NICE National Institute for Health and Care Excellence

Venetoclax with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia

Chair's presentation

2nd appraisal committee meeting

Committee C

Lead team: Prithwiraj Das, Derek Ward and David Chandler

ERG/AG: Warwick Evidence

NICE technical team: Julia Sus and Sally Doss

Company: AbbVie

27 November 2018

Key issues for consideration

- Is the new MAIC or ERG's NMA appropriate for decision making?
- Are the waning rates (5%, 10%, 20%, 40%) proposed by the company plausible?
- Which utility values are the most plausible - MURANO or the literature?
- What is the most plausible ICER?
- Can the cost comparison analysis be used for decision making?
  - How many people will require treatment after 2 years?
- Is venetoclax with rituximab cost-effective?
- Is venetoclax a potential candidate for the CDF ?

[redacted]

Venetoclax, AbbVie

Marketing authorisation	Venetoclax with rituximab is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy

Administration & 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

Mechanism of action	Selective small molecule inhibitor of B-cell lymphoma 2, anti- apoptotic protein overexpressed in 95% of people with CLL
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

ACD: preliminary recommendation

Venetoclax with rituximab is not recommended, within its anticipated marketing authorisation, for treating relapsed or refractory chronic lymphocytic leukaemia in adults

[redacted]

Conclusions from ACD (1)

ACD section	Committee conclusion
MAIC(3.5, 3.9)	• MAIC analysis did not reflect the fixed treatment duration of venetoclax and did not allow for a change in the treatment effect after 2 years.
NMA (3.6)	• NMA had a similar limitation to the company's MAIC because it had not accounted for the fixed duration of venetoclax treatment.
Extrapolation (3.9)	• The committee chose a Weibull distribution as the preferred parametric model for both overall and progression-free survival. • Since the extrapolation was based on the original trial population instead of the matched population, it did not represent the correct population and committee concluded company's approach to extrapolating survival data was not appropriate
Potential loss of treatment effect after 2 years not reflected in the analysis (3.10)	• There were no data from MURANO on the effect of implementing the stopping rule because the data cut was based on a median follow-up of 23.8 months • Data from MURANO was not mature enough to justify extrapolation.

[redacted]

Conclusions from ACD (2)

ACD section	Committee conclusion
Utility values (3.11)	• The utility values used in the company's economic model need to be further explored using the MURANO data.
Cost (3.12)	• The committee concluded that costs of treatment and treatment effect duration with venetoclax plus rituximab were not correctly matched in the economic model.
Cost-effectiveness	• Due to high uncertainty in the model inputs there was no decision made on the most plausible ICER.

[redacted]

ACD consultation responses

- Consultee comments from:
  - AbbVie (company)
  - British Society of Haematology and Royal College of Pathologists Professional
  - Chronic Lymphocytic Leukaemia Support Association and Lymphoma Action
  - Leukaemia Care
  - UK Chronic Lymphocytic Leukaemia
- Commentator comments from:
  - Janssen (Company)
  - Clinical expert
  - Gilead Sciences (Company)
- No web comments submitted

[redacted]

Summary of consultation responses [1] Consultee

- **Clinical evidence**
  - Venetoclax with rituximab achieves deeper remission, MRD negativity and prolonged survival compared to chemotherapy (BSH-RCPath, CLLSA-LA, company)
  - 36 months cut off data from MURANO confirms continued remission in patients off treatment and reduces uncertainty (Leukaemia Care, UKCLL, company)
  - Venetoclax with rituximab is a less toxic treatment with less side effects compared to the current standard of care. It is also a valued treatment option which is well tolerated by patients (BSH-RCPath, CLLSA-LA, Leukaemia Care, UKCLL)
- **Patient preference**
  - The CLL 'patients experience' survey showed that patients prefer a treatment-free period or prefer being able to stop treatment altogether (Leukaemia Care)

[redacted]

Summary of consultation responses [2] Consultee and commentators

- **CDF potential**
  - To enable further data collection for venetoclax with rituximab (BSH-RCPath, Leukaemia Care, company)
  - To enable early access of venetoclax with rituximab to patients (Leukaemia Care)
- **Treatment option**
  - Venetoclax with rituximab and ibrutinib work in different and complementary ways therefore it is important that both options are available to patients (commentator)

[redacted]

Summary of consultation responses [3]

Company's response to ACD and new evidence

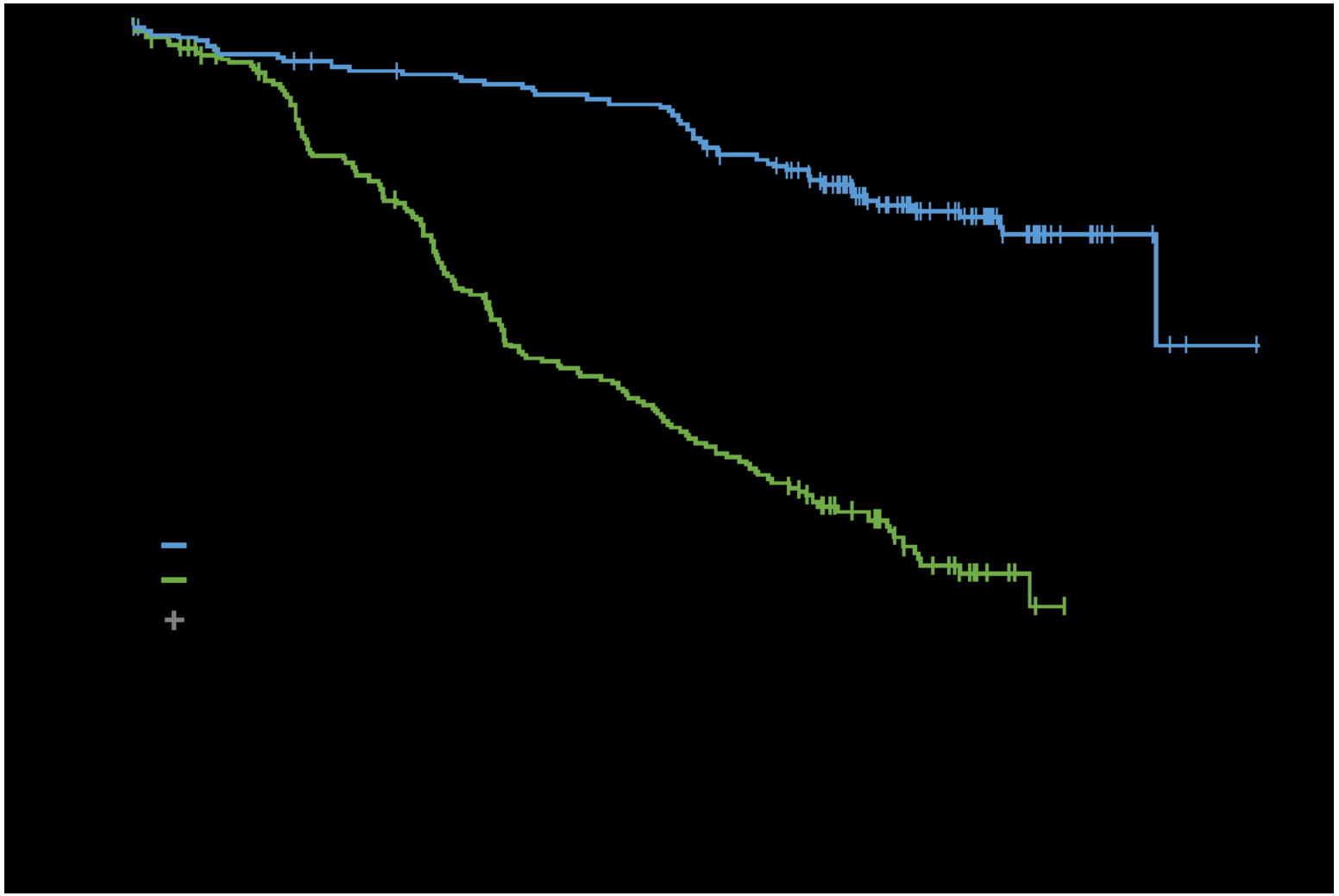
- Response to ACD
  - Corrected factual inaccuracies in the ACD
  - Comments on clinical effectiveness based on May 2018 data cut
- New evidence:
  - New efficacy data (PFS, OS and MRD status)
    - Based on 36 months data cut (May 2018)
- Economic analysis exploring scenarios:
  - Cost comparison VEN+R vs ibrutinib
  - Matched-adjusted indirect comparison analysis based on May 2018 data cut
  - Analysis accounting for loss of treatment effect after 2 years
  - Analysis in which the MURANO matched population is used instead of original trial population (ITT)
  - Analysis including utility values from the MURANO trial

[redacted]

Company's new evidence: new efficacy data

a. Progression free survival, 36 months data cut, ITT, *IA

PFS
VEN+R: the median was not reached.
BR:17 months
HR= 0.17(95% CI 0.16 to 0.22)



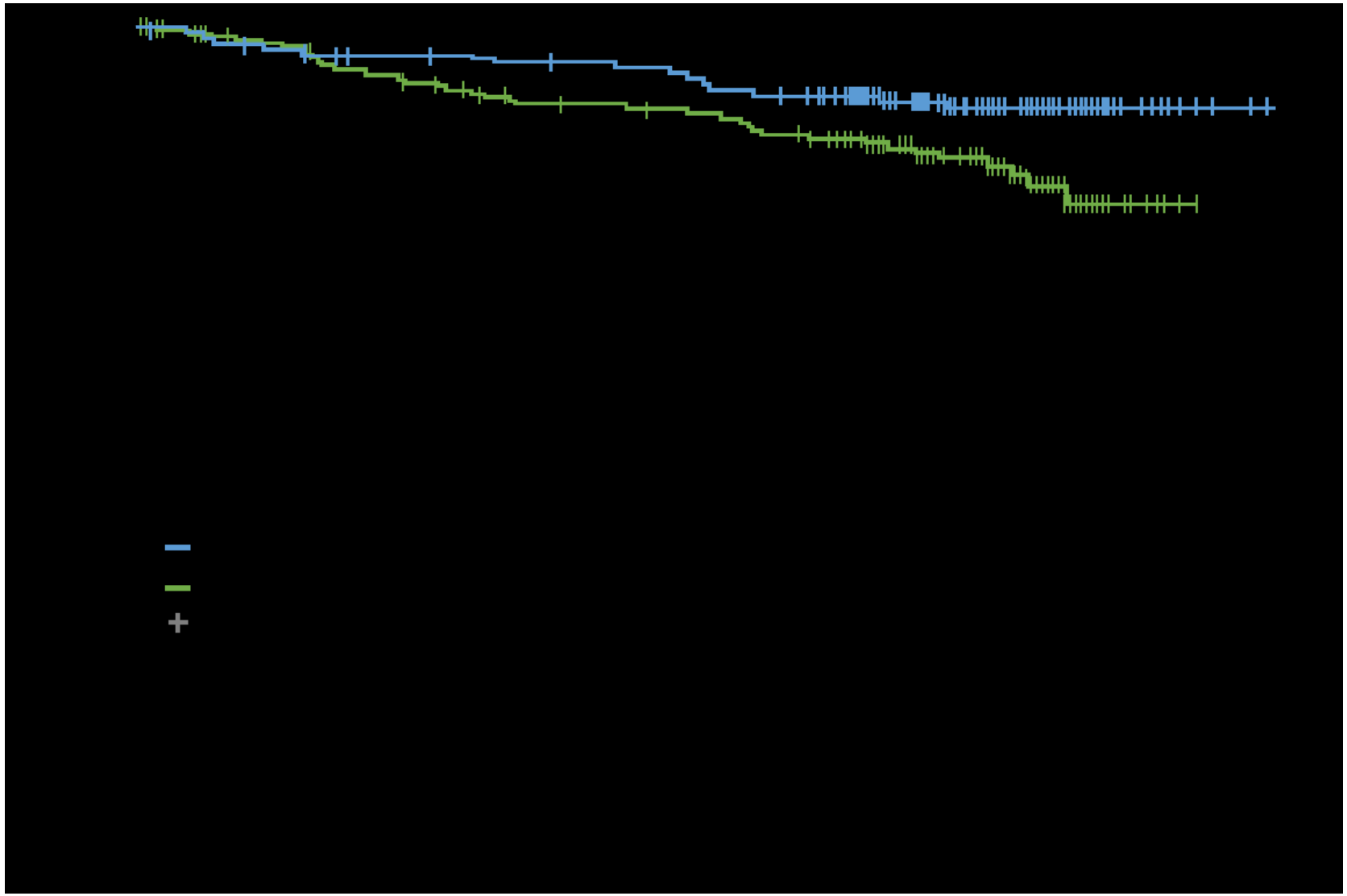
[redacted]

*IA- Investigator assessed

Company's new evidence: new efficacy data

b. Overall survival, 36 months data cut, ITT, *IA

OS
VEN+R: not reached
BR: not reached

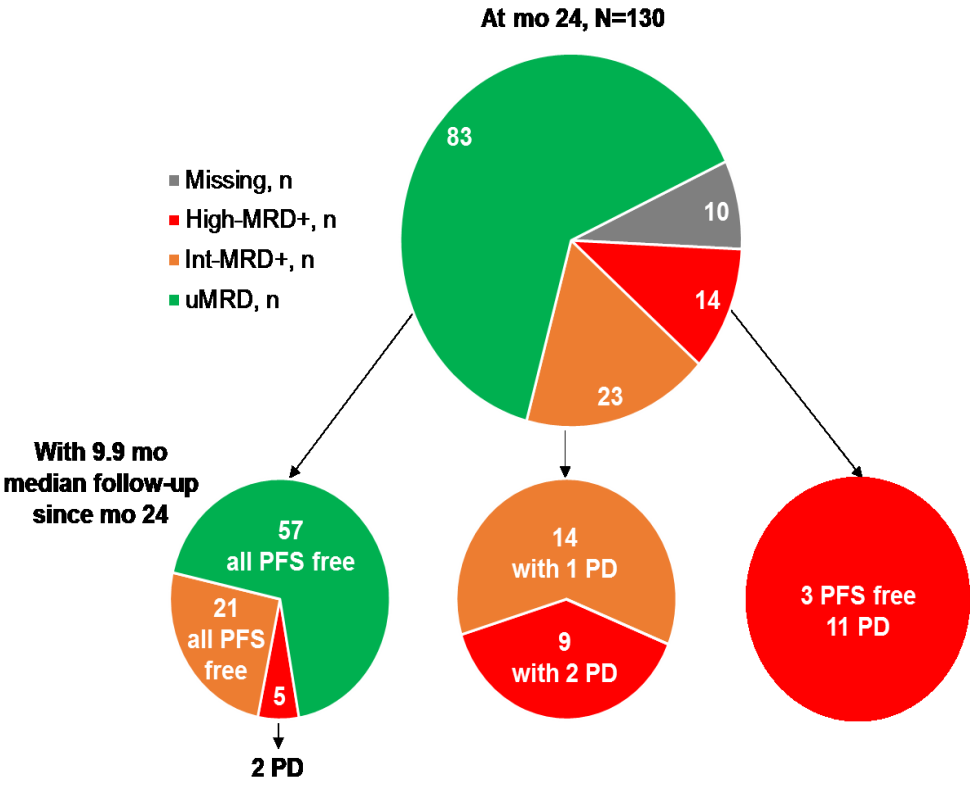


*IA- Investigator assessed

Company's new evidence: new efficacy data

c. MRD status in patients at end of therapy with VEN+R and BR, 24 months data cut

% of pts	VEN+R (N=194)		BR (N=195)	
	Mo 9 (EOCT)	Mo 24	Mo 9 (EOCT)	Mo 24
uMRD (<1 CLL cell per 10,000 leukocytes [$<10^{-4}$]),	62%	48%	13%	2%
Int-MRD+ ($\geq 10^{-4}$ – $<10^{-2}$)	19%	16%	23%	7%
High-MRD+ ($\geq 10^{-2}$)	5%	11%	29%	18%
Missing	7%	7%	15%	7%
disease progression/death/ withdrew	7%	18%	20%	66%



ERG comments on new clinical evidence

- The additional follow-up data shows greater efficacy of VEN+R compared to BR.
- There is a drop in the proportion of patients who achieve MRD negativity in both treatment arms from 9 months to 24 months.

	Appraisal committee 1	Appraisal committee 2
uMRD in VEN+R	62% (at 9 months)	48% (at 24 months)
uMRD in BR arm	13% (at 9 months)	2% (at 24 months)

- This could suggest lack of sustained treatment effect of VEN+R and patients might require additional line of treatment after stopping VEN+R at 2 years.
- It is unclear from the company's evidence if there is data on the MRD status at 36 months.

[redacted]

Company's new evidence: model changes

a. cost comparison of VEN+R vs ibrutinib (1)

ACD: *The committee noted comments from the clinical experts that venetoclax plus rituximab has similar, or better, efficacy to ibrutinib (see section 3.5). It agreed that, because of uncertainties in the company's modelling, a cost comparison of venetoclax plus rituximab and ibrutinib is requested from the company, which might address these uncertainties*.

- The company's cost comparison analysis is based on the assumption that VEN+R and ibrutinib have equal efficacy.

Treatment	Active treatment	Treatment admin	PFS health state costs	PPS health state costs	Terminal care costs	Treatment specific monitoring	AEs	Total
including venetoclax commercial access arrangement (CAA)								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

ERG comment on the cost comparison of VEN+R vs ibrutinib (1)

- The cost comparison provided by the company is correct
- The ERG repeated the analysis using the generalised gamma parametric model

Treatment	Active treatment	Treatment admin	PFS health state costs	PPS health state costs	Terminal care costs	Treatment specific monitoring	AEs	Total
Company (Weibull) (including venetoclax CAA)								
Ibrutinib	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
VEN+R	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
ERG (Generalised Gamma) (including venetoclax CAA)								
Ibrutinib	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
VEN+R	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX

In both scenarios VEN+R is cheaper

[redacted]

Company's new evidence: model changes

a. the cost comparison of VEN+R vs ibrutinib (2)

- Scenarios in which patients after completing 2 years treatment with venetoclax plus rituximab switch to receive ibrutinib until progression.
- The company highlighted that there is evidence from MURANO showing that patients did not continue treatment with ibrutinib after completing treatment with venetoclax plus rituximab

Treatment	Active treatment	Treatment admin	PFS health state costs	PPS health state costs	Terminal care costs	Treatment specific monitoring	AEs	Total
100% of VEN+R patients receive ibrutinib (including venetoclax CAA)								
Ibrutinib	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
VEN+R	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
50% of VEN+R patients receive ibrutinib (including venetoclax CAA)								
Ibrutinib	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
VEN+R	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
30% of VEN+R patients receive ibrutinib (including venetoclax CAA)								
Ibrutinib	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
VEN+R	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX

[redacted]

ERG comment on the cost comparison of VEN+R vs ibrutinib (2)

- The ERG repeated the scenario analyses in which patients after completing 2 years treatment with venetoclax plus rituximab switch to receive ibrutinib until progression, but they used generalised gamma curve for extrapolation of treatment effect.

Treatment	Active treatment	Treatment admin	PFS health state costs	PPS health state costs	Terminal care costs	Treatment specific monitoring	AEs	Total
ERG (Gen Gamma) 100% of pre-progression on ibrutinib (including venetoclax CAA)								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG (Gen Gamma) 50% of pre-progression on ibrutinib (including venetoclax CAA)								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG (Gen Gamma) 30% of pre-progression on ibrutinib (including venetoclax CAA)								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- The ERG concluded that the company's analysis was performed correctly and noted that the results are not sensitive to choice of parametric curve and VEN+R appears to be cheaper than ibrutinib.

[redacted]

ERG comment on the cost comparison of VEN+R vs ibrutinib (3)

- The ERG agrees that the assumption that all patients finishing VEN+R immediately take ibrutinib is not supported by evidence.
- The ERG performed an alternative analysis where 10%, 30% or 50% of post progression patients would receive ibrutinib in addition to 50% of pre-progression patients. It is important to note that patients in the comparator arm do not receive any treatment once they have progressed so this is a pessimistic scenario.

[redacted]

ERG comment the on cost comparison of VEN+R vs ibrutinib (4)

	Active treatment	Treatment admin	PFS health state costs	PPS health state costs	Terminal care costs	Treatment specific monitoring	AEs	Total
ERG alternative 50% of pre-progression and 10% post-progression patients on ibrutinib								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG alternative 50% of pre-progression and 30% post-progression patients on ibrutinib								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG alternative 50% of pre-progression and 50% post-progression patients on ibrutinib								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Only in the most pessimistic scenario where 50% of pre-progression and 50% post-progression patients are given ibrutinib, VEN+R is more costly

[redacted]

Company's new evidence: model changes

b. matched-adjusted indirect comparison results based on May 2018 data cut and the company's revised base case

ACD: *It* [i.e. the committee] *concluded that some of the uncertainty in the modelling could be addressed by additional analyses based on a recent data cut from MURANO and by scenario analyses accounting for loss of treatment effect after 2 years.*

	Adjusted Comparison			Unadjusted Comparison		
	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]	VEN+R= 62 Ibrutinib= 195	[redacted]	[redacted]	VEN+R= 169 Ibrutinib= 195

The company used the above adjusted estimates of hazard ratios for their revised base case

Company's revised base case					
Technologies	**Total costs (£)**	**Total QALYs**	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£/QALY)**
Including venetoclax CAA					
Ibrutinib	[redacted]	4.349	[redacted]	-	**-**
VEN+R	[redacted]	6.356	[redacted]	2.007	VEN+R is Dominant

[redacted]

ERG comments on matched-adjusted indirect comparison (MAIC) based on May 2018 data cut and the ERG's revised base case

- The issues from the original analysis are still present:
  - In the new MAIC hazard ratios for PFS are higher than the estimate for OS

	Old MAIC	New MAIC
MAIC adjusted PFS Hazard Ratio (95% CI)	[redacted]	[redacted]
MAIC adjusted OS Hazard Ratio (95% CI)	[redacted]	[redacted]

  - New NMA hazard ratios, calculated from the new data cut, May 2018.

	Old MAIC	New MAIC
NMA PFS Hazard Ratio (95% CI)	[redacted]	[redacted]
NMA OS Hazard Ratio (95% CI)	[redacted]	[redacted]

  - The ERG base case assumptions are: the hazard ratios from the new NMA based on the new data cut, May 2018 and applied generalised gamma paramedic survival curve

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
ERG base case (Generalised Gamma + NMA) including venetoclax CAA					
Ibrutinib	[redacted]	6.68	-	-	-
VEN+R	[redacted]	6.33	-£228,230	-0.351	£651,136 (SW q)

[redacted]

Company's new evidence: model changes

c. scenario analyses accounting for loss of treatment effect after 2 years based on the company's base case

- The incorporated waning effect is assumed to start after 2 years
- The results of annual increases in loss of treatment effect by 5%, 10%, 20%, 30% and 40% per year after fixed treatment duration

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
VEN+R waning effect (5% per year) including venetoclax CAA					
Ibrutinib	xxxxxxxxxx	4.349	-	-	-
VEN+ R	xxxxxxxxxx	5.736	-£164,238	1.387	VEN+R is Dominant
VEN+R waning effect (10% per year) including venetoclax CAA					
Ibrutinib	xxxxxxxxxx	4.349	-	-	-
VEN+ R	xxxxxxxxxx	5.367	-£166,369	1.018	VEN+R is Dominant
VEN+R waning effect (20% per year) including venetoclax CAA					
Ibrutinib	xxxxxxxxxx	4.349	-	-	-
VEN+R	xxxxxxxxxx	4.918	-£168,810	0.570	VEN+R is Dominant
VEN+R waning effect (30% per year) including venetoclax CAA					
Ibrutinib	xxxxxxxxxx	4.349	-	-	-
VEN+R	xxxxxxxxxx	4.640	-£170,241	0.291	VEN+R is Dominant
VEN+R waning effect (40% per year) including venetoclax CAA					
Ibrutinib	xxxxxxxxxx	4.349	-	-	-
VEN+R	xxxxxxxxxx	4.444	-£171,216	0.095	VEN+R is Dominant

ERG comments on the scenario analyses accounting for loss of treatment effect after 2 years based on the ERG's base case (1)

- The company's choice of the waning rates (5%,10%, 20%,30% and 40%) is not well justified.
- The waning effect has been set to increase year after year after fixed treatment duration, which may underestimate short term waning and overestimate long-term waning.
- The ERG implemented waning effect into its base case, including additional 50%-200% waning rates

Technologies	Total costs(£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
VEN+R waning effect (5% per year) including venetoclax CAA					
Ibrutinib	xxxxxxxxxx	6.682	-	-	-
VEN+ R	xxxxxxxxxx	6.231	-£228,727	-0.451	£507,379 (SW q)
VEN+R waning effect (10% per year) including venetoclax CAA					
Ibrutinib	xxxxxxxxxx	6.682	-	-	-
VEN+ R	xxxxxxxxxx	6.136	-£229,206	-0.546	£419,799 (SW q)
VEN+R waning effect (20% per year) including venetoclax CAA					
Ibrutinib	xxxxxxxxxx	6.682	-	-	-
VEN+ R	xxxxxxxxxx	5.960	-£230,113	-0.723	£318,471 (SW q)
VEN+R waning effect (30% per year) including venetoclax CAA					
Ibrutinib	xxxxxxxxxx	6.682	-	-	-
VEN+ R	xxxxxxxxxx	5.799	-£230,955	-0.883	£261,599 (SW q)
VEN+R waning effect (40% per year) including venetoclax CAA					
Ibrutinib	xxxxxxxxxx	6.682	-	-	-
VEN+ R	xxxxxxxxxx	5.653	-£231,735	-1.029	£225,189 (SW q)

ERG comments on the scenario analyses accounting for loss of treatment effect after 2 years based on the ERG's base case (2)

Technologies	Total costs(£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
VEN+R waning effect (50% per year after fixed treatment duration) including venetoclax CAA					
Ibrutinib	[redacted]	6.682	-	-	-
VEN+ R	[redacted]	6.231	-£232,459	-1.163	£199,876 (SW q)
VEN+R waning effect (70% per year after fixed treatment duration) including venetoclax CAA					
Ibrutinib	[redacted]	6.682	-	-	-
VEN+ R	[redacted]	5.282	-£233,757	-1.4	£166,980 (SW q)
VEN+R waning effect (100% per year after fixed treatment duration) including venetoclax CAA					
Ibrutinib	[redacted]	6.682	-	-	-
VEN+ R	[redacted]	4.988	-£235,394	-1.694	£138,934 (SW q)
VEN+R waning effect (200% per year after fixed treatment duration) including venetoclax CAA					
Ibrutinib	[redacted]	6.682	-	-	-
VEN+ R	[redacted]	4.328	-£239,111	-2.355	£101,550 (SW q)

When the waning effect is applied to the ERG's base case the ICER changed from dominant to the south west quadrant

[redacted]

Company's new evidence: model changes

d. scenario analyses with weighted population of MURANO towards RESONATE, instead of original trial population (ITT) (1)

ACD: *The committee noted that, because the extrapolation was based on the original trial population instead of the matched population, the extrapolation did not represent the correct population*

- Gompertz distribution provides the best fitting model for the weighted MURANO population, however it shows implausibly short survival outcomes.
- Weibull is a second best fitting distribution and has been used by the company as the revised base case model for PFS and OS curves.

	Vs. ibrutinib (including venetoclax CAA)		
PFS/OS extrapolation	Inc. costs (£)	Inc. QALYs	ICER (£)
Company's revised base case (Weibull)	**-136,976**	**1.990**	**VEN+R is Dominant**
Generalised Gamma	-128,127	1.951	VEN+R is Dominant
Gamma	-153,613	2.086	VEN+R is Dominant
Log-logistic	-174,864	2.095	VEN+R is Dominant
Log-normal	-221,983	2.265	VEN+R is Dominant

[redacted]

ERG comments on selection of the parametric model

- The ERG's preferred parametric model is generalised gamma as the curve line is most consistent with experts opinion
- The company's choice is Weibull which is plausible, however ERG noted that it was not well justified by the company if this was suitable parametric model given the new data available. The company did not provide results of the AIC analysis for parametric models based on the new data cut.

Cost comparison results based on the choice of parametric curve

Treatment	Active treatment	Treatment admin	PFS health state costs	PPS health state costs	Terminal care costs	Treatment specific monitoring	AEs	Total
Company (Weibull) (including venetoclax CAA)								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG (Generalised Gamma) (including venetoclax CAA)								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

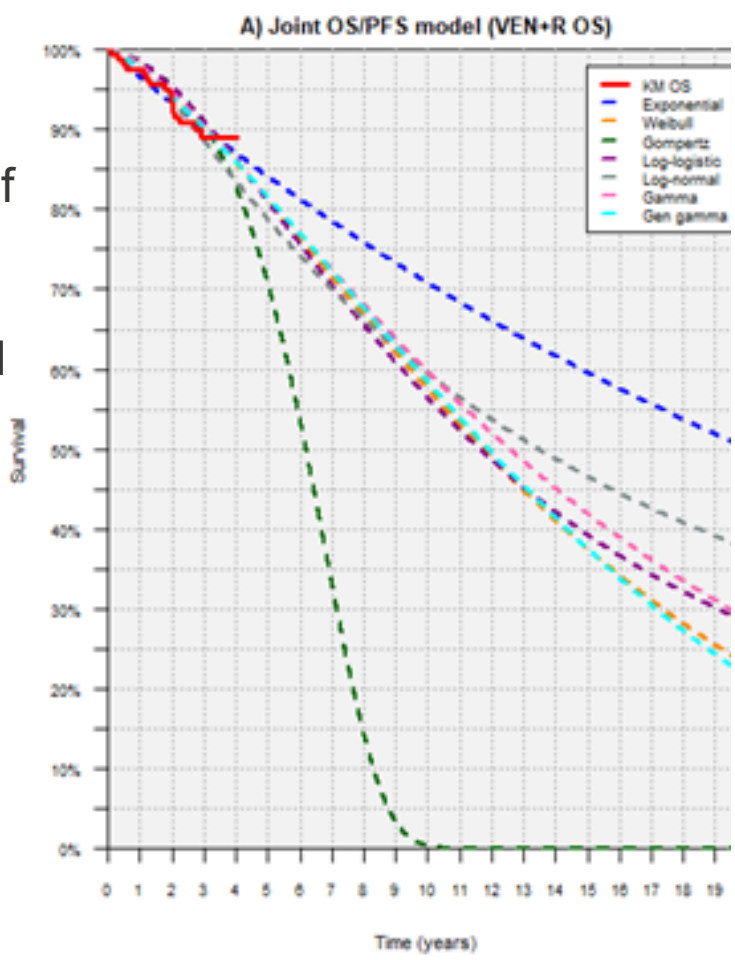
Change of parametric model alone had little impact on the total cost of the treatment

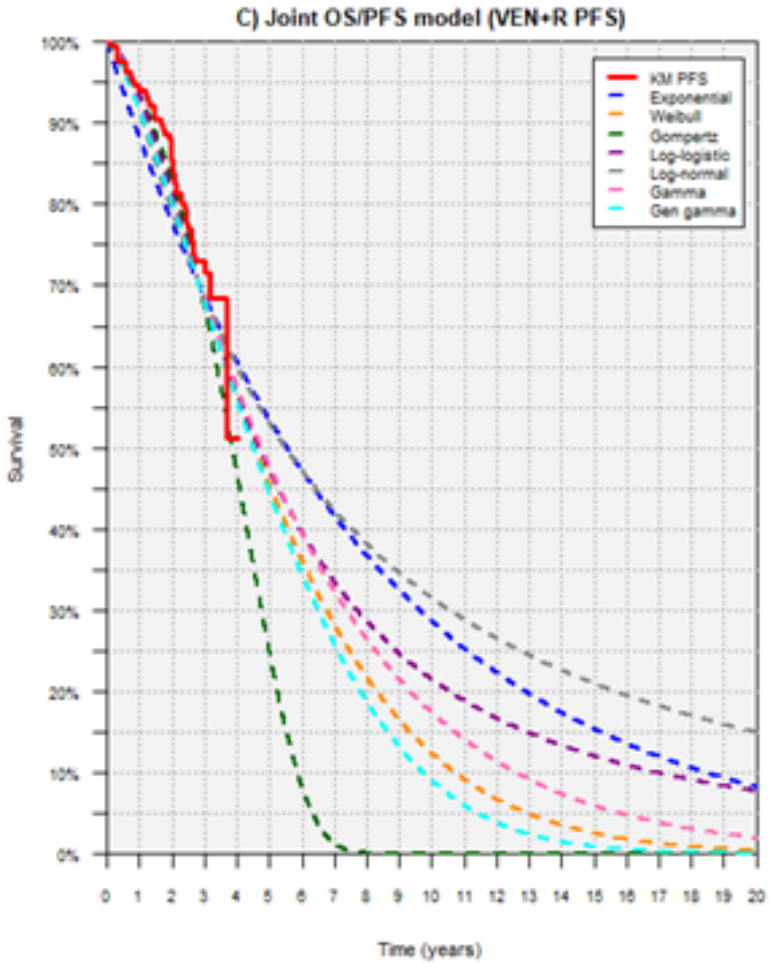
[redacted]

Company's new evidence: model changes

e. scenario analysis with weighted population of MURANO towards RESONATE, instead of original trial population (ITT) (2)

Parametric models for joint estimation of OS and PFS for VEN+R for patients in the MURANO trial weighted by effect modifying characteristics from the RESONATE trial





[redacted]

ERG comments on the modelled population

- It is unclear if the survival is modelled based on the adjusted or unadjusted MAIC population as the parametric extrapolation was carried out based on 169 VEN+R patients, which corresponds with the sample size in the unadjusted comparison (slide 21)
- Not enough information have been provided by the company to verify this analysis.

[redacted]

Company's new evidence: model changes

f. scenario analyses including utility values from the MURANO trial

ACD: *The committee noted that there was a difference of 0.14 between pre-progression and post-progression utilities used in the economic model. It agreed that it would like to see an analysis including the utility values from the MURANO trial to gain a better understanding of the difference between the pre- and post-progression-free survival states and its impact on the cost-effectiveness analysis.*

- The company provided analysis based on the utility values obtained from MURANO for the pre progression state. The company could not provide a utility estimate for the post-progression survival due to lack of available data so it explored a range of potential values whilst maintaining the pre progression utility value from MURANO

MURANO EQ-5D scenario analysis			
	vs. ibrutinib (including venetoclax CAA)		
Diff. between pre and post-progression utility	Inc. costs (£)	Inc. QALYs	ICER (£)
Company's original and revised base case (Literature, Dretzke – PFS:0.748, PPS:0.60) Difference = 0.148	**-160,506**	**2.007**	**VEN+R is Dominant**
(MURANO - PFS:0.840) (Literature, Dretzke - PPS:0.600) Difference = 0.24	-160,506	2.068	VEN+R is Dominant
Difference: 0.3	-160,506	1.916	VEN+R is Dominant
Difference: 0.4	-160,506	1.665	VEN+R is Dominant
Difference: 0.5	-160,506	1.413	VEN+R is Dominant

ERG comments on utility values from the MURANO trial

- The ERG repeated the company's analyses and obtained similar results.
- The ERG provided alternative analysis using the same utility values but based on the ERG's base case.

ERG	Pre Progression	Post Progression	Difference	Sources	Inc Costs + QALYs	ICER
ERG base case	0.748	0.600	0.148	Pre: NICE TA359 Post: Dretzke 2010	-£228,230 -0.351	£651,136 (SW q)
ERG Scenario 1	0.840	0.600	0.240	Pre: MURANO Post: Dretzke 2010	-£228,230 -0.398	£573,364 (SW q)
ERG Scenario 2	0.840	0.540	0.3	Pre: MURANO Post: Diff 0.3	-£228,230 -0.402	£567,692 (SW q)
ERG Scenario 3	0.840	0.440	0.4	Pre: MURANO Post: Diff 0.4	-£228,230 -0.409	£558,483 (SW q)
ERG Scenario 4	0.840	0.340	0.5	Pre: MURANO Post: Diff 0.5	-£228,230 -0.415	£549,569 (SW q)

Both company's and ERG's analyses are not sensitive to the choice of utility values but to the choice of the base case analysis. Using the ERG's base case instead of company's changed the value of the ICER from dominant to the south west quadrant.

[redacted]

Company's new evidence: model changes

Summary of the scenario analyses submitted by the company (1)

Scenario analyses	ICER VEN+R (including venetoclax CAA) vs standard of care
	Individual change
Company's revised base case (including HRs from the new MAIC)	VEN+R is Dominant
VEN+R waning effect (5% per year after fixed treatment duration)	VEN+R is Dominant
VEN+R waning effect (10% per year after fixed treatment duration)	VEN+R is Dominant
VEN+R waning effect (20% per year after fixed treatment duration)	VEN+R is Dominant
VEN+R waning effect (30% per year after fixed treatment duration)	VEN+R is Dominant
VEN+R waning effect (40% per year after fixed treatment duration)	VEN+R is Dominant
Weighted population of MURANO instead of original trial population (company's revised base case - Weibull)	VEN+R is Dominant
Generalised Gamma	VEN+R is Dominant
Gamma	VEN+R is Dominant
Log-logistic	VEN+R is Dominant
Log-normal	VEN+R is Dominant

[redacted]

Company's new evidence: model changes

Summary of the scenario analyses submitted by the company (2)

Scenario analyses	ICER VEN+R (including venetoclax CAA) vs standard of care
	Individual change
Company's original and revised base case (Literature, Dretzke – PFS:0.748, PPS:0.60) Difference = 0.148	VEN+R is Dominant
(MURANO - PFS:0.840) (Literature, Dretzke -PPS:0.600) Difference = 0.24	VEN+R is Dominant
Difference: 0.3	VEN+R is Dominant
Difference: 0.4	VEN+R is Dominant
Difference: 0.5	VEN+R is Dominant

[redacted]

ERG comments on model changes

Summary of the scenario analyses submitted by the company (1)

Scenario analyses	ICER VEN+R (including venetoclax CAA) vs standard of care
	Individual change
ERG's revised base case (including HRs from the new NMA plus Generalised Gamma)	£651,136 (SW q)
VEN+R waning effect (5% per year after fixed treatment duration)	£507,379 (SW q)
VEN+R waning effect (10% per year after fixed treatment duration)	£419,799 (SW q)
VEN+R waning effect (20% per year after fixed treatment duration)	£318,471 (SW q)
VEN+R waning effect (30% per year after fixed treatment duration)	£261,599 (SW q)
VEN+R waning effect (40% per year after fixed treatment duration)	£225,189 (SW q)
VEN+R waning effect (50% per year after fixed treatment duration)	£199,876 (SW q)
VEN+R waning effect (70% per year after fixed treatment duration)	£166,980 (SW q)
VEN+R waning effect (100% per year after fixed treatment duration)	£138,934 (SW q)
VEN+R waning effect (200% per year after fixed treatment duration)	£101,550 (SW q)

[redacted]

ERG comments on model changes

Summary of the scenario analyses submitted by the company (2)

Scenario analyses	ICER VEN+R (including venetoclax discount) vs standard of care
	Individual change
Weighted population of MURANO instead of original trial population (company's revised base case - Weibull)	ERG was unable to verify this analysis
Generalised Gamma	-
Gamma	-
Log-logistic	-
Log-normal	-
ERG's base case (Literature, Dretzke – PFS:0.748, PPS:0.60) Difference = 0.148	£651,136 (SW q)
(MURANO - PFS:0.840) (Literature, Dretzke -PPS:0.600) Difference =0.24	£573,364 (SW q)
Difference: 0.3	£567,692 (SW q)
Difference: 0.4	£558,483 (SW q)
Difference: 0.5	£549,569(SW q)

Key issues for consideration

- Is the new MAIC or ERG's NMA appropriate for decision making?
- Are the waning rates (5%, 10%, 20%, 40%) proposed by the company plausible?
- Which utility values are the most plausible - MURANO or the literature?
- What is the most plausible ICER?
- Can the cost comparison analysis be used for decision making?
  - How many people will require treatment after 2 years?
- Is venetoclax with rituximab cost-effective?
- Is venetoclax a potential candidate for the CDF ?

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