% of patients in the MURANO trial had del(17p) and/or TP53 mutation.

Information on patient characteristics for the subgroup analyses (i.e. del(17p)/TP53 and non-del(17p)/TP53) were not provided in the CS; furthermore, the ERG found that the mean values of the patient characteristics used in the base-case analysis were used in all subgroup analyses for the economic model.

ERG summary

- In the base-case analysis patients age and gender were taken from the overall trial population. However, the use of patient characteristics from only the European sites might result in more representative patients.
- The modelled population in all subgroup analyses were based on the characteristics of patients from the overall trial population, and not on the individual subgroups which were compared.

5.2.4 Interventions and comparators

In the company's base-case analysis, VEN+R is compared with ibrutinib or IDELA+R. Venetoclax is administered for a maximum of two years and rituximab is delivered for six cycles after completion of dose titration for venetoclax. The comparators ibrutinib and idelalisib are

administered until disease progression, and rituximab for the IDELA+R arm is administered for a total of six cycles.

The base-case economic model assumed that treatment effect with venetoclax lasted for a lifetime (approximately 30 years). But, the model also allowed for a treatment waning effect of 3 years after the discontinuation of venetoclax.

ERG summary

- The base-case analysis incorporates appropriate comparators relevant to the UK (ibrutinib or idelalisib+rituximab).

5.2.5 Perspective, time horizon and discounting

The perspective is as per NICE reference case, with benefits from a patient perspective and costs from an NHS and personal social services (PSS) perspective. A lifetime horizon is modelled (approximately 30 years). In the base-case, costs and benefits were discounted at an annual rate of 3.5%.

ERG summary

- The perspective, time horizon and discount rates chosen by the company all follow NICE recommendations, and are appropriate to the decision problem.

5.2.6 Treatment effectiveness and extrapolation

5.2.6.1 Survival Summary and Critique

In section B3.3.3, the company chose a partitioned survival model, and attempted to parameterise the observed OS and PFS curves from the MURANO trial in order to extrapolate and predict the long-term OS and PFS behaviour. Survival curves for the comparators were obtained by applying hazard ratios to the VEN+R curves.

5.2.6.2 VEN+R Time to Event Modelling

The company initially fitted models separately to each treatment arm's PFS and OS events, but, these extrapolations led to most curves predicting implausibly high OS for VEN+R, which exceeded the general population mortality. The ERG accept that these extrapolations were not suitable.

The company then chose to model PFS and OS jointly across both arms, assuming proportionality and the same parametric form between OS and PFS within and across both arms. They also included an interaction between treatment arm and endpoint (OS/PFS) allowing for the relationship between OS and PFS to be different across arms, and an interaction between del(17p)/TP53 status and endpoint, allowing del(17p) status to impact each outcome separately.

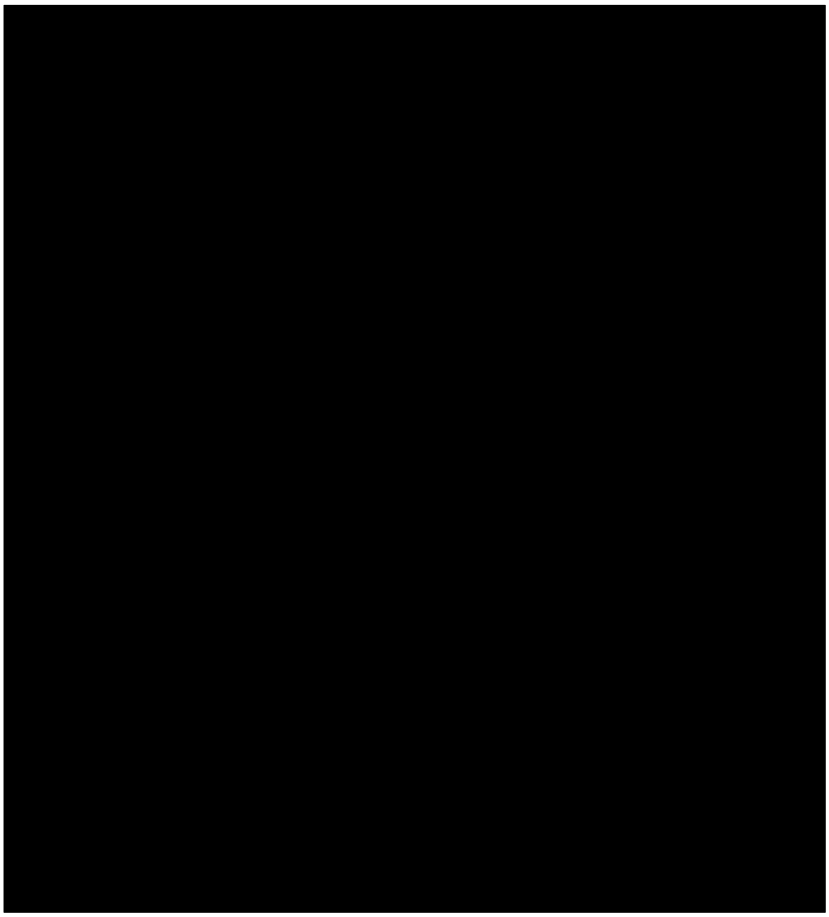
Whilst the model seems reasonable, the company does not provide any strong statistical evidence or description of the selection process of the model covariates, and so the ERG cannot comment on its robustness. It is unclear whether any other terms were considered for inclusion. The inclusion of the del(17p)/TP53 status and its interaction with the endpoint is questionable as the terms coefficients are not statistically significant in any of the parametric models presented in CS Table 35. Whilst the ERG appreciate that its inclusion enabled estimation of survival for the del(17p)/TP53 subgroup, it is not clear how helpful its inclusion is in the estimation of the full population model.

In order to verify the proportional hazards/survival-time assumption, the ERG requested additional evidence in the form of log-cumulative hazard plots. In general, proportionality did not appear strongly violated, though it is clear that the lines are not parallel in any of the plots, most evidently in the comparison of OS across both arms, shown in ***[redacted]3. This means that whilst proportionality was violated, it was not done so to a statistically significant degree.

The ERG is also surprised at the decision of the company to include data from the BR arm of the trial when modelling OS and PFS, as this is not included as a comparator within the economic model. Thus, any HR referring to the relationship between the two arms should not have been estimated, and this means the VEN+R extrapolation of the immature OS data is influenced by the biologically different BR arm. However, the ERG does agree that the models produced without

such strong assumptions on proportionality produce implausible OS estimates (see clarification response B1). Nevertheless, the ERG is concerned that the company's decision to include covariates which may not significantly improve the model, combined with the inclusion of BR data may not result in a statistically robust analysis. This is supported by the resulting models fitted to the VEN+R OS data, shown in [redacted]4. Here it is clear that the fitted curves do not reflect the observed data, which have resulted from the inclusion of BR data, in order to obtain plausible estimates. The ERG acknowledges the importance of an accurate extrapolation, but also feel that any modelling should also reflect observed data.

[redacted]3



4

The company assessed their jointly fitted parametric models through examination of their 20-year outcome predictions. Estimates were compared to the predictions made by five clinical experts, which is provided below in Table 16. These are in contrast to the estimates obtained from the company's jointly fitted survival curves in Table 17. It is apparent that despite the adjustments made by the company, a number of models still give implausible estimates. Exponential and Log-normal are too optimistic, and Gen-Gamma, 3-knot spline, and Gompertz are too pessimistic. However, Weibull, Log-logistic and Gamma all produce estimates of VEN+R 20 year OS that fall within the range of clinical expert opinions.

Table 16: Predictions from clinical experts on VEN+R long-term OS

Source	Expert Number	Prediction
Company	Clinical Expert 1	10% of patients alive at 20 years
Company	Clinical Expert 2	7% to 25% of patients alive at 20 years
Company	Clinical Expert 3	As high as 30% of patients alive at 20 years is reasonable, depending on the population
Company	Clinical Expert 4	Agreed with the more optimistic estimate (3)
Company	Clinical Expert 5	Agreed with the views of colleagues (1-5)
ERG	Clinical Expert 6	20-30% at 20 years
ERG	Clinical Expert 6	10-30% at 20 years (or matching the proportion of patients who are aged under 50 and achieved MRD negative status [17/194 patients])

Table 17: VEN+R OS predictions from company jointly fitted models

Outcomes			Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Gamma	Gen gamma	3 knot spline
AIC			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R OS	Median (years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Survival %	2-year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		5-year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		10-year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		20-year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BR OS	Median (years)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Survival %	2-year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		5-year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		10-year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		20-year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The company compared these estimates to three external data sources: 4-year follow-up from RESONATE,[29] fludarabine, cyclophosphamide, rituximab (FCR) data with 10-year follow-up[30] and 10-year registry data from the Haematological Malignancy Research Network (HMRN).[31]

The FCR data were from 284 patients, recruited in a phase II trial which began in December 1999. They had an observed 10-year OS of 23%, with extrapolations to 20 years performed by the

company ranging from 5% to 13%. This population was described by the company as healthier than that of MURANO due to being younger and in better general health. The HMRN data covered 2,723 patients diagnosed from September 2004 to August 2015, though it is unclear how many contributed to the second-line data considered in this analysis. The extrapolations ranged from 1% to 10% for 20-year OS, with the 8-year observed OS at approximately 18%.

However, the ERG do not believe these external studies are useful for predicting OS of VEN+R patients from MURANO. Firstly, the characteristics of the FCR study population show stark differences to the MURANO trial, as shown in Table 18. Large differences in age, Rai staging and presence of bulky disease. Baseline characteristics for the HMRN second-line population are not available, and so their similarity cannot be compared. Figure 5 demonstrates the large difference in observed OS between MURANO VEN+OS and the FCR data. Secondly, both FCR and HMRN began gathering data over 14 years ago, with major improvements in diagnosis and care increasing the heterogeneity to MURANO. Thirdly, it is unlikely that patients in these external studies received VEN+R, and so the ERG is unclear why they should be used to validate predictions made for VEN+R patients. The ERG believe these studies can only be used to exclude the Gompertz model (0% OS at 10 years), and not to distinguish between the plausibility of the remaining parametric models. Looking just at the observed periods from the external studies, both can be estimated to have 10-year OS in the region of 15%-25% once all participants data has been observed. However, comparing this to the 10-year predictions made from MURANO, it is clear that they are all much higher, ranging from 35.8% to 67%. The ERG are unsure why, given the apparent improvement of VEN+R at 10 years, why the company appear to predict that this benefit is lost at 20 years.

Table 18: Patient characteristics of VEN+R (MURANO) and FCR data

Effect modifier / prognostic characteristics	VEN+R	FCR
AGE >60	67.05%	45.77%
RAI III-IV	27.17%	45.77%
Bulky disease ≥ 5 cm	43.93%	7.14%
Beta Microglobulin > 3.5 mg/L	64.74%	59.93%
Prior therapy>1	44.51%	59.15%
CHROMOSOME 11Q DELETION	35.26%	12.75%
CRCL	26.59%	19.61%
Fludarabine Refractory	14.62%	19.01%
IGVH=Mutated	29.48%	31.40%
ECOG=1	45.56%	NR
Prior Purine Analog	80.47%	NR
Prior AntiCD20	73.96%	NR

NR = not reported

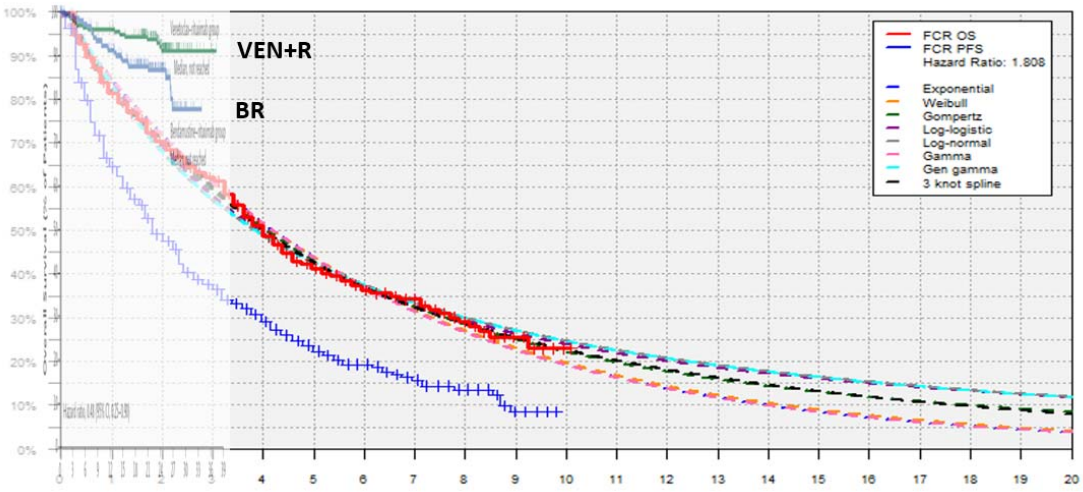


Figure 5: OS of MURANO overlaid onto Kaplan-Meier of FCR data

The ibrutinib data from RESONATE were also extrapolated, however with only four year's follow-up, there remained vast uncertainty in the extrapolations, with 20-year OS estimates ranging from 0% to 30%.

The Akaike information criteria (AIC) for the jointly fitted models were also provided by the company, however their relevance is limited as their calculation reflects the goodness of fit to the BR arm in addition to the VEN+R arm. As a result it is impossible to distinguish which is the best fitting model to the VEN+R arm alone.

The company state that the Weibull is their preferred parametric model for both OS and PFS and is used in their base-case analysis, supported by the external data. This results in 6.1 pre-progression life years (LY), and 4.7 post-progression LY, both undiscounted.

However, the ERG believe that the Weibull long-term predictions for OS may be too low, and expect to see a greater difference between the pre- and post- progression life years. The ERGs preference is to use the Gamma parametric model for OS, as it provides an OS more consistent with the above comparisons, which falls within the range of estimates from the clinical experts and has a lower AIC than the Log-logistic. In order to maintain the proportionality assumptions underlying the analysis, the ERG also chose a Gamma curve to model PFS.

Together, the Gamma curves slightly increases the ratio of PFS LY to post-progression survival (PPS) LY, versus the company's base-case. A comparison of the LY estimates, broken down into progression stage are shown in Table 19.

Table 19: Undiscounted LY estimates for VEN+R

	PFS	OS	PFS LY (% of total LY)	PPS LY (% of total LY)	Total LY
Company base-case	Weibull	Weibull	[redacted]	[redacted]	[redacted]
ERG preferred assumptions	Gamma	Gamma	[redacted]	[redacted]	[redacted]
ERG scenario	Log-logistic	Log-logistic	[redacted]	[redacted]	[redacted]

5.2.6.3 Ibrutinib

For their base-case, the company applied HR obtained from the MAIC to the parametric curves fitted to the VEN+R arm of MURANO. The ERG questioned this approach, given the critique of the MAIC in section 4.7 and section 4.8, the company's own admission that for the comparison to ibrutinib, the "HR estimates leads to a model dynamic which holds no face validity", and the ERG's own face validity checks (see section 5.2.14).

The company's economic model offered the option to model each comparator parametrically, based on curves fitted to the digitized IPD generated by the company. These curves were then adjusted depending on results of the MAIC analysis, to account for differences in baseline characteristics. Had the MAIC results been more clinically plausible, the ERG would have favoured this approach as it relaxed the assumptions of proportionality between the different treatments. However, as this approach is wholly reliant on the MAIC results, the ERG did not consider it an improvement on the HR based analysis.

It is the preference of the ERG to model the OS and PFS of ibrutinib using HR discussed in section 4.8, as this results in more plausible PPS estimates, as seen Table 20.

Table 20: Undiscounted LY estimates of ibrutinib

	PFS and OS Curves and HR	HR Source	PFS LY (% of total LY)	PPS LY (% of total LY)	Total LY
Company base-case	Weibull [redacted]	Company MAIC	4.64 (100%)	0.00 (0%)	4.64
ERG HR, company curves	Weibull [redacted]	ERG NMA	[redacted]	[redacted]	[redacted]
ERG preferred assumptions	Gamma [redacted]	ERG NMA	[redacted]	[redacted]	[redacted]

The survival curves for ibrutinib based on the company's and ERG's preferred assumptions are shown in [redacted]6, alongside the Kaplan-Meier (KM) data from RESONATE. The ERG believe that the company's assumptions result in a model that underestimates the effectiveness of ibrutinib in the MURANO population, given the similarity of the prediction to the observed OS in RESONATE, despite the difference in baseline populations.

[redacted]

[redacted]

5.2.6.4 Idelalisib + R

The ERG are concerned over the reliability of all the MAIC results, given the issues with the ibrutinib results. The ERG are reluctant to also use the resulting HRs for IDELA+R even though they appear plausible. However, the ERG were not able to find any comparisons of IDELA+R to BR and were unable to generate any alternative HRs. Hence, the ERG maintained the HRs estimated by the company, but apply them to the Gamma PFS and OS curves. The ERG also explored using the anchored MAIC results comparing IDELA+BR. The ERG acknowledges that IDELA+BR was not in the scope, and neither, the company or the ERG, found any evidence supporting any equivalence to IDELA+R. However, a comparison of the scenarios in Table 21 shows that it is the only scenario where PFS LY exceeds PPS LY, which the ERG expects in a disease such as CLL.

Table 21: Undiscounted LY estimates of IDELA+R

	PFS and OS Curves	HR Source	PFS LY (% of total LY)	PPS LY (% of total LY)	Total LY
Company base-case	Weibull	MAIC (IDELA+R)	1.80 (47%)	1.99 (53%)	3.79
ERG preferred assumptions	Gamma	MAIC (IDELA +R)	[redacted]	[redacted]	[redacted]
ERG alternative	Gamma	MAIC (IDELA +BR, adjusted)	[redacted]	[redacted]	[redacted]

ERG summary

- Company assume proportionality between OS, PFS and both arms of MURANO trial in order to gain plausible long-term estimates, suggesting data may be too immature to meaningfully extrapolate.
- Company prefer jointly fitted Weibull model for OS and PFS, due to similarity of 20-year OS prediction with external data and clinical expert opinion.
- ERG question the generalisability of the external data, and prefer jointly fitted gamma model, as this sustains some treatment benefit observed throughout the duration of the extrapolation.
- Company apply HR from their MAIC analysis to obtain predictions for ibrutinib and IDELA+R, despite some issues with the results.
- ERG prefer HR obtained from NMA, which result in a plausible balance of PFS and PPS LY for ibrutinib.

5.2.7 Mortality

General population background mortality was estimated using the latest UK life tables from the Office of National Statistics.[32]

5.2.8 Adverse events

The company outline their incorporation of AEs into the economic model in section B.3.3.5 of their submission. The CS state that only events of grade ≥3 that occurred in ≥5% of patients in any of the three main trials (MURANO, RESONATE and Study 116) were included. The ERG

believe this to be slightly inaccurate, as it appears that only AEs from the intervention arms of the three trials were considered (VEN+R; ibrutinib; IDELA+R) and that the AEs of comparator arms were not included. However, the ERG does not believe that this detracts from the relevance of the economic analysis presented by the company. The AEs included are shown below in Table 22 (adapted from CS Table 36), although 'infusion related reactions' were not reported in Table 36, they were included in the economic model. Across the majority of adverse event categories, the proportion of patients with an adverse event was generally higher in the intervention arm of the MURANO trial data than the intervention arms of the RESONATE and Study 116 trials. The only exception is pneumonia (6.19% for VEN+R and 6.67% for ibrutinib) and thrombocytopenia (6.17% for VEN+R, 5.65% for ibrutinib and 10.00% for IDELA+R). TLS was not included in the model as it did not meet the AE inclusion criteria. The ERG believe that AEs reported from MURANO may increase, as there were 78 patients receiving ongoing treatment at the point of data analysis.

Table 22: Adverse events used in the company's base-case analysis

AE	VEN+R	Ibrutinib	IDELA+R
N	194	195	110
Alanine aminotransferase (ALT)/Aspartate Transaminase (AST) elevation	1.55%	-	5.45%
Anaemia	10.82%	4.62%	5.45%
Autoimmune haemolytic anaemia	2.58%	-	-
Neutropenia	57.73%	16.41%	33.64%
Pneumonia	6.19%	6.67%	-
Thrombocytopenia	6.19%	5.64%	10.00%
Infusion Related Reaction	1.55%	-	-
Source	MURANO[11]	RESONATE[29]	Study 116[33]

The ERG note that 17.5% of patients in the venetoclax arm of MURANO experienced grade 3/4 infections or infestations, however, these were not included in the economic model with no explanation given.

The ERG also note that the frequencies of the AEs for VEN+R found in Table 36 (and **Error! eference source not found.** above) do not all correspond to the frequencies found in CS Table 23. Whilst the incidence of events included in the economic model spans across grades 3-5, these frequencies are not presented within the clinical section of the CS or any other evidence found by the ERG. The ERG anticipate that the frequencies used in the company's base-case analysis are some combination of grade 3-4 AEs and SAEs, possibly with additional grade 5 events that have not been presented. The discrepancy of most concern is the frequency of pneumonia. The 6.19% incidence used for pneumonia is less than the pneumonia related SAEs (8.2%), and so the ERG believe this to be an error (see Table 23).

Table 23: Comparison of adverse event frequency across

AE	VEN+R CS Table 36 and company base-case (Grade 3-5)	VEN+R CS Table 23 Grade 3-4 AEs	VEN+R CS Table 23 SAEs
N	194	194	194
ALT/AST elevation	1.55%	-	-
Anaemia	10.82%	10.8%	1.5%
Autoimmune haemolytic anaemia	2.58%	-	-
Neutropenia	57.73%	57.7%	-
Pneumonia	6.19%	5.2%	8.2%
Thrombocytopenia	6.19%	5.7%	5.7%
Infusion Related Reaction	1.55%	1.5%	0.5%
Infection and Infestation	-	17.5%	-

The ERG have confirmed that the AE incidence for the ibrutinib and IDELA+R arms match the numbers reported in their corresponding main trial publications.[12, 13] However, values taken from the RESONATE trial, for ibrutinib, refer only to events of grade 3-4 and not grade 5. Hence, it is likely that AEs for ibrutinib may be slightly under-represented within the economic analysis.

Despite potential under-representation of AEs for ibrutinib and VEN+R, the ERG do not have any major concerns as these AEs are not a major driver of the cost-effectiveness analysis.

The ERG agrees with the CS approach in estimating QALY decrements associated with these adverse events, as a similar approach were used in previous appraisals for venetoclax monotherapy[8] and IDELA+R.[10] In brief, the estimates of the mean utility decrement and the mean duration associated with each adverse event were obtained from published sources including previous NICE technology appraisals and multiplied together to generate the required QALY decrement (CS Table 43). The ERG checked and verified that estimates of QALY decrements for adverse events reported in the CS are consistent with those reported in TA359.[10] No disutilities for TLS were included in the CS base-case model.

ERG summary

- General background mortality was taken from the latest UK lifetable estimates from Office of National Statistics.
- The company model included adverse events of grade ≥3 if they occurred in ≥5% of patients in any of the three main trials (MURANO, RESONATE and Study 116).
- TLS was not included in the model as an AE as it did not meet the AE inclusion criteria and therefore, no disutilities associated with TLS were included in the CS base-case model.
- 17.5% of patients in the venetoclax arm of MURANO experienced grade 3/4 infections or infestations, however, these were not included in the economic model.
- Estimates of QALY decrements for adverse events reported in the CS are consistent with those reported in TA359.

5.2.9 Health related quality of life

Health-related quality of life data were collected for MURANO trial participants using EQ-5D-3L; however, these health-state utility values derived from this data were not used to inform the economic model presented in the CS. The CS did not report the actual utility values derived from the MURANO trial data but explained that they were they were heavily skewed towards 1 or

"perfect health" and lacked face validity when compared to general UK adult population utility norms. Because of this, the CS did not use utility values derived from the MURANO trial to inform the subsequent economic model. However, upon clarification utility values were presented to the ERG; however, these utility values were not split by pre- or post-progression so were not used in any scenario analyses carried out by the ERG.

Instead, the CS used health state utility values from previous NICE technology appraisals of various technologies in CLL including venetoclax monotherapy (TA487)[8] and IDELA+R (TA359).[10] In these appraisals, a utility value of 0.748 was assigned to patients in pre-progression health state in the NICE committees most preferred base-case model [8, 10] and a mean utility of 0.600 for patients in the progressed health state, based on estimates reported in a published HTA report by Dretzke et al (2010)[34] and the subsequent appraisals of technologies in CLL. The company justified using these utility values on the grounds that they informed the committees' most preferred base-case model for venetoclax monotherapy[8] and IDELA+R.[10] Also, the post-progression health state utility value was based on data elicited directly from CLL patients rather than the general population, and was therefore considered the most robust utility value.[34]

In addition, to the health state utility values from the previous NICE technology appraisals mentioned above, the company conducted a systematic literature review to identify studies assessing health-related quality of life in R/R CLL. Detailed results of the review are presented in CS Appendix H with a summary presented in section B.3.4.3 of the CS. In total, 13 full-text articles were included in the final HRQoL review, two of which reported utility scores of 0.748 (CS Table 39) for the pre-progression health state.

The ERG agrees with the approach to health state utility estimation for the pre-progression and post-progression health states as used in the company's base-case model. The ERG notes the pre-progression utility of 0.748 and post-progression utility of 0.600 have been accepted in previous NICE committee deliberations as the most appropriate estimates of health utility in R/R CLL.[8, 10] and the ERG agrees that these utility values are the most appropriate for the patient population in the current appraisal of VEN+R as they are likely to be similar to the populations considered in TA487 and TA359.

The ERG further agrees with the CS reasons for not using utility values derived from the MURANO data in the economic model. It is noted that it highly unlikely that patients with R/R CLL have higher quality of life than the general adult population of a similar age and gender; hence, the health utility values derived from the MURANO data are likely to represent an over estimate of the actual HRQoL in patients with R/R CLL.

Uncertainty around these estimates of the mean pre-progression and post-progression utilities values and estimates of QALY decrements associated with adverse events was incorporated into the economic model by assuming that standard errors associated with each estimate equal to 10% of the mean.

Health-state utility values for pre-progression and post-progression health states and disutility associated with adverse events in the CS model were age-adjusted as recommended in NICE DSU TSD 18 to account for the increasing comorbidities with increasing age due to the resultant deterioration in quality of life in older aged cohorts.[24] Multiplicative adjustment factors were derived for age-groups between 60 and 85+ using pooled data from four consecutive health surveys for England (2003-2006) that reported health-stated utility values generated from the EQ-5D-3L health-state utility values.[35] The ERG agrees with the rationale for and the CS approach to adjusting for age-related utility deterioration.

ERG summary

- HRQoL data collected for MURANO trial participants using EQ-5D-3L lacked face validity to due to the health states utility values being higher than UK adult population norms.
- Health state utility values used in the economic model were taken from previous NICE technology appraisals in CLL.
- Patients in pre-progression health state were assigned a utility value of 0.748 and patients in post-progression health state were assigned a utility value of 0.60. Consistent with previous NICE committee decisions as the most appropriate estimates of health utility in R/R CLL patients.

- Health-state utilities and disutility associated with adverse events in the CS model were age-adjusted as recommended in NICE DSU TSD 18.

5.2.10 Resources and costs

5.2.10.1 Intervention and comparator costs

Tables 46 and 47 of the CS reproduced below for completeness summarises the CS approach to treatment regimen dosing and cost calculations for VEN+R and the comparator interventions (see Table 24 and Table 25). The costs for VEN+R for each cycle (28-days) in the CS were obtained from the BNF. Daily dose for venetoclax was 20 mg/day for week 1, 50 mg/day for week 2, 100 mg/day for week 3, 200 mg/day for week 4, and 400 mg/day for week 5 and beyond, up to a maximum treatment duration of 2 years. The model assumes intravenous (IV) rituximab is administered on day one of cycles 1 to 6 corresponding to a total of six doses of rituximab in first 6 months of treatment with VEN+R. Rituximab costs were estimated based on a dosing regimen of 375 mg/m^2 in day 1 of cycle 1 and 500 mg/m^2 in day 1 of cycles 2 to 6 and applying it to a body surface area of 1.92m^2 observed in the MURANO trial. There were no administration costs for venetoclax. Administration costs for rituximab were applied assuming 12 minutes of pharmacist time costing £9 per infusion based study by Millar et al.[36] and a 30:70 ratio between standard and rapid IV infusions for administration of rituximab containing treatment regimens. Unit costs for administration were obtained from the NHS Reference Costs 2016-17 and were £313.47 (HRG code SB15Z) for rituximab (IV standard) and £250.07 (HRG code SB12Z) for rituximab (IV Rapid).

Table 24: Drug acquisition costs (CS Table 46)

Drug	Pack size	Pack Cost	Per mg Cost	Source
Venetoclax	14 x 10 mg	£59.87	£0.43	BNF – 10, 50 and 100 mg tablets (AbbVie Ltd)
	7 x 50 mg	£149.67	£0.43	
	7 x 100 mg	£299.34	£0.43	
	14 x 100 mg	£598.68	£0.43	
	112 x 100 mg	£4,789.47	£0.43	

Rituximab (IV)	1 x 500 mg	£785.84	£1.57	BNF - Truxima 500 mg/50ml concentrate for solution for infusion vials (Napp Pharmaceuticals Ltd)
Rituximab (SC)	1 x 1,400 mg	£1,344.65	£0.96	NICE Evidence summary ESNM46 (2014)[37]
Ibrutinib	90 x 140 mg	£4,599.00	£0.37	BNF - Imbruvica 140 mg capsules (Janssen-Cilag Ltd)
Idelalisib	60 x 150 mg	£3,114.75	£0.35	BNF - Zydelig 150mg tablets (Gilead Sciences International Ltd)

Key: BNF, British National Formulary; IV, Intravenous; SC, Subcutaneous

Table 25: Treatment regimens (CS Table 47)

Regimen	Drug	Admin	Dosing schedule
VEN+R	Venetoclax	Oral	Daily dose, 20 mg week 1, 50 mg week 2, 100 mg week 3, 200 mg week 4, 400 mg week 5 and beyond until disease progression or 2-year maximum treatment duration.
	Rituximab	IV	375 mg/m^2 D1 C1, 500 mg/m^2 D1 C2-C6 for a total of 6 doses.
Ibrutinib	Ibrutinib	Oral	Daily dose of 420 mg until disease progression.
IDELA+R	Idelalisib	Oral	Daily dose of 300 mg until disease progression.
	Rituximab	IV	375 mg/m^2 D1 C1, 500 mg/m^2 D1 C2-C6 for a total of 6 doses.

The two comparator interventions of ibrutinib and IDELA+R were administered continuously until disease progression. Drug administration costs for ibrutinib was assumed to zero. Administration costs for IDELA+R were applied assuming treatment scheduling and costs similar to the assumptions applied in calculation of rituximab administration costs in the VEN+R (see Table 24 and Table 25).

No drug wastage costs were included in the model.

The ERG identified an error in the way intervention costs for VEN+R were applied in the CS economic model (See CS Table 49). The CS had applied the cost of rituximab in the first 6 cycles corresponding to approximately the first 6 months of treatment with VEN+R. The ERG believed the costs of rituximab should have been included in cycles 2 to 7 of the model because the dose-

titration schedule involves venetoclax monotherapy only in the first 4 weeks of treatment (corresponding to the first cycle of the model). The first dose of rituximab is given in week 5 (cycle 2 of the model) upon completion of venetoclax dose titration followed by 5 further doses of rituximab at the beginning of each cycle.[11] The ERG believe that the impact of this error in the CS model will be minimal because the error affects only the times at which rituximab costs were added in the model and not the total number of rituximab doses in the costing model. The ERG asked the company for clarification on this, please see section 5.3 for more detail.

5.2.10.2 Other health state costs

Other healthcare costs considered in the CS base-case economic model included the costs for TLS prophylaxis, other adverse events, 'routine care and monitoring' including hospital visits, investigations and procedures undertaken during a CLL patient's treatment pathway and the cost of terminal care.

TLS costs

The CS presented costs for TLS prophylaxis which were based on an algorithm along with its associated resource usage and costs in Tables 50 and 51 of the CS and in Appendix N. First, TLS was categorised into lower and greater risk groups based on the tumour mass and absolute lymphocyte count. So patients with lymph node diameter ≤5 cm and ALC <25 x 10^9/L indicates a low risk and all other patients are of a greater risk. Next, the high risk group is subdivided into two groups according to CRCL cut-off at 80 ml/min. The algorithm placed 18.06% of the MURANO trial population in the low risk group, 32.2% in the greater risk (CRCL≥80) group and 49.74% in the greater risk (CRCL<80) group (CS Table 50). Based on this algorithm, the cost of TLS prophylaxis applied in each cycle of the CS model were £1,430 for the low risk group, £2,016.54 for the greater risk (CRCL≥80) and £2,146.81 for the greater risk (CRCL<80).

The ERG notes a similar algorithm was used to derive TLS prophylaxis costs in TA487 (see Table 26). However, the estimated TLS costs were much higher in TA487 compared to the current submission (£1,808 for lower risk group, £2,235 greater risk group with CRCL≥80 and £2,334 for the greater risk group with CRCL<80). The ERG considered scenarios using the alternative higher estimates of TLS prophylaxis costs in its exploratory analyses.

Table 26: TLS prophylaxis costs by risk stratification

Submission	Lower risk	Greater risk	
		CRCL≥80	**CRCL<80**
Current submission	£1,430.40	£2,016.54	£2,146.81
TA487	£1,808	£2,235	£2,334

Key: ALC, absolute lymphocyte count; CRCL, creatinine clearance

Costs of routine care

The routine care costs take into account costs for the visits and procedures which occur during a CLL patient's treatment pathway. The resources and frequency usage were based on a previous NICE submission[9] and expert opinion which were detailed in CS Table 52. Resource use items in the economic model included: full blood counts, lactate dehydrogenase (LDH) tests, chest x-rays, bone marrow exams, haematologist visits, inpatient non-surgical medical stay, and blood and platelet transfusions. Unit costs were estimated based on NHS reference costs 2016/17.[38]

Pre-progression per cycle cost was estimated to be £27.12 and the post-progression per cycle cost was estimated to be £431.14. Table 27 presents the cost estimates associated with routine care from the CS alongside the routine care costs reported in TA487 (CS Table 69 of TA487).[39] The ERG noted that the pre-progression costs of £27.12 per cycle were substantially lower than the pre-progression estimate of £269.94 per cycle used in TA487 (see Table 27 below). The ERG was unable to find out what the key driver for this difference in the pre-progression routine care costs was, but notes that TA487 estimates also included costs for lymphocyte count, inpatient non-surgical medical stays, and nurse home visits that were not included in the pre-progression routine care costs calculations reported in the current submission. However, the CS indicated that feedback from clinician experts suggests the pre-progression health state resource use does not normally involved inpatient non-surgical medical visits and nurse home visits which may have an effect on reducing routine care costs in the pre-progression health state. The ERG considered scenarios using the alternative higher estimates of routine care costs in TA487 in its exploratory analyses.

Table 27: Routine care costs for patients with R/R CLL

Resource/procedure	CS model Table 53 (2017 prices)		TA487 - CS Table 69 (2016 prices)	
	Annual pre-progression frequency	Annual post-progression frequency	Annual pre-progression frequency	Annual post-progression frequency
Full blood count	4	8	4	4
LDH test	2	0	2	0
Lymphocyte count[1]	-	-	3.5	0
Chest x-ray	0	2	2	0
Bone marrow exam	0	1	1	0
Haematologist visit	2	6	4.5	4.9
Inpatient non-surgical medical stays	0	4	2	1
Nurse home visit[1]	-	-	3	4
Full blood transfusion	0	11	2	2
Platelet infusion[1]	-	-	0	0
Total annual cost	£353.78	£5,624.03	£3,509.17	£2,517.32
Per cycle cost	**£27.12**	**£431.14**	**£269.94**	**£193.64**

Other adverse events

The CS presented costs for adverse events in Table 54 (replicated below in Table 28); the majority of unit costs were obtained from NHS reference costs 2016/2017.[38] Adverse event costs associated with ALT/AST elevation were assumed to be zero based on previous NICE submission.[40] Costs used in NICE TA429[9] are shown in the second column in Table 28, which the ERG have explored using in a scenario analysis. Adverse events were applied only to the first cycle of the economic model for simplicity and there was a lack of information on when the AEs occurred for the comparators in the CS economic model.

Table 28: Summary of costs of AEs used in the economic model

AE	Costs used in company base-case	Costs used in NICE TA429	Costs used in ERG scenario analysis for VEN+R
ALT/AST elevation	£ 0.00	-	£0.00
Anaemia	£ 1,170.78	£ 3,042.17	£ 3,042.17
Autoimmune haemolytic anaemia	£ 1,170.78	-	£ 1,170.78
Neutropenia	£ 119.49	£ 2,386.17	£ 2,386.17
Pneumonia	£ 6,149.58	£ 2,733.21	£ 2,733.21
Thrombocytopenia	£ 621.34	£ 2,191.65	£ 2,191.65
Infusion Related Reaction	£ 401.07	-	£ 401.07

Terminal care costs

Terminal care costs were included in the economic model and applied to all patients who died. Cost estimates were based on a published study of end of life care for solid tumour cancer patients by Round et al (2015)[41] and were presented in CS Table 55. The specific cost used was guided by the TA429 appraisal.[9] The CS noted that clinical experts advising on the ibrutinib submission process suggested that the costs of terminal care would be similar between solid tumour and haematology patients. The total cost for terminal care per patient was £6,601.23 (inflated to 2016-17 prices).

ERG summary

- Drug dosing schedules and costs were provided by the company.
- No drug wastage costs were included in the model.
- A two-year stopping rule was applied when calculating intervention costs for VEN+R, whereas treatment with ibrutinib and IDELA+R continued until disease progression.
- Uncertainty exists around the sources used to estimate adverse event costs in the economic model. For this reason, the ERG have performed scenario analyses using estimates for adverse events from other sources identified in the literature.

5.2.11 Cost effectiveness results

5.2.11.1 Base-case analysis

The CS base-case analysis used PFS and OS hazard ratios from the unanchored MAIC, applying a 2-year maximum treatment duration to the VEN+R when estimating treatment costs, and assigning health-state utility values of 0.748 and 0.600 for the pre-progression and post-progression health states respectively.

The unanchored MAIC analysis that informed the base-case analysis generated a PFS HR of [redacted] and an OS HR of [redacted] for VEN+R vs. ibrutinib. For the comparison with IDELA+R, the corresponding HRs were [redacted] for PFS and [redacted] for OS, respectively. The CS noted that applying these HRs in the comparison with ibrutinib leads to PFS exceeding OS for ibrutinib which is impossible and lacks face-validity. Thus, in the CS base-case model, the PFS is restricted to being equal or lower than OS, resulting in zero post-progression period for ibrutinib.

The CS explained that this lacks face validity in the base-case model predictions of ibrutinib survival due to "*predominantly a consequence of the large uncertainty margins surrounding the MAIC estimates"*. However, the ERG notes that although the unanchored MAIC HRs had wide 95% CIs, this would not translate into uncertainty in the final cost-effectiveness estimates, because the MAIC estimates suggests VEN+R significantly improved OS compared to ibrutinib or IDELA+R (note OS estimates are the key drivers of cost-effectiveness in the CS sensitivity analyses).

The base-case model also accounted for disutility and costs associated with adverse events. The cost of TLS prophylaxis for patients on VEN+R are included in the model, but disutility associated with TLS was not taken into account. The CS base-case cost-effectiveness results for adults with R/R CLL who had at least received one prior therapy, with costs and QALYs discounted at 3.5% per annum over the 30-year time horizon are summarised in Table 29.

Table 29: Base-case discounted results, whole population (CS Tables 61 and 62)

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	ICER vs. baseline (£/QALY)	Pairwise ICER vs. VEN+R (£/QALY)
No discount applied to VEN+R						
IDELA+R	[redacted]	2.307	[redacted]	-	[redacted]	[redacted]
VEN+R	[redacted]	5.666	[redacted]	3.358	[redacted]	[redacted]
Ibrutinib	[redacted]	3.067	[redacted]	-0.759	[redacted]	[redacted]
[redacted]**** applied to VEN+R***						
IDELA+R	[redacted]	2.307	-	-	-	£2,625
VEN+R	[redacted]	5.666	-7.003	-3.358	£2,625	-
Ibrutinib	[redacted]	3.067	-0.851	-0.759	£194,048	Dominated

* At net price ([redacted] applied to venetoclax)

For the adults with R/R CLL using list prices, the CS deterministic base-case showed that on average ibrutinib was the most expensive of the three interventions, but VEN+R generated more QALYs than ibrutinib or IDELA+R.

For the comparison with ibrutinib using the list price, the CS deterministic base-case showed VEN+R was [redacted] cheaper and also generated [redacted] more QALYs than ibrutinib. For the comparison with IDELA+R, VEN+R was more expensive, but generated more QALYs. Thus, the CS deterministic base-case analysis showed that VEN+R [redacted] ibrutinib; when VEN+R was compared with IDELA+R it generated an incremental cost-effectiveness ratio (ICER) of [redacted] per QALY gained.

The CS presented a deterministic base-case analysis in which a [redacted] is applied to the list price of venetoclax in the VEN+R regimen (CS Table 62). These cost-effectiveness results were very similar to those based on list price with VEN+R dominating ibrutinib; and generating an ICER of £2,625 per QALY gained when comparing VEN+R with IDELA+R (see Table 29).

5.2.11.2 Probabilistic base-case analysis

The CS presented probabilistic base-case analysis incorporating uncertainty in the model inputs. This allows for the probability that each intervention is the most cost-effective strategy to be calculated. The CS probabilistic base-case results produced similar results to the deterministic analysis with VEN+R dominating ibrutinib, and when compared with IDELA+R generating a probabilistic mean ICER of [redacted] per QALY gained.

Cost-effectiveness planes from the CS clarification response for the probabilistic base-case analysis using both the list and the net prices ([redacted] for VEN+R) are presented in ***[redacted] 7 and

[redacted] 8. When VEN+R is compared with ibrutinib the majority of iterations fall in the south-east quadrant; whereas, when VEN+R is compared with IDELA+R the majority of the iterations fall in the north-east quadrant.

8

The cost-effectiveness acceptability curves (CEACs) from the CS probabilistic base-case analysis using both the list and the net prices (for VEN+R) are presented in *** 9 and

Error! Reference source not found.. These show that the probability that VEN+R is cost-effective compared ibrutinib, and when VEN+R is compared with IDELA+R at a willingness-to-pay threshold of £20,000 per QALY the probability was close to [redacted] based on the list price analysis and over [redacted] when based on the net price analysis.

[redacted]

[redacted]

[redacted]

[redacted]

5.2.12 Sensitivity analyses

5.2.12.1 Deterministic sensitivity analysis

The CS conducted one-way sensitivity analysis (OWSA) to identify key model drivers and important sources of uncertainty by varying or substituting alternative values of parameter inputs one at a time. In each of these analyses, the central estimate of each base-case parameter was replaced with lower and higher estimates that correspond to the lower and upper 95% CIs of parameter inputs. Tornado plots showing the first six-parameters associated with the greatest uncertainty on cost-effectiveness results on the net monetary benefit scale are presented in ***[redacted]10 and

**[redacted]11 for the list price comparisons with ibrutinib and IDELA+R. The plots suggests that the OS and PFS hazard ratios and the VEN+R joint model parameters had the greatest impact on incremental costs and incremental QALYs (and hence the incremental net monetary benefit) in the comparison with ibrutinib.

[redacted]

[redacted] 10

Key: BR, bendamustine+rituximab; HR, hazard ratio; OS, overall survival; PFS, progression free survival; TLS, tumour lysis syndrome; VEN+R, venetoclax+rituximab

[redacted] 11

Key: BR, bendamustine+rituximab; HR, hazard ratio; OS, overall survival; PFS, progression free survival; TLS, tumour lysis syndrome; VEN+R, venetoclax+rituximab

For the comparison with ibrutinib, the ERG believes the CS deterministic OWSA that used the upper and lower 95% CI estimates of the HR for OS from the unanchored MAIC were not that informative and potentially misleading because the unanchored MAIC analysis does not adequately capture the uncertainty in overall survival estimates for VEN+R vs. ibrutinib. This is because the MAIC results suggested VEN+R significantly improved OS compared with ibrutinib by considerable margin (i.e. crudely, OS HRs translate into almost [redacted] in the hazard/risk of death for VEN+R compared with ibrutinib on average, 95% CIs ranging from [redacted] to [redacted] reduction in risk of death). The CS claims that due to the immaturity of the MURANO trial data (see CS section B.2), estimates of HRs for OS based on the MAIC analysis are highly uncertain, but the ERG does not believe the 95% CIs around the OS HR for VEN+R vs. ibrutinib reflected any degree of uncertainty (when used to inform a deterministic cost-effectiveness model) because the HRs suggested that VEN+R significantly improved OS compared with ibrutinib. This combined with the 2-year maximum treatment duration for VEN+R implies VEN+R will continue to dominate ibrutinib when using the estimate of OS HRs from the unanchored MAIC analysis. The ERG believes a more informative OWSA exploring uncertainty with the OS benefit for VEN+R compared with ibrutinib will have been to use the OS HRs from the anchored MAIC analysis that compared VEN+R to ibrutinib under the assumption that the relative efficacy of VEN+R vs. ibrutinib+BR can be extended to VEN+R vs. ibrutinib.[20] The OS HRs from the anchored MAIC suggested [redacted]. This confidence interval crosses 1 and hence reflects a greater degree of uncertainty in the comparison with ibrutinib.

5.2.12.2 Scenario analyses

The CS presented extensive scenario analyses to test the robustness of the model structure and assumptions (see CS Tables 68 and 69). In all, a total of 51 analyses were conducted for R/R CLL using both list and net prices (with the net price analysis applying a [redacted] discount to the cost of VEN in the VEN+R regimen). The CS found the model predictions were generally robust with VEN+R continuing to dominate ibrutinib in the majority of the scenario analyses undertaken. The only exception to this trend reported was when the analyses are restricted to shorter time horizons (1-year and 2-year) when using the list price. When comparing ibrutinib with VEN+R, the ICERs

were [redacted] and [redacted] per QALY gained based on shorter 2-year and 1-year time horizons, respectively.

5.2.13 Subgroup analyses

The CS presented cost-effectiveness results for subgroup of R/R CLL patients with (i) del(17p) and/or TP53 mutation and (ii) without del(17p) and/or TP53 mutation. The CS explained that del(17p) and TP53 mutation are known to negatively affect a patient's prognosis, thus patients with this mutation would generally have a lower survival than the whole R/R CLL population and those patients who do not have this deletion or mutation (see CS Figures 43 to Figure 45).

The net effect of this is that average time to treatment (ToT) for the treatment regimens are considerably shorter for patients with del(17p)/TP53 as shown in
Table 30 (combining data displayed in CS Table 58, Table 70 and Table 75).

Table 30: Average time on treatment

Treatment	Average time on treatment (Mean years)		
	Whole R/R CLL population	del(17p)/TP53 subgroup	Non-del(17p)/TP53 subgroup
VEN+R	1.859	1.823	1.871
Ibrutinib	4.661	3.965	4.880
IDELA+R	1.833	1.535	1.957

Cost-effectiveness results for the subgroup of patients with and without del(17p)/TP53 from the CS are presented in Table 31 and Table 32 respectively, and they are in in line with company's base-case results.

Table 31: Base-case results (del(17p)/TP53) (CS Table 73 and 74)

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	ICER vs. baseline (£/QALY)	Pairwise ICER VS. VEN+R (£/QALY)
No discount applied to VEN+R						
IDELA+R	[redacted]	2.045	[redacted]	-	[redacted]	[redacted]
VEN + R	[redacted]	5.132	[redacted]	-3.087	[redacted]	[redacted]
Ibrutinib	[redacted]	2.726	[redacted]	-0.681	[redacted]	[redacted]
[redacted] ***applied to VEN+R***						
IDELA+R	[redacted]	2.045	-	-	-	£6,013
VEN + R	[redacted]	5.132	-£18,558	-3.087	£6,013	-
Ibrutinib	[redacted]	2.726	-£127,669	-0.681	£187,556	Dominated

Table 32: Base-case results (non-del(17p)/TP53) (CS Table 78 and 79)

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	ICER vs. baseline (£/QALY)	Pairwise ICER VS. VEN+R (£/QALY)
No discount applied to VEN+R						
IDELA+R	[redacted]	2.411	[redacted]	-	[redacted]	[redacted]
VEN + R	[redacted]	5.869	[redacted]	-3.458	[redacted]	[redacted]
Ibrutinib	[redacted]	3.193	[redacted]	-0.782	[redacted]	[redacted]
[redacted] ***applied to VEN+R***						
IDELA+R	[redacted]	2.411	-	-	-	£1,333
VEN + R	[redacted]	5.869	-£4,608	-3.458	£1,333	-
Ibrutinib	[redacted]	3.193	-£152,538	-0.782	£194,985	Dominated

5.2.14 Model validation and face validity check

5.2.14.1 Company's work

The CS reported a number model validation and face-validity checks following the structured format described in the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) checklist.[42] This included:

- Assessment of face-validity and conceptual model structure check by a number of health economists and academics (including [redacted]) experienced in critique of economic models in CLL submitted for reimbursement decisions by NICE.
- Cross validating the model by comparing the model structure and outcomes to that of other economic models in CLL (including models that informed previous TAs). Cross validation of model results of existing models were not explicitly conducted.
- Scenario analyses incorporating alternative input data were used to cross-validate model inputs (section B.3.8.3 of CS).
- Reported quality checks and tests (and tests results) carried by senior economic modeller of the excel model (CS Table 81).

5.2.14.2 ERG's face validity check

As indicated in section 4.7, the ERG has found that the OS HR estimate for the VEN+R versus ibrutinib comparison, which was obtained from the MAIC comparison, was not plausible given its magnitude and the implausible relationship between PFS and OS HRs. The use of this HR in the cost-effectiveness evaluation to compare VEN+R vs ibrutinib led to an estimated life expectancy of 10.78 years for VEN+R and 4.63 years for ibrutinib. Below the ERG has further demonstrated that the estimated life expectancy with ibrutinib derived from the company's model is pessimistic.

First, the ERG has attempted to compare the predictions made by the company to the previous appraisal of ibrutinib[9]. However, the estimated LYs reported in the publicly available committee papers were redacted, and only the incremental LYs were visible, as shown in Table 33. The ERG of NICE TA429 commented that whilst the indirect comparisons of ibrutinib suggested it was

clinically superior to its comparators, there remained significant uncertainty over the magnitude of the benefit.

Table 33: Incremental LYG estimates of ibrutinib

Comparators	Incremental life year gain NICE TA429	Estimates from company's base-case
Ibrutinib vs Ofatumumab	3.47 (Head to Head Trial)	-
Ibrutinib vs Idelalisib+Rituximab	2.60 (Bucher ITC)	0.85
Ibrutinib vs Bendamustine+Rituximab	4.79 (MAIC)	-
Source	Taken from Table 8 from company comments to ACD1 of NICE TA429 [9]. Unclear if discounting has been applied.	Obtained from economic model, undiscounted. (4.635 - 3.785)

It is clear that LY of ibrutinib estimated from the company's base-case compared to that of VEN+R analysis is far more pessimistic than in TA429. Despite the LY being withheld from TA429, it is apparent that the estimate is very likely to exceed 5 years due to the estimated incremental difference against BR. However, the estimate of undiscounted LYs in the company's base-case analysis for ibrutinib was just 4.6 years (information extracted from the company's economic model and CS Table 61).

When using an OS HR of 0.48 for the comparator treatments, as estimated in the clinical section for the relative efficacy of BR to VEN+R (Seymour et al. NEJM[11]), the undiscounted estimated LY is [redacted] years. Adding the 4.79 years incremental LYs estimated for ibrutinib in TA429 would imply a total LY of [redacted] years for ibrutinib. This contrasts greatly with the 4.63 years reported in the CS.

Second, the ERG has undertaken further analysis by digitizing published OS KM graph[29] from the RESONATE study. Using DigitizeIt v2.2.3[43] software, IPD was generated, replicating the ibrutinib population. This IPD was then modelled parametrically using Stata 15 [26], and the mean survival calculated accordingly.

As reported by the company in the modelling of the MURANO data, the more flexible parametric models predicted a decreasing hazard rate over time, which is known not to reflect the true long nature of the disease. As a result, an exponential model provided the most plausible estimate, which assumed a constant hazard over time and so it is possible that this approach produces a slightly optimistic estimate of the ibrutinib life years, however it is similar to the extrapolation used in the appraisal of ibrutinib, where the company initially opted for a log-normal curve followed by an exponential tail.

The resulting life expectancy from the second method is [redacted] years for ibrutinib.

Table 34 shows the LY estimates using our two methods described above compared to that obtained from the company's economic model which used the MAIC-estimated OS HR. The ERG also compared the median OS predicted by the company's base-case, to the ERG's preferred HR under the company's assumptions, and to the ERG's reconstructed IPD (Table 35). Both of the ERG's approaches estimate a much higher median OS than the company's base-case. Our methods demonstrate that the company's estimate of 4.635 years is pessimistic. In addition, published 3-year OS data is available from the RESONATE study[20], with 74% of patients on ibrutinib alive. The company's base-case model predicts that only [redacted] of patients will be alive at 3 years, further demonstrating the poor representation of ibrutinib in the company's model, despite the fact that the baseline characteristics of the trials suggest that MURANO population is healthier.

In section 5.3, we will show that the use of OS HR derived from the indirect treatment comparison undertaken by the ERG (section 4.8) leads to much more plausible life expectancy for ibrutinib which matches with the estimates reported in Table 33.

Table 34: A comparison of the ibrutinib LY estimates

	Company's model (derived using MAIC OS HR, undiscounted)	ERG's method 1: using incremental difference from TA429 of ibrutinib and BR, applied to estimate of BR LYG from MURANO (unclear if discounting is applied)	ERG's method 2: using reconstructed IPD from RESONATE+ extrapolation (undiscounted)
Ibrutinib life expectancy estimate	[redacted]4.635	[redacted]	[redacted]

Table 35: Comparison of median OS for VEN+R and ibrutinib.

Treatment	Scenario	Assumptions	Median OS
VEN+R	Company Base-case	Weibull Curve	[redacted]

Ibrutinib	Company Base-case	MAIC HR applied to VEN+R Weibull survival	[redacted]
Ibrutinib	ERG NMA HR for Ibrutinib	ERG HR applied to VEN+R Weibull survival	[redacted]
Ibrutinib	ERG IPD reconstruction	Exponential Curve	[redacted]

5.3 Exploratory and sensitivity analyses undertaken by the ERG

The ERG undertook extensive exploratory analyses to assess the effect of varying model assumptions and parameter inputs on the cost-effectiveness results. As stated in section 5.2.10, the ERG identified an error in the model that meant the cost of rituximab was applied to the VEN+R regimen in first 6 cycles of the model (corresponding to approximately the first 6 months of treatment). The ERG believed the costs of rituximab should be included in the cycles 2 to 7 of the model because the dose-titration schedule involves venetoclax monotherapy only in the first 4 weeks of treatment (corresponding to the first cycle of the model). The ERG asked the company to clarify whether the costs of rituximab were included in cycle 7 of the model for VEN+R regimen. In response, the company confirmed that "*the cost of rituximab is not included in the 7th cycle onwards for the total treatment costs of VEN+R and idelalisib+R. The dosing regimen of rituximab used in the model is 375 mg/m2 administered on day 1 of cycle 1 and 500 mg/m2 on day 1 of cycles 2-6 for a total of 6 cycles"*. The ERG believes the CS approach to calculation of rituximab costs is not correct for the reasons given, but we don't believe that the total costs or the ICER would change much should a correction be made. The company did not provide an economic model with this correction in the clarification response.

In response to further clarifications raised by the ERG about rituximab in the VEN+R arm after the clarification process was completed, the company stated that "*Rituximab is administered after completion of the dose titration period of venetoclax. However, the model simplifies such that venetoclax (dose titration) and rituximab start on the same day; structural changes would be required to bring this into alignment with the MURANO protocol and would have minimal impact on results*."

However, the company did note the following: "*upon investigating the dose titration assumption in the model more closely, it has come to our attention that an error has occurred regarding the*

time on venetoclax treatment. According to the MURANO protocol, venetoclax dosing at 400mg should be given to progressive disease or 2 years, from start of combination therapy. However, in the model, the dose titration period has been captured in this 2-year duration, and one cycle of venetoclax at 400mg has been erroneously excluded…..." The company then provided guidance for correcting the error so that modelling of VEN+R dosing regimen closely matches that specified in the MURANO trial. The correction involves including an additional cycle for venetoclax (i.e. treatment cycle changes from 24 to 25) and also additional week of venetoclax (400 mg per day) in the titration period. The company provided updated base-case results generated from the corrected models for the R/R CLL population which showed that ICER for VEN+R vs ibrutinib remains [redacted] while the ICER for VEN+R vs IDELA+R increases by [redacted] to [redacted] per QALY gained. The company also stated that "the corrections made also influence the budget impact however, the impact is moderate."

Cost-effectiveness results generated using the company's base-case parameters applied to the corrected model are presented in Table 36. When using the list prices, the results suggest VEN+R remained [redacted] compared with ibrutinib, whilst the ICER for VEN+R compared with IDELA+R increased from [redacted] per QALY gained in the original CS base-case model to [redacted] per QALY gained in the corrected model. Using the net price after applying a [redacted] discount for VEN+R, the ICER increased from £2,625 per QALY gained in the original CS base-case model to £3,492 per QALY gained when compared with IDELA+R.

Table 36: CS base–case corrected model: CS base-case discounted results after ERG applied the corrections to the dosing regimen and treatment costs for VEN+R for R/R CLL population

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	ICER vs. VEN+R (£/QALY)
No discount applied to VEN+R					
VEN+R	[redacted]	5.666	[redacted]	-	
Ibrutinib	[redacted]	3.067	[redacted]	2.599	[redacted]
IDELA+R	[redacted]	2.307	[redacted]	3.358	[redacted]
[redacted] ***applied to VEN+R***					
VEN+R	[redacted]	5.666	-	-	

Ibrutinib	[redacted]	3.067	-£135,650	2.599	Dominated
IDELA+R	[redacted]	2.307	£11,726	3.358	£3,492

The ERG exploratory analyses reported below are based on the corrected model.

The CS base-case model was informed by HRs derived from adjusted MAIC analyses. Thus, the ERG believes the modelled population should therefore have been the competitor trial population when using the MAIC estimates and not from the MURANO trial. For the comparison with ibrutinib, this would involves adjusting the mean age, % male and % with del(17p)/TP53 mutation from 64.2 years, 73.8% and 29.96% observed in MURANO trial to 66.5 years, 68.0% and 32.3% in the RESONATE cohort, respectively. Similarly for the comparison with IDELA+R, the modelled population should be adjusted to median age of 71 years, 73.8% male and 43.64% with del(17p)/TP53 mutation reflecting the distribution of these characteristics in Study 116. Implementing these changes have very minimal impact on the cost-effectiveness estimates with VEN+R continuing to [redacted] ibrutinib in both list and net price comparisons (Table 37). For the comparison with IDELA+R, the ICER increased by [redacted] (list price) and by [redacted] (net price) per QALY gained (Table 38).

Table 37: CS base–case corrected model: changed modelled population to the RESONATE in the comparison with ibrutinib (R/R CLL population)

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	ICER vs. VEN+R (£/QALY)
No discount applied to VEN+R					
VEN+R	[redacted]	5.55	[redacted]	-	
Ibrutinib	[redacted]	3.017	[redacted]	2.533	[redacted]
[redacted] ***applied to VEN+R***					
VEN+R	[redacted]	5.55	-	-	
Ibrutinib	[redacted]	3.017	-£133,765	2.533	Dominated

Table 38: CS base–case corrected model: changed modelled population to Study 116 cohorts in the comparison with IDELA+R (R/R CLL population)

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	ICER vs. VEN+R (£/QALY)
No discount applied to VEN+R					
VEN+R	[redacted]	5.24	[redacted]	-	
IDELA+R	[redacted]	2.156	[redacted]	3.084	[redacted]
[redacted] ***applied to VEN+R***					
VEN+R	[redacted]	5.24	£102,033	-	
IDELA+R	[redacted]	2.156	£13,815	3.084	£4,480

5.3.1 Uncertainty around the OS hazard ratio in the comparison with ibrutinib

For the comparison with ibrutinib, the company provided anchored MAIC estimates in the CS as sensitivity analyses under the assumption that ibrutinib single-agent has equivalent efficacy to ibrutinib+BR based on the results of Hillmen et al (2015).[20] Under this assumption, anchored MAIC analyses could be conducted assuming that relative efficacy of VEN+R vs. ibrutinib+BR could be extended to VEN+R vs. ibrutinib single-agent (see CS section B.2.9.5).

The OS hazard ratio from the anchored MAIC was [redacted] The results presented in Table 39 to Table 41 suggests that:

- Applying the mean and lower 95% CI estimate of the OS HR had minimal impact on the ICER with VEN+R continuing to [redacted] ibrutinib based on both the list and net price comparisons (Table 39 and Table 40).
- Applying the higher 95% CI estimate of the OS HR (i.e. [redacted]) generated an incremental cost of [redacted] (list price analysis), [redacted] (net price analysis) and incremental QALYs of [redacted] for VEN+R vs. ibrutinib (Table 41). This suggests that VEN+R is cheaper but also generated fewer QALYs on average than ibrutinib. The ICER was [redacted] (list price) and [redacted] (net price analysis) [redacted] for VEN+R compared with ibrutinib.

Table 39: CS base–case corrected model: used OS HR from company's anchored MAIC (adjusted) analysis (R/R CLL population)

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	Pairwise ICER (£/QALY)
No discount applied to VEN+R					
Ibrutinib	[redacted]	4.191	[redacted]	-	[redacted]
VEN + R	[redacted]	5.666	[redacted]	1.475	[redacted]
[redacted] ***applied to VEN+R***					
Ibrutinib	[redacted]	4.191			
VEN + R	[redacted]	5.666	-£149,447	1.475	Dominated

Table 40: CS base–case corrected model: used lower 95% CI estimate of the OS HR from company's anchored MAIC (adjusted) analysis (R/R CLL population)

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	Pairwise ICER (£/QALY)
No discount applied to VEN+R					
Ibrutinib	[redacted]	2.397	[redacted]	-	[redacted]
VEN + R	[redacted]	5.666	[redacted]	3.269	[redacted]
[redacted] ***applied to VEN+R***					
Ibrutinib	[redacted]	2.397			
VEN + R	[redacted]	5.666	-£84,647	3.269	Dominated

Table 41: CS base–case corrected model: used upper 95% CI estimate of the OS HR from company's anchored MAIC (adjusted) analysis (R/R CLL population)

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	Pairwise ICER (£/QALY)
No discount applied to VEN+R					
Ibrutinib	[redacted]	6.546	[redacted]	-	[redacted]
VEN + R	[redacted]	5.666	[redacted]	-0.88	[redacted]
[redacted] ***applied to VEN+R***					
Ibrutinib	[redacted]	6.546			
VEN + R	[redacted]	5.666	-£172,056	-0.88	£195,564

Superseded- see erratum

5.3.2 Uncertainty around the OS hazard ratio in the comparison with IDELA+R

The ERG has conducted exploratory analyses similar to those carried out for the ibrutinib comparison to investigate uncertainties around the OS HR for VEN+R vs IDELA+R. Using data that the company provided in response to ERG clarification questions (see point 3, section A9), the company explained that HRs for OS and PFS for VEN+R vs IDELA+BR were based on anchored MAIC analysis and these were not presented in the original CS because there is no published evidence to suggest IDELA+R and IDELA+BR have similar efficacy. Nevertheless, the company provided adjusted anchored MAIC estimates suggesting that VEN+R is associated with PFS HR of [redacted] based on the IRC definition of PFS and OS HR of [redacted] compared with IDELA+BR. The ERG was satisfied with the company's response and appreciates the effort undertaken for the extra set of analysis.

The ERG agrees with the company that HRs generated from the anchored MAIC analysis that compared VEN+R vs. IDELA+BR were not appropriate for the decision problem. The ERG conducted its own literature review but was unable to identify studies that would allow an indirect comparison between VEN+R vs IDELA+R. In the absence of reliable comparative evidence, the ERG conducted a sensitivity analyses to test the impact of assuming similar effect for VEN+R and IDELA+R by setting the HR for OS for VEN+R vs. IDELA+R to 1 (Table 42). Under this assumption, VEN+R was more costly but generated more QALYs than IDELA+R generating an ICER of [redacted] per QALY gained in the list price analysis. For the net price analysis, VEN+R was cheaper and generated more QALYs than IDELA+R, therefore dominated IDELA+R.

Table 42: CS base–case corrected model: assumed an OS HR of 1 for VEN+R vs. IDELA+R (R/R CLL population)

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	Pairwise ICER (£/QALY)
No discount applied to VEN+R					
IDELA+R	[redacted]	5.154	[redacted]	-	[redacted]
VEN + R	[redacted]	5.666	[redacted]	0.512	[redacted]
[redacted] ***applied to VEN+R***					
IDELA+R	[redacted]	5.154			
VEN + R	[redacted]	5.666	-£14,944	0.512	Dominated

5.3.3 ERG preferred method of estimating the hazard ratio for VEN+R vs. ibrutinib

The company's adjusted unanchored MAIC analysis produced an OS HR of [redacted] for VEN+R vs. ibrutinib, suggesting a [redacted]% risk reduction in OS with VEN+R compared with ibrutinib. As already stated, the ERG believed this HR is highly uncertain.

Therefore, the ERG conducted an indirect comparison using a fixed-effect NMA to compare survival outcomes for VEN+R vs. ibrutinib (see section 4.8), using these new HRs from the indirect comparison the ERG applied this to corrected base-case model. As seen in Table 43, the CS base-case corrected ICER changed from VEN+R dominating ibrutinib, to an ICER of [redacted] (list price) and £790,988 (net price) per QALY lost (i.e. VEN+R was cheaper but also generated on average 0.354 fewer QALYs compared with ibrutinib).

Table 43: CS base–case corrected model: used central estimate of PFS and OS HR for VEN+R vs. ibrutinib from ERG's indirect comparison analysis (R/R CLL population)

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	Pairwise ICER (£/QALY)
No discount applied to VEN+R					
Ibrutinib	[redacted]	6.019	[redacted]	-	[redacted]
VEN + R	[redacted]	5.666	[redacted]	-0.354	[redacted]
[redacted] ***applied to VEN+R***					
Ibrutinib	[redacted]	6.019			
VEN + R	[redacted]	5.666	-£279,766	-0.354	£790,988

Using the lower and upper 95% CI estimate of HRs generated from the ERG's indirect comparison in OWSA suggested that the cost-effectiveness results were most sensitive to the HR for OS with ICERs ranging from VEN+R [redacted] ibrutinib using the lower 95% CI estimate to VEN+R being comparatively cheaper, but also generating fewer QALYs than ibrutinib using the upper 95% CI estimate for OS (see Table 51 for further sensitivity analyses results).

5.3.4 Further exploratory analyses undertaken by ERG

The ERG considered the company's approach to parameterisation and long-term extrapolation of the OS and PFS curves for VEN+R and the comparators (see section 5.2.6). The ERG conducted a series of exploratory analysis based on the corrected model to investigate the impact of assuming alternative parametric modelling of PFS and OS. The results suggest changing the parametric modelling from joint-Weibull to joint-Gamma survival curves for both OS and PFS (Table 44) had minimal impact on the ICER with VEN+R continuing the [redacted] ibrutinib in both list and net price comparisons. For the comparison with IDELA+R, the ICER decreased from [redacted] to [redacted] per QALY gained based on list price analysis and from [redacted] to £2,903 per QALY gained based on net price analysis (Table 44).

Table 44: CS base–case corrected model: changed PFS and OS parametric curves from joint-Weibull to joint-Gamma: VEN+R vs ibrutinib (R/R CLL population)

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	ICER vs. VEN+R (£/QALY)
No discount applied to VEN+R					
VEN+R	[redacted]	6.04	[redacted]	-	
Ibrutinib	[redacted]	3.157	[redacted]	2.884	[redacted]
IDELA+R	[redacted]	2.351	[redacted]	3.69	[redacted]
[redacted] ***applied to VEN+R***					
VEN+R	[redacted]	6.04	-	-	
Ibrutinib	[redacted]	3.157	-£142,716	2.884	Dominated
IDELA+R	[redacted]	2.351	£10,711	3.69	£2,903

The ERG also tried further analyses, for example, where we choose joint-Gamma for PFS and joint-Weibull for OS (or vice versa), but this had minimal impact on the ICER, whereby VEN+R continued to [redacted] ibrutinib and the ICERs ranged between [redacted] and [redacted] per QALY gained for VEN+R compared with IDELA+R (see Table 51 and Table 52).

The ERG considered scenarios using the alternative higher estimates of routine care costs and TLS prophylaxis costs based on the figures in TA487 and adverse events costs based on Figures reported in TA439 (see Section 5.2.10.2). Implementing all these changes together had minimal impact on the ICER with VEN+R continuing to [redacted] ibrutinib (Table 45). For the comparison with IDELA+R, the ICER increased from the CS corrected base-case value of [redacted] to [redacted] per QALY gained based on list price and from [redacted] to £5,694 per QALY gained based on the net price (Table 45).

Table 45: CS base–case corrected model: changed TLS prophylaxis, adverse events costs and routine care costs (R/R CLL population)

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	ICER vs. VEN+R (£/QALY)
No discount applied to VEN+R					
VEN+R	[redacted]	5.666	[redacted]	-	
Ibrutinib	[redacted]	3.157	[redacted]	2.884	[redacted]
IDELA+R	[redacted]	2.307	[redacted]	3.358	[redacted]
[redacted] ***applied to VEN+R***					
VEN+R	[redacted]	5.666	-	-	
Ibrutinib	[redacted]	3.157	-£142,716	2.884	Dominated
IDELA+R	[redacted]	2.307	£19,123	3.358	£5,694

5.3.5 ERGs preferred base-case model

5.3.5.1 ERGs preferred base-case for the ibrutinib comparison

The ERG's preferred base-case model for the ibrutinib comparison involves making the following assumptions and changes to the CS corrected base-case model:

- Changing the parametric survival curves from joint-Weibull to joint-Gamma for both PFS and OS
- Changing the unanchored MAIC PFS and OS HRs to ERGs indirect comparison using estimates of PFS and OS for ibrutinib vs BR reported in Hillmen (2015)[20] and for VEN+R vs BR based on the MURANO data.

The ERGs preferred base-case for the comparison with ibrutinib is presented in Table 46.

Table 46: ERG preferred base–case corrected model for the comparison with ibrutinib (R/R CLL population)

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	ICER vs. VEN+R (£/QALY)
No discount applied to VEN+R					
VEN+R	[redacted]	6.04	[redacted]	-	
Ibrutinib	[redacted]	6.431	[redacted]	-0.39	[redacted]
[redacted] ***applied to VEN+R***					
VEN+R	[redacted]	6.04	-	-	
Ibrutinib	[redacted]	6.431	-£322,979	-0.39	£827,252

The results in Table 46 suggest VEN+R is [redacted] (list prices) and -£322,979 (net prices) cheaper than ibrutinib, but also generated 0.39 fewer discounted QALYs on average. The corresponding ICERs were [redacted] and £827,252 per QALY lost for VEN+R compared with ibrutinib based on list and net price comparisons, respectively. The ERG preferred base-case corrected model thus produced similar estimate of incremental costs as the CS base-case corrected model but differed in the direction of incremental QALYs generated. The ERG probabilistic base-case results (not presented) produced similar ICERs as the deterministic analyses. The probability that VEN+R is cost-effective compared with ibrutinib at £20,000 per QALY is close to [redacted] in both the list and net price comparisons.

The ERG applied its preferred base-case model to the populations with and without del(17p)/TP53 mutation for the ibrutinib comparison. The results of these analyses were similar to the ERGs preferred base-case results with VEN+R being cheaper but also generating fewer QALYs compared with ibrutinib in both list and net prices comparison (Table 47 and Table 48).

Table 47: ERG preferred base–case corrected model (del(17p)/TP53 mutation) for the comparison with ibrutinib

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	ICER vs. VEN+R (£/QALY)
No discount applied to VEN+R					
VEN+R	[redacted]	5.494	[redacted]	-	
Ibrutinib	[redacted]	5.87	[redacted]	-0.376	[redacted]
[redacted] ***applied to VEN+R***					
VEN+R	[redacted]	5.494	-	-	
Ibrutinib	[redacted]	5.87	-£269,728	-0.376	£718,043

Table 48: ERG preferred base–case corrected model (nondel(17p)/TP53 mutation)) for the comparison with ibrutinib

No discount applied to VEN+R					
VEN+R	[redacted]	6.245	[redacted]	-	
Ibrutinib	[redacted]	6.638	[redacted]	-0.393	[redacted]
[redacted] ***applied to VEN+R***					
VEN+R	[redacted]	6.245	-	-	
Ibrutinib	[redacted]	6.638	-£343,718	-0.393	£873,858

5.3.5.2 ERGs preferred base-case model with a waning effect for the ibrutinib comparison

Due to the two-year treatment course of venetoclax for patients receiving VEN+R, the ERG believe it is plausible that the effects of VEN+R on OS and PFS may wane over time, thus increasing the hazard. Waning effects are often implemented through a steady or sudden increase in a hazard rate of the intervention relative to the hazard rate of one of the comparators. However in this appraisal, a waning effect was incorporated into the model through a percentage increase in the predicted hazards for VEN+R, after 5 years, i.e. increasing the hazard of VEN+R relative to itself. The ERG are unclear why the company chose this approach and they did not instead chose to wane the hazard of VEN+R to either BR, external data or to one of the main comparators.

The ERG are also unsure over the justification for the fixed 5-year implementation point and would have preferred greater flexibility over the beginning of the waning effect. The company also chose to explore the effect of various hazard increases applied simultaneously to PFS and OS (20%, 50% and 100%), again the percentages were chosen arbitrarily. Without any suitable reference or anchor treatment, the ERG found it difficult to establish a range of plausible values for their own sensitivity analysis, and so applied the company's hazard increases onto the ERG base-case assumptions, and also considered scenarios with 10% and 70% hazard increases.

Table 49: ERG preferred base–case model with waning effect applied to PFS and OS estimates for VEN+R in the comparison with ibrutinib (R/R CLL population)

ERG exploration	Total costs VEN+R	Total LYs VEN+R	Total QALYs VEN+R	Total costs Ibrutinib	Total LYs Ibrutinib	Total QALYs Ibrutinib	Incremental costs	Incremental LYs	Incremental QALYs	ICER (LYs)	ICER (QALYs)
No discount applied to VEN+R											
ERG preferred base-case model	[redacted]	8.976	6.04	[redacted]	9.302	6.431	[redacted]	-0.326	-0.39	[redacted]	[redacted]
Applied 10%	[redacted]	8.647	5.832	[redacted]	9.302	6.431	[redacted]	-0.655	-0.599	[redacted]	[redacted]
Applied 20%	[redacted]	8.351	5.645	[redacted]	9.302	6.431	[redacted]	-0.951	-0.786	[redacted]	[redacted]
Applied 50%	[redacted]	7.621	5.182	[redacted]	9.302	6.431	[redacted]	-1.682	-1.249	[redacted]	[redacted]
Applied 70%	[redacted]	7.234	4.937	[redacted]	9.302	6.431	[redacted]	-2.068	-1.494	[redacted]	[redacted]
Applied 100%	[redacted]	6.761	4.636	[redacted]	9.302	6.431	[redacted]	-2.541	-1.795	[redacted]	[redacted]
[redacted] ***applied to VEN+R***											
ERG preferred base-case model	[redacted]	8.976	6.04	[redacted]	9.302	6.431	-£322,979	-0.326	-0.39	£989,832	£827,252
Applied 10%	[redacted]	8.647	5.832	[redacted]	9.302	6.431	-£323,590	-0.655	-0.599	£493,888	£540,430
Applied 20%	[redacted]	8.351	5.645	[redacted]	9.302	6.431	-£324,179	-0.951	-0.786	£340,860	£412,418
Applied 50%	[redacted]	7.621	5.182	[redacted]	9.302	6.431	-£325,781	-1.682	-1.249	£193,730	£260,920
Applied 70%	[redacted]	7.234	4.937	[redacted]	9.302	6.431	-£326,700	-2.068	-1.494	£157,946	£218,679
Applied 100%	[redacted]	6.761	4.636	[redacted]	9.302	6.431	-£327,878	-2.541	-1.795	£129,028	£182,682

The ERG's exploratory analyses in which it applied different rates of waning effect to the venetoclax had the effect of reducing survival outcomes and hence, the total number of life-years lived, total costs and total QALYs for VEN+R. For the list price comparisons, the ICER for VEN+R versus ibrutinib decreased from [redacted] per QALY lost in the ERG's preferred base-case model to between [redacted] per QALY lost for a 10% waning effect and [redacted] per QALY lost with 100% waning effect (Table 49). A similar downward trend in the ICER with an increasing waning effect is observed in the net price comparisons when a [redacted] discount is applied to venetoclax (Table 49).

5.3.5.3 ERGs preferred base-case for the IDELA+R comparison

The ERG was unable to conduct a preferred base-case analysis for the comparison with IDELA+R because no robust estimates of relative efficacy between VEN+R vs. IDELA+R was available. The ERG does not have confidence in the robustness of HRs generated from the company's unanchored MAIC analysis. The ERG conducted a scoping review of the literature but was unable to find relevant information that could be used to estimate the relative effectiveness of VEN+R vs. IDELA+R.

5.4 Conclusions of the cost effectiveness section

The CS presented an economic model that evaluated the cost-effectiveness of VEN+R vs. ibrutinib and IDELA+R as treatment options for adult patients with R/R CLL. The MURANO trial was the main source of clinical effectiveness evidence.

The company extrapolated OS and PFS using a jointly fitted Weibull model to both arms and to both outcomes of the MURANO trial, with strong assumptions of proportionality necessary to obtain plausible OS predictions for VEN+R. The ERG preferred to use a gamma model, which is more consistent with the external data considered by the company, but have concerns of the immaturity of the OS data and its suitability for extrapolation.

The two main drivers of cost-effectiveness versus ibrutinib were the 2-year fixed treatment duration for VEN+R and the HR for OS. The latter was estimated from an unanchored MAIC that

the company had performed. However, the ERG had major reservations about the robustness of the MAIC analyses and the HRs generated from it. For example, the magnitude of the OS benefit that VEN+R had over ibrutinib in the unanchored MAIC would suggest that ibrutinib had worse OS than BR. This the ERG felt is highly implausible based on published evidence on relative efficacy of ibrutinib versus BR.

The ERG identified an error in the calculation of intervention costs for VEN+R which the company corrected upon clarification.

In the company's original and corrected base-case models, VEN+R [redacted] ibrutinib and generated ICERs between [redacted] and [redacted] per QALY gained in the comparison with IDELA+R.

The ERG's preferred base-case model that used HRs from an indirect comparison performed by the ERG suggested that VEN+R was associated with lower costs and lower QALYs compared with ibrutinib with ICERs between [redacted] and £827,252 per QALY lost in the analyses that used list and net prices for VEN+R, respectively.

The ERG was unable to conduct a preferred base-case analysis for the comparison with IDELA+R due to lack of clinical effectiveness evidence for VEN+R vs. IDELA+R.

Further exploratory analyses conducted by the ERG suggested the ICERs were robust to different model inputs and very similar for patients with and without the del(17p)/ TP53 mutation.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

Alterations to the base-case assumptions were made by the ERG as identified in Chapter 5. Further exploratory analyses undertaken by the ERG to test the robustness of the CS base-case assumptions and parameter inputs are in the Appendix. Results are presented in Table 51 for the comparison with ibrutinib and Table 52 for comparison with IDELA+R.

The impact on each change individually on the base-case analysis in comparison with ibrutinib is shown in Table 50.

Table 50: ERG re-estimation of cost-effectiveness

	ΔC	**ΔQALY**	**ΔC/QALY**	**Ratio[+]**
Comparison with ibrutinib – list price				
CS base-case corrected model	[redacted]	2.599	[redacted]	-
ERG models				
Changing the unanchored MAIC PFS and OS HRs to ERGs indirect comparison using estimates of PFS and OS for ibrutinib vs BR reported in Hillmen and for VEN+R vs BR based on the MURANO data	[redacted]	-0.354	[redacted]	[redacted]
ERG preferred base-case analysis	[redacted]	-0.39	[redacted]	[redacted]
Comparison with ibrutinib – net price				
CS base-case model	-£135,650	2.599	Dominated	-
ERG models				
Changing parametric survival curves from joint Weibull to joint-Gamma for both PFS and OS	-£142,716	2.884	Dominated	-

Changing the unanchored MAIC PFS and OS HRs to ERGs indirect comparison using estimates of PFS and OS for ibrutinib vs BR reported in Hillmen and for VEN+R vs BR based on the MURANO data	-£279,766	-0.354	£790,988	-
ERG preferred base-case analysis	-£322,979	-0.39	£827,252	-

+ The ERG have not calculated the ratio

The ERG was unable to conduct a preferred base-case model for the comparison with IDELA+R because no robust estimates of relative efficacy between VEN+R vs. IDELA+R was available.

7 END OF LIFE

End of life considerations do not apply.

8 OVERALL CONCLUSION

8.1 Clinical effectiveness evidence

Although the absence of relevant direct evidence justified the company's decision to conduct a MAIC analysis of VEN+R versus single agent ibrutinib, and the methods used in matching trial populations have been previously validated, the ERG remains concerned about the imprecise estimates of the resulting treatment effect of VEN+R (confidence intervals of HRs for PFS and OS were wide) as well as the implausible HRs for OS. Additional work undertaken by the ERG indirectly comparing estimates of the treatment effect of VEN+R from the MURANO trial against single-agent ibrutinib from Hillmen and colleagues[20] supports the ERG's position.

8.2 Cost-effectiveness evidence

The ERG conducted extensive exploratory analyses to understand the key drivers of cost-effectiveness and to explore the full extent of uncertainty in the economic model results. Absolute lymphocyte count However, there remains a considerable degree of uncertainty associated with the final estimates of cost-effectiveness because the key parameter in the economic model, the hazard ratio for overall survival that measures the magnitude of treatment benefit for VEN+R versus the comparator interventions was estimated with high degree of uncertainty in both the company's submission and the ERG exploratory analyses.

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10 APPENDIX

Table 51: Further exploratory analyses undertaken by the ERG for the comparison with ibrutinib

ERG exploration	List price comparisons			Net price comparisons			Cell changes in GEN SETTINGS sheet in economic model*
	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER	
CS corrected base-case	[redacted]	[redacted]	[redacted]	-£135,650	2.599	Dominated	-
Changed mean age, % male and % del(17p) to values in RESONATE	[redacted]	[redacted]	[redacted]	-£133,765	2.533	Dominated	C8, C9 & C11
Changed routine care costs to £269.94 (pre-progression) and £193.64 (post-progression) figures in TA487	[redacted]	[redacted]	[redacted]	-£141,853	2.599	Dominated	G15 & H15 in CostCalcs sheet
Changed all AE costs to values used in TA439	[redacted]	[redacted]	[redacted]	-£134,524	2.599	Dominated	C34 to C39
Changed TLS prophylaxis costs to £1,808, £2,235 & £2,334 (TA487) for lower risk, greater risk (CRCL ≥80) & greater risk (CRCL<80) groups respectively	[redacted]	[redacted]	[redacted]	-£135,419	2.599	Dominated	M126, N126 & O126 in TLS prophylaxis sheet
Changed TLS prophylaxis and routine care costs to figures reported in TA487; and AE costs to the figures in NICE TA439	[redacted]	[redacted]	[redacted]	-£140,496	2.599	Dominated	C34 to C39; G15 & H15 in CostCalcs sheet; M126, N126 & O126 in TLS prophylaxis sheet
Changed OS HR 0.555 (mean OS HR, CS adjusted anchored MAIC)	[redacted]	[redacted]	[redacted]	-£149,447	1.475	Dominated	C142
Changed OS HR to 0.201 (lower 95% CI, CS adjusted anchored MAIC)	[redacted]	[redacted]	[redacted]	-£84,647	3.269	Dominated	C142
Changed OS HR to 1.534 (upper 95% CI, adjusted anchored MAIC)	[redacted]	[redacted]	[redacted]	-£172,056	-0.88	£195,564	C142
Changed OS HR 1.075 (OS HR, ERGs IC)	[redacted]	[redacted]	[redacted]	-£163,766	-0.027	£6,117,189	C142
Changed OS HR to 0.423 (lower 95% CI, ERGs IC)	[redacted]	[redacted]	[redacted]	-£144,557	.999	Dominated	C142

Changed OS HR to 2.728 (upper 95% CI, ERGs IC)	[redacted]	[redacted]	[redacted]	-£183,238	-2.025	£90,504	C142
Changed PFS HR to 1.429 (PFS HR, ERGs IC)	[redacted]	[redacted]	[redacted]	-£135,650	2.599	Dominated	C132
Changed PFS HR to 0.780 (PFS HR, lower 95% CI, ERGs IC)	[redacted]	[redacted]	[redacted]	-£135,650	2.599	Dominated	C132
Changed PFS HR to 2.615 (PFS HR, upper 95% CI, ERGs IC)	[redacted]	[redacted]	[redacted]	-£89,952	2.599	Dominated	C132
Changed PFS and OS to joint Gamma	[redacted]	[redacted]	[redacted]	-£142,716	2.884	Dominated	C112 & C113
Changed PFS and OS to joint-Gamma, used mean HR for PFS and OS from ERGs IC	[redacted]	[redacted]	[redacted]	-£322,979	-0.39	£827,252	C112 & C113; C142 & C132
Changed PFS and OS joint-Gamma, lower 95% CI for PFS from ERGs IC	[redacted]	[redacted]	[redacted]	-£142,716	2.884	Dominated	C112 & C113; C132
Changed PFS and OS fits to joint-Gamma, upper 95% CI for PFS HR from ERGs IC	[redacted]	[redacted]	[redacted]	-£142,716	2.884	Dominated	C112 & C113; C132
Changed PFS and OS joint-Gamma, lower 95% CI of OS from ERGs IC	[redacted]	[redacted]	[redacted]	-£162,911	2.197	Dominated	C112 & C113; C142
Changed PFS and OS to joint-Gamma, upper 95% CI of OS HR from ERGs IC	[redacted]	[redacted]	[redacted]	-£201,819	-1.846	£109,308	C112 & C113; C142
Changed PFS and OS to joint-Log-logistic	[redacted]	[redacted]	[redacted]	-£137,588	3.066	Dominated	C112 & C113
Changed PFS and OS HR to 1.429 and 1.075 on joint Weibull (ERGs IC)	[redacted]	[redacted]	[redacted]	-£279,766	-0.354	£790,988	C132 & C142
Applied ERGs preferred base-case model to del(17p)/TP53 population	[redacted]	[redacted]	[redacted]	-£269,728	-0.376	£718,043	B2; C112 & C113, C132 & C142
Applied ERGs preferred base-case model to non-del(17p)/TP53 population	[redacted]	[redacted]	[redacted]	-£343,718	-0.393	£873,858	B2; C112 & C113, C132 & C142

* unless stated; IC = indirect comparison

Table 52: Further exploratory analyses undertaken by the ERG for the comparison with IDELA+R

ERG exploration	List price comparisons			Net price comparisons			Cell changes in GEN SETTINGS sheet in economic model*
	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER	
CS corrected base-case	[redacted]	[redacted]	[redacted]	£11,726	3.358	£3,492	-
Changed mean age, % male and % del(17p) to Study 116 figures	[redacted]	[redacted]	[redacted]	£13,815	3.084	£4,480	C8, C9 & C11
Changed routine care costs to figures in TA487	[redacted]	[redacted]	[redacted]	£18,468	3.358	£5,499	G15 & H15 in CostCalcs sheet
Changed TLS prophylaxis costs to estimates used in TA487	[redacted]	[redacted]	[redacted]	£11,958	3.358	£3,561	M126, N126 & O126 in TLS prophylaxis sheet
Changed all AE costs: (Anaemia, Anaemia (Autoimmune haemolytic) , Neutropenia, Pneumonia, Thrombocytopenia) to estimates in NICE TA439	[redacted]	[redacted]	[redacted]	£12,150	3.358	£3,618	C34 to C39
Changed TLS prophylaxis costs and routine care costs to figures in TA487; and AE costs to the figures in TA439	[redacted]	[redacted]	[redacted]	£19,123	3.358	£5,694	C34 to C39; G15 & H15 in CostCalcs sheet; M126, N126 & O126 in TLS prophylaxis sheet
Changed PFS to joint-Gamma	[redacted]	[redacted]	[redacted]	£8,100	3.431	£2,361	C112
Changed OS to joint-Gamma	[redacted]	[redacted]	[redacted]	£14,337	3.617	£3,963	C113
Changed PFS and OS to joint-Gamma	[redacted]	[redacted]	[redacted]	£10,711	3.69	£2,903	C112 & C113
Changed PFS and OS to joint-Log-logistic	[redacted]	[redacted]	[redacted]	£7,737	3.837	£2,017	C112 & C113
Changed OS hazard ratio to 1 (equal efficacy assumption between VEN+R and IDELA+R	[redacted]	[redacted]	[redacted]	-£14,944	0.512	Dominated	C143

* unless stated

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

Pro-forma Response

ERG report

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]

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

If you do identify any factual inaccuracies you must inform NICE by **5pm on Tuesday 11 September 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

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

Limitations of the ERG's ITC analyses, some of which arise from factual inaccuracies

Description of the issue: We welcome the ERG's acceptance that there is no connected network of evidence, therefore there are significant challenges in indirectly comparing VEN+R to ibrutinib. Both AbbVie and the ERG have thus sought to synthesise the evidence, but recognise the limitations of the data and the methodologies used to synthesise the data. The ERG broadly agrees with AbbVie's approach to conducting an unanchored matched adjusted indirect comparison (MAIC) using individual patient data (IPD) from MURANO and aggregate data from RESONATE – in line with NICE DSU guidance. However, the ERG has identified limitations to AbbVie's unanchored MAIC, which are detailed in the ERG report. The ERG has therefore undertaken further exploratory analyses using the results of the Hillmen et al abstract which, although have not been obtained from a direct comparison, was deemed, by the ERG, to provide reasonable estimates of the ibrutinib vs BR comparison. The ERG then conducted a network meta-analysis (NMA) using the HRs of ibrutinib vs BR and the MURANO HRs of VEN+R vs BR to estimate the HRs of VEN+R vs ibrutinib. However, there are limitations to the ERG's approach, some of which have already been stated by the ERG; "*NMA may seem simplistic because we cannot assess whether the transitivity assumption does hold",* and others which are outlined below:

- ***Limitation 1:*** The Hillmen abstract is conducted in a population where 17p del patients are excluded while the MURANO trial includes both 17p del and non 17p del patients. No further effect modifier adjustments were made with respect to the VEN+R population in the ERG analysis, which is a major limitation, particularly considering the ERG statement on page 51 *"Hence, it is important to carefully consider the population of interest, and may not be appropriate to assume generalizability of a relative treatment effect from one trial population to another"'.*

- ***Limitation 2:*** Further to limitation 1, the ERG uses HRs from MURANO that describe the general population rather than the non 17p del sub-population. On page 13, *"the ERG acknowledges that patients in MURANO who would not have been eligible for these comparator trials (RESONATE or Study 116) were appropriately excluded from the MAIC"* and therefore a similar approach should have been applied to ERG's exploratory analysis, as well.

- ***Limitation 3:*** The ERG considers that the most appropriate definition of PFS to be used in the analysis is the IRC-assessed PFS and suggests that this was used in their analysis from the Hillmen abstract. However, this appears factually inaccurate as the methods section of the Hillmen abstract indicates that the exploratory analysis presented in the abstract was based on the PFS definition, as assessed by investigator. The methods section of the Hillmen abstract states: *"the current exploratory analysis was based on the latest available data from each trial (median time on study: RESONATE, 19 months; HELIOS, 17 months) using investigator assessments, but excluding del17p pts from RESONATE"* (please refer to Issue 2 below)

- ***Limitation 4:*** On page 58 (Table 15) of the ERG report, the ERG presents HRs for PFS and OS of VEN+R vs ibrutinib as derived from their NMA: PFS HR 1.43 (CI 0.78 -2.61) and OS HR 1.08 (CI 0.42 -2.73). The estimates are uncertain since the confidence intervals are wide, and cross 1, suggesting no difference (please refer to Issue 1 below)

Proposed amendment: Collectively, these limitations make the results of the ERG's exploratory analyses uncertain. The ERG have indicated a preference for an anchored MAIC over an unanchored MAIC as stated on page 48 of the ERG report: *An anchored MAIC is a standard indirect treatment comparison with a common comparator for the treatments in the network……*" and "*The ERG agrees with this approach to sensitivity analysis*". Therefore as an alternative to the unanchored MAIC results used in the current base case, AbbVie recommends that HRs from the anchored MAIC of VEN+R vs ibrutinib+BR (given the similar efficacy of ibrutinib vs ibrutinib+BR as concluded by Hillmen et al 2015) should be used for the base case analysis. For additional analyses, unadjusted anchored

comparison of VEN+R vs ibrutinib+BR based on PFS IRC data have recently been presented at the European Hematology Association conference in Stockholm 2018[1].

Leveraging the results from an anchored analysis using BR as a common comparator may be a more appropriate approach as it utilises evidence directly from RCT trials (MURANO and HELIOS), as recommended by ERG, implicitly controls for observed and unobserved cross-study differences, and makes a clinically and evidentially justified assumption of equal efficacy between ibrutinib single agent vs ibrutinib+BR. In contrast, the ERG's exploratory NMA utilises a secondary source of information, which Abbvie believes does not necessarily respect within-study randomisation and is subject to additional unaccounted biases. Of note, although Hillmen et al conducted a multivariate analysis using IPD data from both RESONATE and HELIOS, the abstract does not report whether effect modifiers and prognostic factors were accurately balanced/matched in a way propensity score weighting methodology can achieve, which may contribute to why the authors describe their analysis as "exploratory".

Possible likely impact on ICER: AbbVie would like to present the ICERs for the above recommendation for two scenarios using the ERG preferred base-case corrected model; one scenario using the HRs from the adjusted anchored MAIC of VEN+R vs ibrutinib+BR (INV-assessed PFS definition) and the other using the HRs from the adjusted anchored MAIC of VEN+R vs ibrutinib+BR (IRC-assessed PFS definition as reported in Mato et al[1] abstract). Assuming the assumption of equal efficacy of ibrutinib and ibrutinib+BR holds, then the ICERs below of VEN+R vs ibrutinib+BR can be extended to the comparison of VEN+R vs ibrutinib.

	Incr Costs	**Incr QALYs**	**ICER**
ERG Base Case: NMA using MURANO and Hillmen et al abstract	[redacted]	[redacted]	[redacted]
Base Case 1: anchored MAIC HRs OS=[redacted] and **INV-assessed PFS**=[redacted]	[redacted]	[redacted]	[redacted]
Base Case 2: anchored MAIC HRs OS=0.70 (0.27-1.83) and **IRC-assessed PFS** as in Mato et al 2018=0.90 (0.50-1.64)	[redacted]	[redacted]	[redacted]

Finally, as stated above, AbbVie anticipates that uncertainties in clinical and cost-effectiveness results will be reduced by collecting longer term follow-on data from the MURANO trial. Furthermore, the ERG preferred probabilistic base-case model results are similar to AbbVie's probabilistic base-case corrected model results: i.e. *"the probability that VEN+R is cost-effective compared with ibrutinib at £20,000 per QALY is close to* [redacted] *in both the list and net price comparisons"*

[1] Mato A, Follows G, Sail K, Diakite I, Nicoloso D, Dietz B, Maher J, Alexiou D, Chirikov V. Indirect treatment comparison of venetoclax plus rituximab with B-cell receptor inhibitors in patients with relapsed/refractory chronic lymphocytic leukemia. European Hematology Association, Stockholm 2018

ERG response to AbbVie's response to the limitations of the ERG's ITC analyses

Regarding limitation 1 and limitation 2 of the ERG's ITC, it is true that MURANO included both 17p del and non 17p del patients, whereas the Hillmen study only considered a non-17p deletion population. However, the majority of MURANO patients (73%) were non-del 17p, suggesting similarity to the Hillmen population.

Regarding limitation 3, whilst the ERG agrees there are differences in the definition of PFS used between the Hillmen and MURANO studies, however as demonstrated in the MURANO trial, there is likely to be minimal disagreement between IRC assessed PFS and investigator assessed PFS. Additionally, the ERG believes the Hillmen abstract provided useful information for decision making in this context given the paucity of published effectiveness evidence comparing VEN+R with ibrutinib.

Regarding the fourth comment by the company, the ERG is unclear how this is a limitation of the analysis.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
There is inconsistency in the reporting of uncertainty around HRs based on confidence intervals. When critiquing AbbVie's MAIC generated HRs, the ERG has tended to use arguments such as: 1. "*the wide confidence intervals for the primary endpoint (PFS) HRs suggest that the treatment effect of VEN+R may be somewhat biased*" (page 16), and "*the ERG is concerned about the imprecise estimates of the treatment effect of VEN+R (confidence intervals of HRs for PFS and OS were wide)*" (page 59). 2. "*this confidence interval crosses 1 and hence reflects a greater degree of uncertainty in the comparison with ibrutinib*" (page 96 and 105). However when reporting the ERG's NMA HRs (page 58, table 15), which have confidence intervals for PFS and OS HRs that cross 1 and in some cases the CIs are even wider than AbbVie's MAIC, the ERG has not stated that their results also have a high degree of uncertainty or that the treatment effect may be imprecise.	Please amend pages 14 and 58 where ERG NMA OS and PFS HRs are reported, to include the explanation that confidence intervals cross 1 and CIs are wide, thus reflecting a great degree of uncertainty in the results.	Potential misinterpretation: inconsistency in the reporting of uncertainty could lead the reader to conclude (incorrectly) that the ERG's NMA results are less uncertain than AbbVie's MAIC results	Not a factual error.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 56, first sentence states: "*The ERG compared hazard ratio (95% CI) estimates for PFS and OS across these two studies. For PFS outcomes, we used estimates obtained from IRC analyses"*	Please change to "*The ERG compared hazard ratio (95% CI) estimates for PFS and OS across these two studies. For PFS outcomes, we used estimates obtained from ~~IRC~~ **INV assessed** analyses"*	This statement is factually inaccurate and potentially misleading. The methods section of the Hillmen abstract indicates that the exploratory analysis presented in the abstract was based on the INV-assessed PFS definition. The methods section of the Hillmen abstract states: "*the current exploratory analysis was based on the latest available data from each trial (median time on study: RESONATE, 19 months; HELIOS, 17 months) using investigator assessments, but excluding del17p pts from RESONATE*"	ERG have amended statement. *For PFS outcomes, we used estimates obtained from investigator-assessed analyses*

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The net price is not currently marked CIC: • Page 90, footnote to Table 29: *"* At net price ([redacted] applied to venetoclax*)"	Please highlight the net price CIC	Confidential information not marked appropriately	ERG has updated the marking across the tables recommended by the company.

• Page 105, Table 39 "[redacted] ***applied to VEN+R***" • Page 107, Table 42 "[redacted] ***applied to VEN+R***" • Page 108, Table 43 "[redacted] ***applied to VEN+R***"			

Issue 4

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG Response**
Page 40, first paragraph states: "*Results based on these pre-defined subgroups did not identify any subgroups more or less likely to benefit significantly from VEN+R. For instance, the risk of death or progression as assessed by the investigators was significantly higher in the VEN+R arm than the BR arm among R/R CLL patients with positive (HR 0.13, 95% CI 0.05 to 0.29) and negative (HR 0.19, 95% CI 0.12 to 0.32) 17p deletion status alike. Similarly, R/R CLL patients with TP53 mutation (HR 0.15, 95% CI 0.09 to 0.25) and non-mutation (HR 0.19, 95% CI 0.10 to 0.36) experienced significantly higher rates of death or progression in the VEN+R arm compared to the BR arm. Overall, the treatment benefit of VEN+R over BR was consistent across all subgroups*"	Please change to "*Results based on these pre-defined subgroups did not identify any subgroups more or less likely to benefit significantly from VEN+R. For instance, the risk of death or progression as assessed by the investigators was significantly higher in the* ***BR*** ~~*VEN+R*~~ *arm than the* ~~*BR*~~ ***VEN+R*** *arm among R/R CLL patients with positive (HR 0.13, 95% CI 0.05 to 0.29) and negative (HR 0.19, 95% CI 0.12 to 0.32) 17p deletion status alike. Similarly, R/R CLL patients with TP53 mutation (HR 0.15, 95% CI 0.09 to 0.25) and non-mutation (HR 0.19, 95% CI 0.10 to 0.36) experienced significantly higher rates of death or progression in*	ERG error in reporting	ERG have amended statement. *For instance, the risk of death or progression as assessed by the investigators was significantly higher in the BR arm than the VEN+R arm among R/R CLL patients with positive (HR 0.13, 95% CI 0.05 to 0.29) and negative (HR 0.19, 95% CI 0.12 to 0.32) 17p deletion status alike. Similarly, R/R CLL patients with TP53 mutation (HR 0.15, 95% CI 0.09 to 0.25) and non-mutation (HR 0.19, 95% CI 0.10 to 0.36) experienced significantly higher rates of death or progression in the BR arm compared to the VEN+R arm.*

	*the **BR** ~~VEN+R~~ arm compared to the ~~BR~~ **VEN+R** arm. Overall, the treatment benefit of VEN+R over BR was consistent across all subgroups*"		

Issue 5

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG Response**
Page 19 states: "*Venetoclax monotherapy is recommended by NICE technology appraisal (TA) guidance TA487 as a second line treatment for patients with del(17p) and/or TP53 mutation experiencing disease progression after receiving B-cell receptor inhibitor (BCRi) treatment.[8] NICE TA429 recommends ibrutinib for patients who have had at least 1 prior chemo-immunotherapy treatment (CIT)*"	Please change to: ""*Venetoclax monotherapy is recommended by NICE technology appraisal (TA) guidance TA487 as a second line treatment for patients with del(17p) and/or TP53 mutation experiencing disease progression after receiving B-cell receptor inhibitor (BCRi) treatment **or when a BCRi is unsuitable**.[8] NICE TA429 recommends ibrutinib for patients who have had at least 1 prior chemo-immunotherapy treatment (CIT) **or who have a 17p deletion or TP53 mutation, and in whom chemo-immunotherapy is unsuitable***"	The proposed amendment is a more accurate reflection of the NICE recommendations for TA487 and TA429. Furthermore the amendment contains important contextualising text: the words '*and in whom chemo-immunotherapy is unsuitable*' suggest that there is an acknowledgement by NICE that some patients (albeit small numbers) who have a 17p deletion or TP53 mutation may receive chemo-immunotherapy front line. A point which is important for discussions introduced later in the document around the positioning of VEN+R	ERG have amended statement. *Venetoclax monotherapy is recommended by NICE technology appraisal (TA) guidance TA487 as a second line treatment for patients with del(17p) and/or TP53 mutation experiencing disease progression after receiving B-cell receptor inhibitor (BCRi) treatment or when a BCRi is unsuitable. NICE TA429 recommends ibrutinib for patients who have had at least 1 prior chemo-immunotherapy treatment (CIT) or who have a 17p deletion or TP53 mutation, and in whom chemo-immunotherapy is unsuitable.*

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 21 states: "*The ERG considers this evidence to be largely anecdotal, and should not have informed the population selection in the decision problem"*	Please change to: "*The ERG* ***is unable to provide evidence to the contrary and*** *considers this evidence to be largely anecdotal.* ***However the ERG notes the precedence in TA429 which recommends ibrutinib for patients who have had at least 1 prior chemo-immunotherapy treatment (CIT) or who have a 17p deletion or TP53 mutation, and in whom chemo-immunotherapy is unsuitable. This indicates an acceptance by NICE that some patients may be suitable*** **for CIT which is consistent with the company's position**. ~~*and should not have informed the population selection in the decision problem*~~*"*	The current text is factually inaccurate and potentially misleading. It is also inconsistent with the NICE TA429 recommendation, which was published only last year. The revised text provides clarity on this matter.	Not a factual error. The TA429 guidance states that ibrutinib monotherapy is recommended for patients "who have a 17p deletion or TP53 mutation, and in whom chemo-immunotherapy is unsuitable". The ERG does not dispute that some patients who have 17p deletion and/or TP53 mutation may also be suitable for CIT. However, the ERG maintains that the TA429 guidance does not suggest that patients who have 17p deletion and/or TP53 mutation and are suitable for CIT may be considered eligible for ibrutinib monotherapy.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 21 states: "*Following consultations with their clinical experts, the company further specify that patients were eligible to be included as part of the submission only if they previously received chemo-immunotherapy – in line with the anticipated position of the technology*"……..	Please change to "***The MURANO trial inclusion criteria included patients treated with at least one but not more than three lines of therapy, one of which had to be chemotherapy. Furthermore only 2% of patients In the MURANO trial received a prior BCRi***. ***Therefore*** *following consultations with their clinical experts, the company further specify that patients were eligible to be included as part of the submission only if they previously received chemo-immunotherapy – in line with the anticipated position of the technology* ***and the available evidence***"……..	The current text is factually inaccurate and potentially misleading. The amendment enables the reader to have an understanding of the available evidence, which in addition to clinical expert opinion on the current NHS treatment pathway provides a more accurate rationale for the proposed position of VEN+R.	Not a factual error. However, the ERG has added in parts of the proposed amendment to provide some context for the paragraph in question. *The key trial (MURANO) inclusion criteria included patients treated with at least one but not more than three lines of therapy, one of which had to be chemotherapy. Furthermore only 2% of patients in this trial received a prior BCRi.*

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 23 states: "*However, the company did not provide MAIC analyses of the MRD status,*	Please change to: "~~*However,*~~ *The company did not provide*	The omission of AbbVie's response at the clarification	ERG agree, and have extended the sentence.

when the ERG requested this at the clarification stage".	*MAIC analyses of the MRD status, when the ERG requested this at the clarification stage.* ***The rationale provided is that comparator data on MRD is not publicly available***	stage may lead to inadvertent misinterpretation of the reasons why AbbVie was unable to provide MAIC analyses of the MRD status.	*However, the company did not provide MAIC analyses of the MRD status, when the ERG requested this at the clarification stage, citing MRD data for comparators not being publicly available.*

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 23 final sentence states: "*The company also anticipates that the European Medicines Agency (EMA) license for VEN+R will be issued in* [redacted]*"*	Please change to "*The company also anticipates that the European Medicines Agency (EMA)* ~~*license*~~ ***CHMP positive opinion*** *for VEN+R will be issued in* [redacted]*"*	This is factually inaccurate as CHMP opinion is anticipated in [redacted], not the licence. In addition, the anticipated date should be highlighted CIC pending publication of the CHMP opinion.	ERG have amended statement. *The company also anticipates that the European Medicines Agency (EMA) CHMP positive opinion for VEN+R will be issued in* [redacted].

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 24, final paragraph states *"Although the company did not search trial registers and Health Technology Assessment (HTA) agencies*	Please change to: ~~*Although*~~ *The company* ~~*did not search*~~ ***searched*** *trial registers and Health Technology Assessment (HTA) agencies for studies*	This is factually inaccurate as AbbVie did search HTA agencies via the Cochrane search. Please check Table 83 of the appendix	HTA agency websites weren't searched directly, but we accept that the Cochrane Library search included the HTA database and have amended

for studies eligible for their systematic review, the ERG considers…."	*eligible for their systematic review, and the ERG considers……."*	to Document B for the clinical search strategy.	the report to say *"Although the company did not search trial registers for studies eligible for their systematic review, the ERG considers…."*

Issue 11

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG Response**
Page 105, Table 39 and Table 40 and Page 107, Table 42: These three tables report VEN+R as being dominated when in-fact it should be the other way round.	Please amend Tables 39, 40 and 42 to show that it is ibrutinib that is dominated	Error	ERG agree. Table 39, 40 and 42 have been updated.

Issue 12

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG Response**
Page 117, Table 50, second row presents a dominant ICER numerically	Please amend Table 50, second row, changing the ICER currently reported as -£33,661 to "**Dominated**"	This avoids inadvertent misinterpretation and ensures consistency with the row above	ERG agree. Table 50 has been updated

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Multiple times throughout the ERG report, the presentation of some ICERs (i.e. SW quadrant ICERs) is potentially misleading. The first paragraph of page 115 gives an example of how this is problematic. There is discussion of these ICERs decreasing or increasing, but an increasing ICER is actually indicative of improved CE which is the opposite conclusion typical of a NE quadrant ICER Another example is ICERs presented in Table 50 (although the proximity to incremental cost and QALY values removes some ambiguity). The same ICERs when reported in the body of the text may be misinterpreted	We would suggest at a minimum adding an explanation to each of these reported ICERs, which cautions the reader that these ICERs (and their changes under certain scenarios) need to be interpreted differently, as AbbVie have done in the table on page 5 of this response under 'Limitations of the ERG's ITC analyses, some of which arise from factual inaccuracies'	In situations whereby VEN+R is associated with fewer costs and fewer QALYs (most notably in the ERG preferred base case, using the alternative hazard ratios for ibrutinib) the resultant ICER is presented numerically as a +ve value. This could cause confusion in interpretation, due to how similar this looks to a more conventional 'north east quadrant' ICER (from +ve incremental costs and QALYs).	ERG agree. Relevant tables (41, 43, 46, 48 and 49) have now had footnote added explaining interpretation of the ICERs. We have also edited the text on p115.

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 119, last paragraph states: "*The ERG conducted extensive exploratory analyses to understand the key drivers of cost-effectiveness and to explore the full extent of uncertainty in the economic model results. Absolute lymphocyte count However…..*"	Please change to "*The ERG conducted extensive exploratory analyses to understand the key drivers of cost-effectiveness and to explore the full extent of uncertainty in the economic*	Minor error	ERG agree. Text on page 119 has been updated as recommended.

	model results. ~~Absolute lymphocyte count~~ However….."		

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 18, second paragraph states: "*There were 3,709 new diagnoses of CLL in 2015 which is slightly higher than reported in the CS*."	Please change to *"There were 3,709 new diagnoses of CLL in the UK in 2015 which is slightly higher than 3,252 new diagnoses of CLL in England in 2015 reported in the CS".*	The 3,709 new diagnoses in the UK and 3,252 new diagnoses in England are based on the same source but reflect different geographical scopes.	ERG have amended statement. *There were 3,709 new diagnoses of CLL in the UK in 2015 which is slightly higher than the 3,252 new diagnoses in England reported in the CS.*

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 21, final sentence states: "*According to the summary of product characteristics, VEN+R is indicated for"…….*	Please change to "*According to the* **draft** *summary of product characteristics, VEN+R is indicated for"…….*	The SmPC is currently in draft form and has not yet been approved by the EMA.	ERG have amended statement. *According to the draft summary of product characteristics, VEN+R is indicated …*

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 22, first sentence states: "*Venetoclax is initially administered (orally) in weekly dose increments up to 400 mg at week 5. At this time, rituximab is commenced simultaneously as a monthly injection up to a total of six months/cycles (375 mg/m^2 in the first cycle and 500 mg/m^2 in cycles 2 to 6). From week 5 onwards, venetoclax is given at a dose of 400 mg daily up to a maximum of two years*"	Please change to "*Venetoclax is initially administered (orally) in weekly dose increments up to 400 mg at week 5.* ***After completion of the 5 week dose escalation period for venetoclax****, ~~At this time,~~ rituximab is commenced simultaneously as a monthly injection up to a total of six months/cycles (375 mg/m^2 in the first cycle and 500 mg/m^2 in cycles 2 to 6). From week 5 onwards, venetoclax is given at a dose of 400 mg daily up to a maximum of two years* **unless disease progression or unacceptable toxic effects occurred sooner**"	The proposed amendment is more accurate and avoids potential confusion.	ERG have amended statement. *Venetoclax is initially administered (orally) in weekly dose increments up to 400 mg at week 5. After completion of the 5 week dose escalation period for venetoclax, rituximab is commenced simultaneously as a monthly injection up to a total of six months/cycles (375 mg/m2 in the first cycle and 500 mg/m2 in cycles 2 to 6). From week 5 onwards, venetoclax is given at a dose of 400 mg daily up to a maximum of two years unless disease progression or unacceptable toxic effects occurred sooner.*

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 29, third paragraph states: "*After a median follow-up duration of 24.8 months, 78 of the 194 patients who*"……	Please amend to "*After a median follow-up duration of **23.8** ~~24.8~~ months, 78 of the 194 patients who*"……	This is factually inaccurate as the median follow-up duration is 23.8 months as stated in the company submission.	ERG have amended statement. *After a median follow-up duration of 23.8 months…..*

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 29, third paragraph states: "*Forty-eight patients in the VEN+R arm discontinued venetoclax with or without rituximab, including 10 patients who stopped following disease progression or relapse and 24 patients who*"……	Please amend to "*Forty-eight patients in the VEN+R arm discontinued venetoclax with or without rituximab, including **9** ~~10~~ patients who stopped following disease progression or relapse and 24 patients who*"……	This is factually inaccurate – as per the CONSORT diagram on page 41 of the company submission, 9 patients discontinued during the combination phase.	ERG have amended statement. *…including 9 patients….*

Issue 20

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 42, Table 6 states: *SAEs — no. of patients (%)* | *90 (46.4)* | *81 (43.1)*	Please change to: **SAEs with at least 2% incidence in either** | *90 (46.4)* | *81 (43.1)*	This appears to be an error in transcribing Table 23 of the company submission into Table 6 of the ERG report.	Not a factual error. Table 1 of page 32 of the CSR confirms that the total numbers

	group — no. of patients (%)			of SAEs were 90 and 81 for VEN+R and BR respectively. No information was presented for SAEs with at least 2% incidence in either group

Issue 21

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 14 states "*These results showed that VEN+R* [redacted] *progression or death (PFS) events, however…"*	Please highlight the following text as ACIC: [redacted]	Confidential information not marked appropriately	ERG have added confidential marking.

Issue 22

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 55-56, penultimate sentence states "*Therefore, the ERG has decided to undertake exploratory analyses to provide more robust estimates for the key clinical effectiveness outcome measures between ibrutinib and VEN+R"*	Please change to: "*Therefore, the ERG has decided to undertake exploratory analyses to provide ~~more robust~~ estimates for the key clinical effectiveness outcome measures between ibrutinib and VEN+R"*	The use of the word 'robust' to describe exploratory analyses, which yield HRs with wide confidence intervals is factually inaccurate	Not a factual error, however sentence has been updated for clarity. *Therefore, the ERG has decided to undertake an alternative analysis to provide plausible estimates for the key clinical effectiveness outcome measures between ibrutinib and VEN+R. This was done using BR as common comparator.*

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097] – ERG Erratum

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia: A Single Technology Appraisal. Warwick Evidence, 2018.

Contributions of authors

Chidozie Nduka (Research Fellow) helped co-ordinate the report, and reviewed and critiqued the clinical effectiveness evidence; Felix Achana (Senior Research Fellow) reviewed and critiqued the indirect and matched adjusted indirect comparisons, and the cost-effectiveness evidence and undertook additional analyses; Daniel Gallacher (Research Associate) reviewed and critiqued the statistical and the survival analysis and undertook additional analyses; Xavier Armoiry (Senior Research Fellow) reviewed and critiqued the clinical effectiveness evidence and the indirect and matched adjusted indirect comparisons; Rachel Court (Information Specialist) critiqued the company searches and undertook additional searches; Kate Evans (Research Project Administrator) reviewed and critiqued the background section; Renata Walewska (Consultant Haematologist) provided expert clinical advice; Hema Mistry (Assistant Professor) co-ordinated the project and the report, and reviewed and critiqued the cost-effectiveness evidence.

Word count: 33,220 (including references and appendices)

Please note that: Sections highlighted in yellow and underlined are [redacted] Sections highlighted in aqua and underlined are [redacted]. Figures that are CIC have been bordered with blue.

the MAIC. To adjust for any residual cross-trial differences in the MAIC, patients in the MURANO trial were weighted such that their weighted mean baseline characteristics matched those reported for the RESONATE and Study 116 trials.

The ERG reviewed the results of the unanchored MAIC with emphasis on the comparison of VEN+R with ibrutinib. These results showed that VEN+R [redacted]progression or death (PFS) events, however, this treatment effect remains statistically not significant given the wide confidence intervals in the hazard ratio ([redacted]). For OS, the MAIC results showed that VEN+R lowered the rate of death events overall by [redacted] compared to ibrutinib ([redacted]). Given this degree of contrast between the PFS and OS benefits, the ERG considers that the magnitude of the latter may not be realistic. Sensitivity analysis undertaken by the ERG indirectly comparing estimates of the treatment effect of VEN+R (from the MURANO trial) against single-agent ibrutinib (from a previously published indirect treatment comparison of ibrutinib vs BR vs ibrutinib+BR) validated the ERG's concerns: HRs = [redacted] and [redacted] for PFS and OS respectively.

1.4 Summary of cost-effectiveness submitted evidence by the company

The company conducted a systematic literature search to identify published cost-effectiveness studies and economic models, but found none comparing the cost-effectiveness of VEN+R with ibrutinib or IDELA+R as treatment options for R/R CLL. Thus, the company developed a *de novo* partitioned survival model (consistent with the NICE reference case) to simulate lifetime economic costs and outcomes associated with the comparator interventions from the UK NHS and personal social services (PSS) perspective. The base-case model simulated survival outcomes for patients on VEN+R based on evidence from the MURANO trial with extrapolation over a lifetime horizon. In the model, this was assumed to be 30-years for an R/R CLL cohort with a mean age of 64 years. Survival outcomes for comparator interventions were generated by applying hazard ratios derived from unanchored MAIC comparisons to model predictions of outcomes for patients on VEN+R. The CS base-case applied a discount rate of 3.5% per annum to both costs and outcomes over the modelled time-horizon. The model suggested that VEN+R dominated ibrutinib (i.e. VEN+R was cheaper and generated more quality-adjusted life years (QALYs) compared with ibrutinib). For the comparison with IDELA+R, the model generated an

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The company submission (CS) provides an overview of chronic lymphocytic leukaemia (CLL) (CS section B 1.3.1). The CS correctly states that 'CLL is the most common of the chronic leukaemias'.[1] The CS describes CLL as a disease of unknown aetiology characterised by the accumulation of mature B lymphocytes in blood, lymph nodes, spleen, liver, and bone marrow. This description is broadly consistent with the final scope provided by the National Institute of Health and Care Excellence (NICE). According to the CS, this accumulation of B lymphocytes can lead to a wide variety of symptoms that manifest as fatigue, loss of appetite, weight loss, night sweats and shortness of breath on exertion. However, it should be noted that CLL is often asymptomatic and diagnosed by chance. The clinical pattern ranges from no treatment needed to rapid progression. These symptoms are also consistent with those described by the British Committee for Standards in Haematology (BCSH).[2] The CS identifies recurrent genetic abnormalities (deletions or mutations) as the main cause of CLL. The disease is subject to clonal variation during the disease course (due to mutation of the tumour suppressor gene TP53) which mediates resistance to chemotherapy. TP53 dysregulation is observed in 5-10% of untreated CLL patients and present in 40-50% of patients with refractory disease. The ERG finds research to support these statements.[3]

There were 3,709 new diagnoses of CLL in the UK in 2015 which is slightly higher than the 3,252 new diagnoses in England reported in the CS.[4] The ERG agrees that the age-standardised incidence of CLL is 6.5 per 100,000.[4] Based on a study by Shanafelt et al (2010), the company states that survival of CLL patients is observed to be significantly shorter than that of the age-matched general population ($p < 0.001$).[5] However, this study was conducted in Minnesota, USA. The company does not provide incidence statistics by age or survival rates. According to Cancer Research UK, CLL incidence is strongly related to age, with the highest incidence rates being in older people. In the UK in 2013-2015, on average each year more than 4 in 10 (43%) of new cases were in people aged 75 and over'.[6] More so, the five-year survival rate for men in the UK is 51% - 72% and 73% - 81% for women.[7]

The company provides an overview of the disease burden (CS section B.1.3.2) for symptomatic CLL patients. They discuss reduction of health-related quality of life (HRQoL) and attribute it primarily to disease progression and fatigue, which the ERG verifies to be accurate.

2.2 Critique of company's overview of current service provision

The current treatment of CLL is outlined in section B.1.3.4 and is consistent with the final scope. The CS makes reference to NICE guidance and guidelines published by the BCSH. Key recommendations are summarised in CS Table 3 and pathways shown in Table 3 and Figure 1. The current treatment pathway depends on diagnosis and previous treatments. Venetoclax monotherapy is recommended by NICE technology appraisal (TA) guidance TA487 as a second line treatment for patients with del(17p) and/or TP53 mutation experiencing disease progression after receiving B-cell receptor inhibitor (BCRi) treatment or when a BCRi is unsuitable.[8] NICE TA429 recommends ibrutinib for patients who have had at least 1 prior chemo-immunotherapy treatment (CIT) or who have a 17p deletion or TP53 mutation, and in whom chemo-immunotherapy is unsuitable.[9] This is in alignment with the final scope. Additionally, NICE TA359 recommends idelalisib in combination with rituximab for adults with relapsed or refractory (R/R) CLL disease.[10] However, the CS states that ibrutinib is the more commonly used BCRi therapy due to toxicity concerns associated with idelalisib and ibrutinib being more effective than idelalisib in combination with rituximab (IDELA+R). The ERG clinical advisor agrees that this treatment strategy reflects the current position of the National Health Service (NHS).

Unmet need

The CS considers the high unmet need for the treatment of CLL patients with relapsed or refractory disease and high risk genetic subtypes (including TP53 dysregulation). They describe a need to identify effective therapies with alternative mechanisms of action and acceptable side effect profiles (CS section B.1.3.1). The CS states that early intervention with chemotherapy does not improve the natural history of the disease, may drive clonal evolution and later treatment resistance and hence, therapy is only recommended for patients with rapidly progressive or symptomatic disease. The company suggests that once treatments are stopped, due to disease progression and no other treatment options available, survival is poor (CS section B.1.3.2). The company also details that there is increased negative impact on both the patients' and their carers' HRQoL as the disease progresses. They highlight an increased economic burden reporting that

3 Critique of company's definition of decision problem

The company described the decision problem in Table 1 of the submission (CS, pg 15-17).

3.1 Population

In their decision problem, the company describes adults with R/R CLL as the target population for the technology appraisal, which is broadly consistent with the final scope and the trial populations in the key evidence submitted.[11-13]

The key trial (MURANO) inclusion criteria included patients treated with at least one but not more than three lines of therapy, one of which had to be chemotherapy. Furthermore only 2% of patients in this trial received a prior BCRi. Following consultations with their clinical experts, the company further specify that patients were eligible to be included as part of the submission only if they previously received chemo-immunotherapy – in line with the anticipated position of the technology (VEN+R) in the treatment pathway for R/R CLL in the UK (CS, Figure 1). However, the ERG is concerned that restricting the target population to patients post CIT potentially excludes CLL patients with del(17p) and/or TP53 mutation. In this high-risk subgroup, the ERG clinical advisor questions the position of VEN+R as illustrated in the proposed treatment pathway in the CS (CS Figure 1). The ERG clinical advisor considers that patients with del(17p)/TP53 mutation CLL may never receive CIT, given that these patients receive BCRi therapy (ibrutinib) as first-line in clinical practice.

Although the company recognises ibrutinib as the mainstay for the first-line treatment of del(17p)/TP53 mutation CLL as recommended in NICE TA429, they maintain that a small number of these patients receive CIT as first-line treatment (CS pg 26). The ERG considers this evidence to be largely anecdotal, and should not have informed the population selection in the decision problem.

3.2 Intervention

The intervention in the submission is venetoclax in combination with rituximab, which is the same as the final scope. The company provides a description of the technology and the mechanism of action of venetoclax (CS Table 2, pg 18) which the ERG's clinical advisor confirms to be accurate. According to the draft summary of product characteristics, VEN+R is indicated for the treatment of adult patients with CLL who have received at least one prior

therapy. Venetoclax is initially administered (orally) in weekly dose increments up to 400 mg at week 5. After completion of the 5 week dose escalation period for venetoclax, rituximab is commenced simultaneously as a monthly injection up to a total of six months/cycles (375 mg/m^2 in the first cycle and 500 mg/m^2 in cycles 2 to 6). From week 5 onwards, venetoclax is given at a dose of 400 mg daily up to a maximum of two years unless disease progression or unacceptable toxicity occured sooner. The ERG clinical advisor agrees with this two-year stopping rule, irrespective of the treatment outcome, as time limited treatment would increase compliance, would be a more acceptable option to some patients and reduce the cost of the treatment. However, it is anticipated that most patients would have achieved negative MRD status by this time.

3.3 Comparators

Ibrutinib and IDELA+R were listed comparators in the decision problem and final scope. The CS stated that in the absence of head-to-head trials comparing VEN+R with ibrutinib or IDELA+R, together with the absence of randomised controlled trial (RCT) evidence that could have enabled an indirect treatment comparison using network meta-analysis, the company carried out a matched adjusted indirect comparison (MAIC) of VEN+R versus single-agent ibrutinib.

In contrast to the final scope, the company deemed best supportive care (BSC) inappropriate as a comparator in the appraisal, while asserting that BSC is only reserved for later lines of therapy after all treatment options have failed. The ERG clinical advisor agrees that BSC is the last course of action given for palliation as opposed to disease modification.

Although venetoclax monotherapy was not included in the NICE scope and therefore was not discussed by the company, the ERG's clinical advisor has emphasized that venetoclax monotherapy appears to have a more favourable safety profile compared to ibrutinib, and is the mainstay of treatment in CLL patients who do not tolerate ibrutinib irrespective of TP53 mutation status.

3.4 Outcomes

The outcomes of interest in the final scope match those specified in the decision problem as well as trial evidence submitted.

The ERG has noted that its clinical advisor considered MRD to be the single most important clinical indicator to assess in trials in patients with CLL, emphasising strongly that a MRD negative status is the closest a patient gets to a cure. However, the company did not provide MAIC analyses of the MRD status, when the ERG requested this at the clarification stage, citing MRD data for comparators not being publicly available.

The ERG also agrees that progression free survival (PFS) was a reasonable primary endpoint considering that data from the MURANO trial was not mature enough to estimate the overall survival (OS) and that PFS is a valid surrogate outcome for OS.[14]

3.5 Other relevant factors

The CS reports that there are no equality issues presented by VEN+R. The company also anticipates that the European Medicines Agency (EMA) CHMP positive opinion for VEN+R will be issued in [redacted].

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The company undertook a broad systematic review aimed at identifying randomised and non-randomised clinical trials investigating the clinical effectiveness of VEN+R and comparator interventions for treating patients with R/R CLL. Comparator interventions include those defined in the company decision problem for this submission and many others as reported in CS Table 5, pg 29. One trial of VEN+R (MURANO) was identified and considered relevant to the decision problem.[11] Overall the ERG found the company's systematic review to be of reasonable quality. Table 1 summarises the ERG's quality assessment of the company's systematic review.

Table 1: Quality assessment of the CS systematic review of clinical effectiveness

CRD Quality Item	Yes/No/Uncertain with comments
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all relevant research?	Yes
3. Is the validity of included studies adequately assessed?	The validity of the MURANO trial alone was assessed, including issues pertaining to the external validity of the study outcomes (CS Table 10, pg 39).
4. Is sufficient detail of the individual studies presented?	Sufficient details were presented for the MURANO trial alone
5. Are the primary studies summarised appropriately?	The MURANO trial alone was summarised appropriately.

4.1.1 Searches (Description of company's search strategy)

Although the company did not search trial registers for studies eligible for their systematic review, the ERG considers the literature searches to be comprehensive using a number of relevant bibliographic databases (such as MEDLINE and Embase via the ProQuest interface). The searches ─ undertaken on 21 July 2017 and updated on 30 April 2018 ─ were conducted using appropriate search terms; without any restriction on publication date (except for the 2014 publication date limit applied to the search for conference proceedings); and excluded published letters, notes, errata and editorials. While restricting the searches to studies published in English language may have introduced some language bias, the ERG has found no missing relevant studies published in a different language. The ERG also

therapy, and geographic region. Cross-over to the VEN+R arm in the event of disease progression was not allowed, however, treatment post-progression was at the investigators' discretion. Key inclusion criteria are reported in CS Table 7 (pg 33) including age ≥18 years, CLL with R/R status, no more than three previous treatments, and an ECOG performance status score of 0 or 1. Key exclusion criteria were: (a) receiving warfarin or any strong inhibitor of the cytochrome P450 family of enzymes responsible for metabolising most prescribed drugs; b) aggressive forms of CLL with central nervous system involvement; c) previous allogeneic or autologous stem-cell transplant. The ERG considers that these inclusion/exclusion criteria are appropriate.

A flow-chart of the participants in the MURANO trial was presented in CS pg 41. Of the 389 randomised patients in the trial, 382 (98%) received at least one dose of the assigned treatment, including 194 in the VEN+R arm and 188 in the BR arm. Twenty-eight patients withdrew from the trial: eight in the VEN+R group and 20 who were randomised to the BR group. The difference in withdrawal rates was significant (4% vs 10%, $p < 0.02$). However, the ERG would be more concerned if withdrawal rates were much higher in the VEN+R arm compared to BR, especially considering that BR is administered for a total of six 28-day cycles and VEN+R is given for two years.

After a median follow-up duration of 23.8 months, 78 of the 194 patients who received at least one dose of either venetoclax or rituximab remained on treatment, however, 68 participants already completed the two-year venetoclax treatment. Forty-eight patients in the VEN+R arm discontinued venetoclax with or without rituximab, including 9 patients who stopped following disease progression or relapse and 24 patients who discontinued treatment as a result of adverse events (AEs) (clarification response A7). Patients in the BR arm were also assessed and followed similarly as patients in the VEN+R arm. After a median follow-up duration of 22.1 months in the BR group, 154 of 188 patients who received at least one dose of either bendamustine or rituximab completed the treatment schedule. Expectedly, there were fewer discontinuations in the BR arm (n = 27) given the relatively shorter course of treatment. However, the main reasons for BR discontinuations were also disease progression or relapse (n = 6) and AEs (n = 11).

The baseline characteristics of patients enrolled in MURANO are reported in Table 3. Although it would appear that patients were seemingly healthy (as determined by CLL staging and ECOG

Results based on these pre-defined subgroups did not identify any subgroups more or less likely to benefit significantly from VEN+R. For instance, the risk of death or progression as assessed by the investigators was significantly higher in the BR arm than the VEN+R arm among R/R CLL patients with positive (HR 0.13, 95% CI 0.05 to 0.29) and negative (HR 0.19, 95% CI 0.12 to 0.32) 17p deletion status alike. Similarly, R/R CLL patients with TP53 mutation (HR 0.15, 95% CI 0.09 to 0.25) and non-mutation (HR 0.19, 95% CI 0.10 to 0.36) experienced significantly higher rates of death or progression in the BR arm compared to the VEN+R arm. Overall, the treatment benefit of VEN+R over BR was consistent across all subgroups.

4.5.2 Safety

Table 6 compares the safety of VEN+R and BR. Overall, there were more AEs in the VEN+R arm (n = 335) than in the BR arm (n = 255). Discontinuation rates due to AEs were also significantly higher in the VEN+R arm compared to BR (12.4% versus 5.9%, p = 0.03). However, it is not specified in the CS or CSR if AEs were treatment-related. The ERG also notes that the EMA is yet to ascertain the safety of VEN+R.

Grade 3 or 4 adverse events

Although the proportions of all patients with grade 3 or 4 AEs, defined using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) criteria (Protocol, pg 111), were significantly higher in the VEN+R arm compared to BR (82% versus 70.2%, P = 0.007), the only grade 3 or 4 AE with a significantly higher occurrence in VEN+R compared to BR was neutropenia (57.7% versus 38.8%, P = 0.0002). In this condition, the serum concentrations of white blood cells called neutrophils are decreased below the normal range, predisposing the patient to a number of infections. However, the ERG agrees that the low neutrophil count can easily be corrected if treated promptly; this is consistent with previous evidence analysing the safety of VEN+R.[19] The percentages of the other grade 3 or 4 AEs were either comparable between treatment arms (infections, anaemia, thrombocytopaenia, tumour lysis syndrome (TLS) and grade 3 or 4 AEs with less than 2% difference in incidence between VEN+R and BR) or significantly higher in the BR arm (febrile neutropaenia, infusion-related reaction and hypotension).

	from relapse since last line of treatment.			
Included in Matching	8/20	8/13	8/9	11/11

Bold indicates variable was included in company's matching.

4.8 Additional work on clinical effectiveness undertaken by the ERG

For the purpose of cost-effectiveness modelling, the ERG has proposed another method to estimate the relative benefit of VEN+R compared to ibrutinib given the implausible OS findings obtained from the MAIC.

The ERG agrees with the company's network of evidence for drugs used in R/R CLL presented in CS Figure 14, which suggests that there is no sufficient evidence to indirectly compare ibrutinib to VEN+R using results from RCTs.

However, the ERG has identified an abstract by Hillmen et al.[20] that compared single-agent ibrutinib to BR. This abstract was cited in the CS but the company did not use the results presented from this abstract for the purpose of comparing ibrutinib to BR. In this study, the authors use IPD data from the RESONATE and HELIOS RCTs to compare the efficacy of ibrutinib against BR after adjusting for a number of covariates, namely age, gender, Rai staging, ECOG score, del(11q) status, refractory status, number of prior lines of therapy, bulky disease, IGVH status. Results from this indirect comparison are reported in Table 12.

Table 12: Indirect comparison of ibrutinib versus BR

Study	**Treatment 1**	**Treatment 2**	**PFS HR** $_{1 \text{ vs } 2}$	**OS HR** $_{1 \text{ vs } 2}$
Hillmen et al. (2015)[20]	BR	Ibrutinib	7.52 (95% CI 4.72- 11.99)	2.24 (95% CI 1.14 -4.4)

Although the Hillmen et al. (2015)[20] results have not been obtained from a direct comparison, the use of IPD and appropriate methods of adjustment was deemed by the ERG to provide reasonable estimates of the ibrutinib vs BR comparison. Therefore, the ERG has decided to undertake

an alternative analysis to provide plausible estimates for the key clinical effectiveness outcome measures between ibrutinib and VEN+R. This was done using BR as common comparator.

The ERG compared hazard ratio (95% CI) estimates for PFS and OS across these two studies. For PFS outcomes, we used estimates obtained from investigator-assessed analyses. We used the package '*network*' in Stata 15[26] to conduct a network meta-analysis (NMA). Because this package operates in a frequentist paradigm, there was no need to perform sensitivity analysis on prior distributions. Given that the network was very sparse, we used a fixed-effects model. We used a common heterogeneity model, where the between-studies variance is assumed equal across comparisons. Since there was no mixed (direct + indirect) comparisons between interventions, there was no need to check networks for inconsistency. We did not present any rankograms or surface under the cumulative ranking curve (SUCRA) scores for these interventions.

PFS network meta-analyses

The data we used for the NMA for PFS are presented in Table 13.

Table 13: Data used in the ERG's NMA for PFS

Study	**Year**	**Treatment 1**	**Treatment 2**	**PFS_HR$_{1vs2}$**	**PFS_HR_ LCI$_{1vs2}$**	**PFS_HR_ UCI$_{1vs2}$**
Murano	2018	VEN+R	BR	0.19	0.13	0.28
Hillmen RESONATE+HELIOS	2015	BR Ibrutinib	Ibrutinib BR	7.52 0.13	4.72 0.083	11.99 0.211

LCI – lower confidence interval; UCI – upper confidence interval

The network of interventions is presented in Figure 1.

Table 29: Base-case discounted results, whole population (CS Tables 61 and 62)

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	ICER vs. baseline (£/QALY)	Pairwise ICER vs. VEN+R (£/QALY)
No discount applied to VEN+R						
IDELA+R	[redacted]	2.307	[redacted]	-	[redacted]	[redacted]
VEN+R	[redacted]	5.666	[redacted]	3.358	[redacted]	[redacted]
Ibrutinib	[redacted]	3.067	[redacted]	-0.759	[redacted]	[redacted]
[redacted] **** applied to VEN+R***						
IDELA+R	[redacted]	2.307	-	-	-	£2,625
VEN+R	[redacted]	5.666	-£8,816	-3.358	£2,625	-
Ibrutinib	[redacted]	3.067	-£147,377	-0.759	£194,048	Dominated

* At net price ([redacted] applied to venetoclax)

For the adults with R/R CLL using list prices, the CS deterministic base-case showed that on average ibrutinib was the most expensive of the three interventions, but VEN+R generated more QALYs than ibrutinib or IDELA+R.

For the comparison with ibrutinib using the list price, the CS deterministic base-case showed VEN+R was [redacted] cheaper and also generated [redacted] more QALYs than ibrutinib. For the comparison with IDELA+R, VEN+R was more expensive, but generated more QALYs. Thus, the CS deterministic base-case analysis showed that VEN+R [redacted] ibrutinib; when VEN+R was compared with IDELA+R it generated an incremental cost-effectiveness ratio (ICER) of [redacted] per QALY gained.

The CS presented a deterministic base-case analysis in which a [redacted] is applied to the list price of venetoclax in the VEN+R regimen (CS Table 62). These cost-effectiveness results were very similar to those based on list price with VEN+R dominating ibrutinib; and generating an ICER of £2,625 per QALY gained when comparing VEN+R with IDELA+R (see Table 29).

The OS hazard ratio from the anchored MAIC was [redacted] The results presented in Table 39 to Table 41 suggests that:

- Applying the mean and lower 95% CI estimate of the OS HR had minimal impact on the ICER with VEN+R continuing to [redacted] ibrutinib based on both the list and net price comparisons (Table 39 and Table 40).
- Applying the higher 95% CI estimate of the OS HR (i.e. [redacted]) generated an incremental cost of [redacted] (list price analysis), [redacted] (net price analysis) and incremental QALYs of [redacted] for VEN+R vs. ibrutinib (Table 41). This suggests that VEN+R is cheaper but also generated fewer QALYs on average than ibrutinib. The ICER was [redacted] (list price) and [redacted] (net price analysis) [redacted] for VEN+R compared with ibrutinib.

Table 39: CS base–case corrected model: used OS HR from company's anchored MAIC (adjusted) analysis (R/R CLL population)

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	Pairwise ICER (£/QALY)
No discount applied to VEN+R					
VEN + R	[redacted]	5.666	[redacted]	-	[redacted]
Ibrutinib	[redacted]	4.191	[redacted]	-1.475	[redacted]
[redacted] ***applied to VEN+R***					
VEN + R	[redacted]	5.666	-	-	-
Ibrutinib	[redacted]	4.191	£149,447	-1.475	Dominated

Table 40: CS base–case corrected model: used lower 95% CI estimate of the OS HR from company's anchored MAIC (adjusted) analysis (R/R CLL population)

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	Pairwise ICER (£/QALY)
No discount applied to VEN+R					
VEN + R	[redacted]	5.666	[redacted]	-	[redacted]
Ibrutinib	[redacted]	2.397	[redacted]	-3.269	[redacted]
[redacted] ***applied to VEN+R***					
Ibrutinib	[redacted]	2.397			

VEN + R	[redacted]	5.666	-£84,647	3.269	Dominated

Table 41: CS base–case corrected model: used upper 95% CI estimate of the OS HR from company's anchored MAIC (adjusted) analysis (R/R CLL population)

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	Pairwise ICER (£/QALY)
No discount applied to VEN+R					
Ibrutinib	[redacted]	6.546	[redacted]	-	[redacted]
VEN + R	[redacted]	5.666	[redacted]	-0.88	[redacted]
[redacted] ***applied to VEN+R***					
Ibrutinib	[redacted]	6.546			
VEN + R	[redacted]	5.666	-£172,056	-0.88	£195,564[a]

[a] These ICERs are in the south west quadrant of the cost-effectiveness plane indicating VEN+R is cheaper and generates less QALYs compared to ibrutinib.

5.3.2 Uncertainty around the OS hazard ratio in the comparison with IDELA+R

The ERG has conducted exploratory analyses similar to those carried out for the ibrutinib comparison to investigate uncertainties around the OS HR for VEN+R vs IDELA+R. Using data that the company provided in response to ERG clarification questions (see point 3, section A9), the company explained that HRs for OS and PFS for VEN+R vs IDELA+BR were based on anchored MAIC analysis and these were not presented in the original CS because there is no published evidence to suggest IDELA+R and IDELA+BR have similar efficacy. Nevertheless, the company provided adjusted anchored MAIC estimates suggesting that VEN+R is associated with PFS HR of [redacted] based on the IRC definition of PFS and OS HR of [redacted] compared with IDELA+BR. The ERG was satisfied with the company's response and appreciates the effort undertaken for the extra set of analysis.

The ERG agrees with the company that HRs generated from the anchored MAIC analysis that compared VEN+R vs. IDELA+BR were not appropriate for the decision problem. The ERG conducted its own literature review but was unable to identify studies that would allow an indirect comparison between VEN+R vs IDELA+R. In the absence of reliable comparative evidence, the ERG conducted a sensitivity analyses to test the impact of assuming similar effect for VEN+R and IDELA+R by setting the HR for OS for VEN+R vs. IDELA+R to 1 (Table 42). Under this assumption, VEN+R was more costly but generated more QALYs than IDELA+R generating an

ICER of [redacted] per QALY gained in the list price analysis. For the net price analysis, VEN+R was cheaper and generated more QALYs than IDELA+R, therefore [redacted] IDELA+R.

Table 42: CS base–case corrected model: assumed an OS HR of 1 for VEN+R vs. IDELA+R (R/R CLL population)

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	Pairwise ICER (£/QALY)
No discount applied to VEN+R					
IDELA+R	[redacted]	5.154	[redacted]	-	[redacted]
VEN + R	[redacted]	5.666	[redacted]	0.512	[redacted]
[redacted] ***applied to VEN+R***					
VEN + R	[redacted]	5.666	-	-	-
IDELA+R	[redacted]	5.154	£14,944	-0.512	Dominated

5.3.3 ERG preferred method of estimating the hazard ratio for VEN+R vs. ibrutinib

The company's adjusted unanchored MAIC analysis produced an OS HR of [redacted] for VEN+R vs. ibrutinib, suggesting a [redacted] % risk reduction in OS with VEN+R compared with ibrutinib. As already stated, the ERG believed this HR is highly uncertain.

Therefore, the ERG conducted an indirect comparison using a fixed-effect NMA to compare survival outcomes for VEN+R vs. ibrutinib (see section 4.8), using these new HRs from the indirect comparison the ERG applied this to corrected base-case model. As seen in Table 43, the CS base-case corrected ICER changed from VEN+R dominating ibrutinib, to an ICER of [redacted] (list price) and £790,988 (net price) per QALY lost (i.e. VEN+R was cheaper but also generated on average 0.354 fewer QALYs compared with ibrutinib).

Table 43: CS base–case corrected model: used central estimate of PFS and OS HR for VEN+R vs. ibrutinib from ERG's indirect comparison analysis (R/R CLL population)

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	Pairwise ICER (£/QALY)
No discount applied to VEN+R					
Ibrutinib	[redacted]	6.019	[redacted]	-	[redacted]
VEN + R	[redacted]	5.666	[redacted]	-0.354	[redacted]
[redacted] ***applied to VEN+R***					
Ibrutinib	[redacted]	6.019			
VEN + R	[redacted]	5.666	-£279,766	-0.354	£790,988[a]

[a] These ICERs are in the south west quadrant of the cost-effectiveness plane indicating VEN+R is cheaper and generates less QALYs compared to ibrutinib.

Using the lower and upper 95% CI estimate of HRs generated from the ERG's indirect comparison in OWSA suggested that the cost-effectiveness results were most sensitive to the HR for OS with ICERs ranging from VEN+R [redacted] ibrutinib using the lower 95% CI estimate to VEN+R being comparatively cheaper, but also generating fewer QALYs than ibrutinib using the upper 95% CI estimate for OS (see Table 51 for further sensitivity analyses results).

5.3.4 Further exploratory analyses undertaken by ERG

The ERG considered the company's approach to parameterisation and long-term extrapolation of the OS and PFS curves for VEN+R and the comparators (see section 5.2.6). The ERG conducted a series of exploratory analysis based on the corrected model to investigate the impact of assuming alternative parametric modelling of PFS and OS. The results suggest changing the parametric modelling from joint-Weibull to joint-Gamma survival curves for both OS and PFS (Table 44) had minimal impact on the ICER with VEN+R continuing the [redacted] ibrutinib in both list and net price comparisons. For the comparison with IDELA+R, the ICER decreased from [redacted] to [redacted] per QALY gained based on list price analysis and from [redacted] to £2,903 per QALY gained based on net price analysis (Table 44).

Table 46: ERG preferred base–case corrected model for the comparison with ibrutinib (R/R CLL population)

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	ICER vs. VEN+R (£/QALY)
No discount applied to VEN+R					
VEN+R	[redacted]	6.04	[redacted]	-	
Ibrutinib	[redacted]	6.431	[redacted]	-0.39	[redacted]
[redacted] ***applied to VEN+R***					
VEN+R	[redacted]	6.04	-	-	
Ibrutinib	[redacted]	6.431	-£322,979	-0.39	£827,252[a]

[a] These ICERs are in the south west quadrant of the cost-effectiveness plane indicating VEN+R is cheaper and generates less QALYs compared to ibrutinib.

The results in Table 46 suggest VEN+R is [redacted] (list prices) and -£322,979 (net prices) cheaper than ibrutinib, but also generated 0.39 fewer discounted QALYs on average. The corresponding ICERs were [redacted] and £827,252 per QALY lost for VEN+R compared with ibrutinib based on list and net price comparisons, respectively. The ERG preferred base-case corrected model thus produced similar estimate of incremental costs as the CS base-case corrected model but differed in the direction of incremental QALYs generated. The ERG probabilistic base-case results (not presented) produced similar ICERs as the deterministic analyses. The probability that VEN+R is cost-effective compared with ibrutinib at £20,000 per QALY is close to [redacted] in both the list and net price comparisons.

The ERG applied its preferred base-case model to the populations with and without del(17p)/TP53 mutation for the ibrutinib comparison. The results of these analyses were similar to the ERGs preferred base-case results with VEN+R being cheaper but also generating fewer QALYs compared with ibrutinib in both list and net prices comparison (Table 47 and Table 48).

Table 47: ERG preferred base–case corrected model (del(17p)/TP53 mutation) for the comparison with ibrutinib

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	ICER vs. VEN+R (£/QALY)
No discount applied to VEN+R					
VEN+R	[redacted]	5.494	[redacted]	-	
Ibrutinib	[redacted]	5.87	[redacted]	-0.376	[redacted]
[redacted] ***applied to VEN+R***					
VEN+R	[redacted]	5.494	-	-	
Ibrutinib	[redacted]	5.87	-£269,728	-0.376	£718,043[a]

[a] These ICERs are in the south west quadrant of the cost-effectiveness plane indicating VEN+R is cheaper and generates less QALYs compared to ibrutinib.

Table 48: ERG preferred base–case corrected model (nondel(17p)/TP53 mutation)) for the comparison with ibrutinib

Technologies	Total Costs, £	Total QALYs	Incremental Costs, £	Incremental QALYs	ICER vs. VEN+R (£/QALY)
No discount applied to VEN+R					
VEN+R	[redacted]	6.245	[redacted]	-	
Ibrutinib	[redacted]	6.638	[redacted]	-0.393	[redacted]
[redacted] ***applied to VEN+R***					
VEN+R	[redacted]	6.245	-	-	
Ibrutinib	[redacted]	6.638	-£343,718	-0.393	£873,858[a]

[a] These ICERs are in the south west quadrant of the cost-effectiveness plane indicating VEN+R is cheaper and generates less QALYs compared to ibrutinib.

5.3.5.2 ERGs preferred base-case model with a waning effect for the ibrutinib comparison

Due to the two-year treatment course of venetoclax for patients receiving VEN+R, the ERG believe it is plausible that the effects of VEN+R on OS and PFS may wane over time, thus increasing the hazard. Waning effects are often implemented through a steady or sudden increase in a hazard rate of the intervention relative to the hazard rate of one of the comparators. However in this appraisal, a waning effect was incorporated into the model through a percentage increase in the predicted hazards for VEN+R, after 5 years, i.e. increasing the hazard of VEN+R relative to

Table 49: ERG preferred base–case model with waning effect applied to PFS and OS estimates for VEN+R in the comparison with ibrutinib (R/R CLL population)

ERG exploration	Total costs VEN+R	Total LYs VEN+R	Total QALYs VEN+R	Total costs Ibrutinib	Total LYs Ibrutinib	Total QALYs Ibrutinib	Incremental costs	Incremental LYs	Incremental QALYs	ICER (LYs)	ICER[a] (QALYs)
No discount applied to VEN+R											
ERG preferred base-case model	[redacted]	8.976	6.04	[redacted]	9.302	6.431	[redacted]	-0.326	-0.39	[redacted]	[redacted]
Applied 10%	[redacted]	8.647	5.832	[redacted]	9.302	6.431	[redacted]	-0.655	-0.599	[redacted]	[redacted]
Applied 20%	[redacted]	8.351	5.645	[redacted]	9.302	6.431	[redacted]	-0.951	-0.786	[redacted]	[redacted]
Applied 50%	[redacted]	7.621	5.182	[redacted]	9.302	6.431	[redacted]	-1.682	-1.249	[redacted]	[redacted]
Applied 70%	[redacted]	7.234	4.937	[redacted]	9.302	6.431	[redacted]	-2.068	-1.494	[redacted]	[redacted]
Applied 100%	[redacted]	6.761	4.636	[redacted]	9.302	6.431	[redacted]	-2.541	-1.795	[redacted]	[redacted]
[redacted] ***applied to VEN+R***											
ERG preferred base-case model	[redacted]	8.976	6.04	[redacted]	9.302	6.431	-£322,979	-0.326	-0.39	£989,832	£827,252
Applied 10%	[redacted]	8.647	5.832	[redacted]	9.302	6.431	-£323,590	-0.655	-0.599	£493,888	£540,430
Applied 20%	[redacted]	8.351	5.645	[redacted]	9.302	6.431	-£324,179	-0.951	-0.786	£340,860	£412,418
Applied 50%	[redacted]	7.621	5.182	[redacted]	9.302	6.431	-£325,781	-1.682	-1.249	£193,730	£260,920
Applied 70%	[redacted]	7.234	4.937	[redacted]	9.302	6.431	-£326,700	-2.068	-1.494	£157,946	£218,679
Applied 100%	[redacted]	6.761	4.636	[redacted]	9.302	6.431	-£327,878	-2.541	-1.795	£129,028	£182,682

[a] These ICERs are in the south west quadrant of the cost-effectiveness plane indicating VEN+R is cheaper and generates less QALYs compared to ibrutinib.

The ERG's exploratory analyses in which it applied different rates of waning effect to venetoclax had the effect of reducing survival outcomes and hence, the total number of life-years lived, total costs and total QALYs for VEN+R. For the list price comparisons, the ICER for VEN+R versus ibrutinib changed from [redacted] per QALY lost in the ERG's preferred base-case model to between [redacted] per QALY lost for a 10% waning effect and [redacted] per QALY lost with 100% waning effect (Table 49). A similar trend with increasing waning effect is observed in the ICER in the net price comparisons when a [redacted] discount is applied to venetoclax (Table 49).

5.3.5.3 ERGs preferred base-case for the IDELA+R comparison

The ERG was unable to conduct a preferred base-case analysis for the comparison with IDELA+R because no robust estimates of relative efficacy between VEN+R vs. IDELA+R was available. The ERG does not have confidence in the robustness of HRs generated from the company's unanchored MAIC analysis. The ERG conducted a scoping review of the literature but was unable to find relevant information that could be used to estimate the relative effectiveness of VEN+R vs. IDELA+R.

5.4 Conclusions of the cost effectiveness section

The CS presented an economic model that evaluated the cost-effectiveness of VEN+R vs. ibrutinib and IDELA+R as treatment options for adult patients with R/R CLL. The MURANO trial was the main source of clinical effectiveness evidence.

The company extrapolated OS and PFS using a jointly fitted Weibull model to both arms and to both outcomes of the MURANO trial, with strong assumptions of proportionality necessary to obtain plausible OS predictions for VEN+R. The ERG preferred to use a gamma model, which is more consistent with the external data considered by the company, but have concerns of the immaturity of the OS data and its suitability for extrapolation.

The two main drivers of cost-effectiveness versus ibrutinib were the 2-year fixed treatment duration for VEN+R and the HR for OS. The latter was estimated from an unanchored MAIC that

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

Alterations to the base-case assumptions were made by the ERG as identified in Chapter 5. Further exploratory analyses undertaken by the ERG to test the robustness of the CS base-case assumptions and parameter inputs are in the Appendix. Results are presented in Table 51 for the comparison with ibrutinib and Table 52 for comparison with IDELA+R.

The impact on each change individually on the base-case analysis in comparison with ibrutinib is shown in Table 50.

Table 50: ERG re-estimation of cost-effectiveness

	ΔC	**ΔQALY**	**ΔC/QALY**	**Ratio[+]**
Comparison with ibrutinib – list price				
CS base-case corrected model	[redacted]	2.599	[redacted]	-
ERG models				
Changing parametric survival curves from joint Weibull to joint-Gamma for both PFS and OS	[redacted]	2.884	[redacted]	-
Changing the unanchored MAIC PFS and OS HRs to ERGs indirect comparison using estimates of PFS and OS for ibrutinib vs BR reported in Hillmen and for VEN+R vs BR based on the MURANO data	[redacted]	-0.354	[redacted]	[redacted]
ERG preferred base-case analysis	[redacted]	-0.39	[redacted]	[redacted]
Comparison with ibrutinib – net price				
CS base-case model	-£135,650	2.599	Dominated	-
ERG models				
Changing parametric survival curves from joint Weibull to joint-Gamma for both PFS and OS	-£142,716	2.884	Dominated	-

7 END OF LIFE

End of life considerations do not apply.

8 OVERALL CONCLUSION

8.1 Clinical effectiveness evidence

Although the absence of relevant direct evidence justified the company's decision to conduct a MAIC analysis of VEN+R versus single agent ibrutinib, and the methods used in matching trial populations have been previously validated, the ERG remains concerned about the imprecise estimates of the resulting treatment effect of VEN+R (confidence intervals of HRs for PFS and OS were wide) as well as the implausible HRs for OS. Additional work undertaken by the ERG indirectly comparing estimates of the treatment effect of VEN+R from the MURANO trial against single-agent ibrutinib from Hillmen and colleagues[20] supports the ERG's position.

8.2 Cost-effectiveness evidence

The ERG conducted extensive exploratory analyses to understand the key drivers of cost-effectiveness and to explore the full extent of uncertainty in the economic model results. However, there remains a considerable degree of uncertainty associated with the final estimates of cost-effectiveness because the key parameter in the economic model, the hazard ratio for overall survival that measures the magnitude of treatment benefit for VEN+R versus the comparator interventions was estimated with high degree of uncertainty in both the company's submission and the ERG exploratory analyses.