Evidence Review Group's Report

Title: *Venetoclax for treating chronic lymphocytic leukaemia (CDF review of TA487) [ID3886] – ERG Report*

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Contributions of authors
Toyin Lamina conducted and led the review and critique of the clinical evidence. Mandy Maredza conducted and led the review and critique of the cost-effectiveness evidence and performed additional analyses. Kate Evans reviewed and critiqued the clinical evidence. Felix Achana reviewed and critiqued the cost-effectiveness evidence. Rachel Court performed all necessary literature searches. Scott Marshall provided expert clinical opinion. Daniel Gallacher led the project, contributed to the

clinical and cost-effectiveness sections and performed additional statistical analyses. All authors contributed to the production of this report and approved the final version.

Please note that: *Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.* Depersonalised Data (DPD) is highlighted in pink.

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List of Abbreviations

AIC	Akaike Information Criterion
ASH	American Society of Haematology
BIC	Bayesian Information Criterion
BOR	Best Overall Response
BSC	Best Supportive Care
BTKi	Bruton Tyrosine Kinase Inhibitor
CAA	Commercial Access Agreement
CDF	Cancer Drugs Fund
CEAC	Cost-Effectiveness Acceptability Curve
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukaemia
CMU	Commercial Medicines Unit
CS	Company Submission
EAMS	Early Access to Medicines Scheme
ERG	Evidence Review Group
HR	Hazard Ratio
ICER	Incremental Cost-Effectiveness Ratio
ITT	Intention-To-Treat
KM	Kaplan Meier
LYG	Life Year Gained
NHS	National Health Service
ORR	Overall Response Rate
OS	Overall Survival
PAS	Patient Access Scheme
PFS	Progression-Free Survival
PI3K	Phosphoinositide 3-kinase
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
SACT	Systemic Anti-Cancer Therapy
ToE	Terms of Engagement
TOT	Time on Treatment
TP53	Tumour Protein p53
UK	United Kingdom
Ven	Venetoclax
VenR	Venetoclax Rituximab

Executive Summary

The summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the ERG's key issues

An overview of the ERG's key issues is presented in Table 1. These are the topics the ERG identified as the most influential to the committee's decision-making process.

Table 1: Summary of key issues

Key Issue #	Summary of issue	Report section
Key issue 1: Generalisability of venetoclax data to UK practice	The company used systemic anti-cancer therapy (SACT) Cancer Drugs Fund (CDF) data to estimate the efficacy of venetoclax. The generalisability issues include: that the SACT CDF data contains the additional benefit of some patients receiving rituximab therapy, and that the majority of patients have not had prior venetoclax therapy.	Section 3.1.2
Key issue 2: Uncertainty and potential for bias in data modelling of Best Supportive Care (BSC)	No additional data for BSC was presented by the company. Considerable uncertainty of the generalisability of this data persists as was raised in the original appraisal (TA487).	Section 3.2 Section 4.1.2.1
Key issue 3: Lack of a statistical comparison of venetoclax and BSC	At no point have the company presented a statistical model quantifying the clinical benefit of venetoclax over BSC.	Section 3.4
Key issue 4: Average age and gender of the patient population in the economic model	The company take the starting age and gender ratio of patients in the economic model from pooled data of their venetoclax trials, despite more relevant data being available from the SACT report.	Section 6.1.1 Section 6.1.2
Key issue 5: Unexpectedly high post-progression survival modelled for venetoclax, and potential inconsistency with clinical evidence	The ERG compared the modelled post-progression survival benefit to observed post-progression survival times and notice a large disparity. The modelled benefit appears to exceed the ERG's analysis.	Section 4.1.2.2
Key Issue 6: Inconsistent survival modelling	The company's survival modelling of venetoclax data is inconsistent to their survival modelling of BSC. For venetoclax, separate models are used for each deletion/mutation subgroup, whilst for BSC one model is fitted simultaneously to both groups.	Section 4.1.2.2
Key Issue 7: Use of time on treatment data to model progression-free survival	The company use time on treatment data to represent progression-free survival without providing evidence supporting this assumption.	Section 4.1.2.2
BSC, best supportive care; CDF, Cancer Drugs Fund; EAMS, early access to medicines scheme; ERG, evidence review group; SACT, systemic anti-cancer therapy		

1.2 Critique of the adherence to committee's preferred assumptions from the Terms of Engagement in the company's submission

The company adhered to the majority of the committee's preferred assumptions as outlined in the terms of engagement. The only deviation was in regard to the source of data for best supportive care (BSC). The terms of engagement stated the company should fully explore the most appropriate source of data for BSC, however the company have not systematically searched for or considered any new or alternative evidence. Whilst this is in part due to the failure of the SACT report to provide a source of data for BSC as expected, the company did not present evidence of considering any other potential sources of information. The company implemented the same approach as they did in the original appraisal (TA487) and did not present any alternative modelling approaches, such as the ERG's preferred approach in the original appraisal to use post-progression survival information from the idelalisib arm of trial 116. Neither did the company conduct a systematic search for new sources of information, relying on their clinical expert to identify potential sources.

The terms of engagement are discussed in further detail in section 2.3

1.3 Summary of the key issues in the clinical effectiveness evidence

The ERG identified three key concerns with the clinical effectiveness evidence included in the company submissions. These were:

- Issue 1: The generalisability of the SACT CDF data to routine venetoclax usage
- Issue 2: The uncertainty around BSC efficacy and the company's failure to consider alternative sources of data for BSC
- Issue 3: The lack of matching-adjusted or naïve statistical comparison of venetoclax and BSC.

They are described in more detail in Tables Table 2-4.

Table 2*:* Generalisability of the CDF SACT data

Report section	Sections 3.1.2 and 3.4.2
Description of issue and why the ERG has identified it as important	Whilst the SACT CDF data are an improvement over the previous pooling over multiple venetoclax trials, there are important limitations. The ERG notes that a number of patients in the CDF SACT data received rituximab and are not excluded from the main results presented by the company. They may have received additional benefit from rituximab. Furthermore, the changing treatment pathway for CLL and the influence of

	previous venetoclax therapy may affect the efficacy of venetoclax in this indication, which is not represented in the data. The SACT CDF data are also more optimistic than the SACT EAMS data. Combining these two UK RWE datasets would reduce the efficacy of venetoclax.
What alternative approach has the ERG suggested?	The ERG has been unable to suitably adjust for the clinical effects of rituximab or earlier lines of venetoclax therapy, or to pool the EAMS and CDF cohorts together by deletion/mutation status. The ERG has performed analyses where the cost of rituximab therapy is applied for the proportion of patients who received rituximab in the SACT CDF data.
What is the expected effect on the cost-effectiveness estimates?	The SACT CDF data used by the company may overestimate the efficacy of venetoclax in routine use moving forward, and underestimate the time on treatment, suggesting the benefits of venetoclax therapy may decrease, whilst the associated costs increase. Factoring in the costs of rituximab therapy on the venetoclax arm slightly increases the ICER.
What additional evidence or analyses might help to resolve this key issue?	Economic analyses based on pooling together EAMS and CDF data of patients who did not receive rituximab will maximise the relevant information contributing to this appraisal.

Table 3: Uncertainty around the BSC data

Report section	Sections 3.2 and 4.1.2.1
Description of issue and why the ERG has identified it as important	The company has not performed a systematic search or identified any alternative sources of BSC data and repeated its use of data from the rituximab arm of trial 116. It was expected that the SACT report would be a source of this information, but this was not the case.
What alternative approach has the ERG suggested?	The ERG has been unable to perform a comprehensive, systematic search but has identified other potential sources of data. The ERG was unable to contact the authors of these papers to request the data in a useable format. Extended follow-up from trial 116 has also been published but is not reported in sufficient detail for use in this appraisal.
What is the expected effect on the cost-effectiveness estimates?	There remains tremendous uncertainty over the comparability of the BSC and venetoclax data sources. It is possible that the data used by the company is representative of BSC meaning the modelling of BSC is likely to be accurate, but it may also over or under-estimate BSC.
What additional evidence or analyses might help to resolve this key issue?	Obtaining relevant data from authors of other key studies would allow additional analyses to be performed and reduce the uncertainty.

Table 4: Lack of matching-adjusted or naïve statistical comparison of venetoclax and BSC.

Report section	Section 3.4.1
Description of issue and why the ERG has identified it as important	The company was unable to perform any comparison due to a lack of access to the patient level data to their preferred sources of information for venetoclax and BSC. At no point in this or the original appraisal has the company presented a statistical model demonstrating the superiority of venetoclax to BSC.
What alternative approach has the ERG suggested?	The ERG has estimated a hazard ratio for overall survival (OS) of venetoclax relative to BSC in a population ignoring deletion/mutation status, using EAMS and CDF cohorts along with two published sources.
What is the expected effect on the cost-effectiveness estimates?	The hazard ratio suggests a lower magnitude of benefit relative to the company's modelling. When the hazard ratio is applied to the BSC OS extrapolations, the benefit of venetoclax reduces considerably, having a large effect on the ICER.
What additional evidence or analyses might help to resolve this key issue?	Obtaining relevant data from authors of other key studies would allow additional analyses to be performed and reduce the uncertainty.

1.4 Summary of the key issues in the cost effectiveness evidence

The ERG identified a further four key issues relevant to the cost-effectiveness evidence provided by the company. These are:

- Issue 4: The source of baseline characteristics inputs
- Issue 5: Over-optimistic post-progression survival modelling
- Issue 6: Inconsistent modelling of survival data
- Issue 7: Use of time on treatment (TOT) data to model progression-free survival (PFS)

These issues are described in more detail in Tables 5-8.

Table 5: The source of baseline characteristics inputs

Report section	Sections 6.1.1 and 6.1.2
Description of issue and why the ERG has identified it as important	The company has maintained the use of age and gender inputs from the pooled data of its venetoclax trials. The SACT report contains this information relevant to the UK population.
What alternative approach has the ERG suggested?	The ERG has taken the data for each deletion/mutation subgroup from the SACT CDF data, as provided in response to the ERG's clarification request.
What is the expected effect on the cost-effectiveness estimates?	The combined impact of changing the starting age and gender ratio increases the ICER relative to the company's base case.
What additional evidence or analyses might help to resolve this key issue?	No further evidence is required.

Table 6: Over-optimistic post-progression survival modelling

Report section	Sections 4.1.2.2 and 6.1.4
Description of issue and why the ERG has identified it as important	The company's modelling of venetoclax results in estimates of post-progression survival that exceed estimates that come from an alternative published source identified by the ERG.
What alternative approach has the ERG suggested?	The ERG requested alternative modelling approaches be implemented into the model but the company were not able to provide this. The ERG has performed exploratory analyses that yield more plausible estimates of post-progression survival.
What is the expected effect on the cost-effectiveness estimates?	The ERG anticipates that if it were possible to model more plausible estimates of post-progression survival, the ICER would increase considerably.
What additional evidence or analyses might help to resolve this key issue?	Additional flexible models, or an inclusion of the more mature EAMS data may produce extrapolations with more plausible estimates of post-progression survival for venetoclax.

Table 7: Inconsistent modelling of survival data

Report section	4.1.2.2
Description of issue and why the ERG has identified it as important	The company's modelling for BSC fits one survival model simultaneously to data both deletion/mutation subgroups. The company's modelling for venetoclax fits models independently to the two deletion/mutation subgroups. No justification for this was provided and it is a potential source of bias.
What alternative approach has the ERG suggested?	The ERG has not been able to attempt to resolve this problem.
What is the expected effect on the cost-effectiveness estimates?	It is unclear what influence this might have on the ICER.
What additional evidence or analyses might help to resolve this key issue?	Fitting parametric models simultaneously to venetoclax data for both deletion/mutation subgroups would mean a more consistent modelling for both arms.

Table 8: Use of TOT data to model PFS

Report section	4.1.2.2
Description of issue and why the ERG has identified it as important	The company use TOT data from the SACT CDF population to model PFS as PFS data were not available. This is inconsistent with the modelling for BSC and potentially leads to incorrect estimation of PFS and treatment costs.
What alternative approach has the ERG suggested?	The ERG requested that the company produce evidence to support their assumption of equivalence of TOT and PFS but the company were not able to provide this. The ERG have not been able to resolve this problem.
What is the expected effect on the cost-effectiveness estimates?	Incorrect estimation of costs and benefits has the possibility to shift the ICER in either direction.
What additional evidence or analyses might help to resolve this key issue?	Evidence to support the equivalence of the PFS and TOT outcomes would alleviate the ERG's concerns.

1.5 Summary of ERG's preferred assumptions and resulting ICER

The ERG's preferred assumptions deviate from those of the company's base case. Note, that the ERG have additional concerns around the generalisability of the data, and the suitability of the candidate parametric models that we were not able to address in our base case. The ERG's recommendations for the ERG preferred base case analysis are:

- Use a starting age of 71 years, consistent with SACT CDF and EAMS data
- Change the ratio of males to females to be consistent with SACT CDF data
- Apply to BSC data the overall survival (OS) and PFS hazard ratios estimated using the BSC data for effect of non-deletion/mutation in BSC as measured in idelalisib appraisal [1]

Note the ICERs presented below does not include Commercial Medicines Unit (CMU) pricing of other therapies, and this is presented separately within the confidential appendix.

Table 9: ICER resulting from ERG's preferred assumptions for deletion/mutation population

Technology	Total		Incremental: venetoclax vs BSC		ICER, £/ QALY
	Costs, £	QALYs	Costs, £	QALYs	
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	£46,325
BSC	[redacted]	0.605			

Table 10: ICER resulting from ERG's preferred assumptions for non-deletion/mutation population

Technology	Total		Incremental: venetoclax vs BSC		ICER, £/ QALYs
	Costs, £	QALYs	Costs, £	QALYs	
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	£52,169
BSC	[redacted]	1.068			

1.6 Summary of additional analyses undertaken by the ERG

A summary of the ERG's additional analyses can be found in Table 11 and Table 12.

Table 11: Exploratory analyses undertaken by ERG for deletion/mutation population

Scenario	*Section in main ERG report*	*Technology*		*Comparator*		*ICER £/QALY*
		QALYs	*Costs*	*QALYs*	*Costs*	
Change baseline age at start of treatment to match SACT CDF data	6.1.1	[redacted]	[redacted]	0.605	[redacted]	£46,355
Base gender distribution (proportion male) on SACT CDF data	6.1.2	[redacted]	[redacted]	0.627	[redacted]	£43,219
Applying 6 months of rituximab costs for 20% of venetoclax patients to match the clinical data	3.1.2.2.3 6.1.3	[redacted]	[redacted]	0.627	[redacted]	£44,110
Changing survival for 10% of post-progression survivors on venetoclax	4.1.2.2 6.1.4	[redacted]	[redacted]	0.627	[redacted]	£61,135
Apply venetoclax OS hazard ratio to BSC extrapolation	3.4.1 6.1.6	[redacted]	[redacted]	0.627	[redacted]	£73,753
Using Previous ERG modelling for BSC	6.1.7	[redacted]	[redacted]	1.058	[redacted]	£63,973

Table 12: Exploratory analyses undertaken by the ERG non-deletion/mutation population

Scenario	*Section in main ERG report*	*Technology*		*Comparator*		*ICER £/QALY*
		QALYs	*Costs*	*QALYs*	*Costs*	
Change baseline age at start of treatment to match SACT CDF data	6.1.1	[redacted]	[redacted]	1.115	[redacted]	£53,273
Base gender distribution (proportion male) on SACT CDF data	6.1.2	[redacted]	[redacted]	1.160	[redacted]	£49,175
Applying 6 months of rituximab costs for 20% of venetoclax patients to match the clinical data	3.1.2.2.3 6.1.3	[redacted]	[redacted]	1.160	[redacted]	£50,123
Changing survival for 10% of post-progression survivors on venetoclax	4.1.2.2 6.1.4	[redacted]	[redacted]	1.160	[redacted]	£68,408
Apply correct BSC hazard ratio for deletion mutation effect in populations without TP53 mutation	4.1.2.1.2	[redacted]	[redacted]	1.110	[redacted]	£48,329
Apply venetoclax OS hazard ratio to BSC extrapolation	3.4.1 6.1.6	[redacted]	[redacted]	1.160	[redacted]	£77,265
Using Previous ERG modelling for BSC	6.1.7	[redacted]	[redacted]	2.087	[redacted]	£103,370

Evidence Review Group Report

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

Venetoclax has been available in England since October 2017 through the Cancer Drugs Fund (CDF), within its marketing authorisation, as an option for treating chronic lymphocytic leukaemia, 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.[2]

In the appraisal committee's recommendations following the original appraisal of this technology (TA487), it was noted that in the M12-175, M13-982, and M14-032 trials, venetoclax appeared to improve PFS and OS, that there was potential for venetoclax to be cost-effective. However, there was uncertainty regarding the generalisability of these trials to routine use of venetoclax.[3] In addition, there were uncertainties around the appropriateness of the comparator evidence. Additional data in terms of real-world evidence was required to resolve these uncertainties and establish the cost-effectiveness of venetoclax therapy. Consequently, venetoclax was commissioned through the CDF for a period of managed access, supported by additional data collection to answer the clinical uncertainty.[4]

2.2 Background

For this CDF review, venetoclax is used for adults with CLL who have 17p deletion or TP53 mutation who are unsuitable for B-cell receptor pathway inhibitor or whose disease progressed after a B-cell receptor pathway inhibitor; and adults with CLL without 17p deletion or TP53 mutation and whose disease has progressed following both chemo-immunotherapy and a B-cell receptor pathway inhibitor. This is consistent with NICE's recommended use within the CDF and was accepted by the ERG as the appropriate place for the technology in the treatment pathway in the original appraisal (TA487). Within this

CDF review, an updated treatment pathway was submitted by the company in response to clarification question A1. The pathway includes treatments that have been commissioned for use in the NHS following the conclusion of TA487, potentially affecting the generalisability of the CDF data. The ERG considers the implications of this in section 3.4.2.

In this report the ERG will describe patients with 17p deletion or TP53 mutation as deletion/mutation, and those without 17p deletion or TP53 mutation as non-deletion/mutation.

2.3 Critique of company's adherence to committee's preferred assumptions from the Terms of Engagement

The ERG's critique of the company's adherence to the committee's preferred assumptions and expectations as listed in the terms of engagement document can be found in Table 13.

Table 13: Preferred assumption from Terms of Engagement

Assumption	Terms of engagement	Addressed to by the company submission	Rationale if different	ERG comment
Population	Population 1a – adults with 17p deletion or TP53 mutation whom a B-cell receptor pathway inhibitor is unsuitable. Population 1b – adults with 17p deletion or TP53 mutation whose disease has progressed after a B-cell receptor pathway inhibitor. Population 2 – adults without 17p deletion or TP53 mutation whose disease has progressed after both chemoimmunotherapy and a B-cell receptor pathway inhibitor.	Yes		No comment required.
Comparators	Best supportive care	Yes		No comment required.
Generalisability of trial data	SACT data should inform the generalisability of the trial data	Yes – the company now use venetoclax efficacy data from SACT CDF instead of from the single arm trials.		No comment required.
Survival data	Extrapolation approach to be informed with more mature trial data and SACT data	Yes		Company did not consider any alternative methods of extrapolation that may better represent the data.
Source of best supportive care data	Company should explore most appropriate source of BSC data.	No – Company have maintained the use of the placebo/rituximab arm of Trial 116.	SACT data for BSC were not available. The company has not presented any evidence to	New and extended follow-up from trials of ibrutinib and of study 116 but it does not appear the

			suggest they have considered any alternative sources of data for BSC or conducted any formal literature search.	company attempted to obtain or use this data.
Utility values	Progression free health state should have a utility value of 0.748	Yes		No comment required.
Most plausible ICER	NA – no recommendation made	NA		
End of life	Venetoclax meets end of life criteria for both of the main populations.	Yes		No comment required.
BSC, best supportive care; CDF, Cancer Drugs Fund; ERG, evidence review group; SACT, systemic anti-cancer therapy				

3 CLINICAL EFFECTIVENESS

3.1 Critique of new clinical evidence

The company submission included data from multiple sources. The company presented extended follow-up from some of their existing trials of venetoclax therapy, and also included data presented in the SACT report. This information is summarised and critiqued below.

3.1.1 Updated trial evidence - venetoclax

In the original appraisal (TA487), the key source for the effectiveness of venetoclax in patients with chronic lymphocytic leukaemia (CLL) were three single-arm clinical trials: M12-175, M13-982, and M14-032. Due to uncertainty regarding the study designs (single arm), differences with the patient characteristics (see original submission) with the comparator trial data and generalisability to UK clinical practice highlighted by the NICE Appraisal committee, these three trials are not the main contributors of evidence to the economic model in the current submission. The company provided updated data for the M13-982 and M14-032 trials (CS section A.6 page 15 and Appendices A1 and A2) up to their latest data cut-off points (4th April 2017 and 30th June 2017, respectively). These data-cuts are several years old, and updated data could be valuable to demonstrate the long-term efficacy of venetoclax. The company did not provide updated data for the M12-175 trial in this submission. In response to clarification question A7 the company stated no additional follow-up was available.

In M14-032 the number of patients contributing information to the key outcomes has now increased (N=91) compared to the original appraisal (N=64), however this is still lower than the previously reported plan to recruit a total of 124 participants. Data from the M13-982 and M14-032 trials are still relatively immature in the new data cut. The median progression free survival (PFS) outcome for the M14-032 trial is now evaluable at 24.7 months, previously not being reached at the point of appraisal of TA487. Median PFS for the M13-982 trial is unchanged (27.2 months) with the new data cut. The median overall survival (OS) outcomes for the M13-982 and M14-032 updated data has not been reached. The pooled patient characteristics, and efficacy outcomes measures for M12-175, M13-982, and M14-032 trials from the original appraisal,[5] and new data cut-off points for M13-982, and M14-032 (see CS Appendix A) are summarised in Table 14.

Table 14: Baseline characteristics and key outcomes for relevant studies

Trial		Total pooled population M12-175/ M13-982/ M14-032 (del(17p)/TP53 patients) – original appraisal	Total pooled population M12-175/ M14-032 (without del(17p)/TP53 patients) – original appraisal	M13-982 (with and without deletion/ mutation) – April 4, 2017	M14-032 (with and without deletion/ mutation) – 30th June 2017	Trial 116 (rituximab arm)	SACT Data CDF Cohort			SACT Data EAMS Cohort
Study design		Phase 1/Phase 2 studies	Phase 1/Phase 2 studies	Phase 2, open-label study	Multicentre, open-label, non-randomised, phase 2 trial	Multicentre, randomised, double-blind, placebo-controlled, phase 3 study	Real world data			Real world data
Intervention		Venetoclax	Venetoclax	Venetoclax	Venetoclax	Rituximab monotherapy	Venetoclax			Venetoclax
							With deletion/ mutation	**Without deletion/ mutation**	**Total**	
N		[redacted]	[redacted]	158	91	110	161	245	406	102
Mean age, years (STD)		[redacted]	[redacted]	NR	66	70	[redacted]	[redacted]	71.3 (95% CI: 70.3, 72.2)	NR
Median age, years (CI)		NR	NR	67	NR	71	[redacted]	[redacted]	72 (95% CI: 71, 73)	72
Gender, N (%)	**Male**	[redacted]	[redacted]	59 (37%)	64 (70%)	(62%)	[redacted]	[redacted]	275 (68%)	67 (66%)
	Female	[redacted]	[redacted]	99 (63%)	27 (30%)	(38%)	[redacted]	[redacted]	131 (32%)	35 (34%)
No. of prior therapies	**Mean (SD)**	[redacted]	[redacted]	2	4	3	NR	NR	NR	NR
ECOG, N (%)	**0**	[redacted]	[redacted]	69 (44%)	29 (32%)	NR	[redacted]	[redacted]	84 (21%)	30 (29%)

	1	[redacted]	[redacted]	78 (49%)	54 (59%)	NR	[redacted]	[redacted]	146 (36%)	44 (43%)
	2	[redacted]	[redacted]	11 (7%)	8 (9%)	NR	[redacted]	[redacted]	40 (10%)	7 (7%)
	3	NR	NR	NR	NR	NR	[redacted]	[redacted]	7 (2%)	0 (0%)
	4	NR	NR	NR	NR	NR	[redacted]	[redacted]	0 (0%)	0 (0%)
	Missing	NR	NR	NR	NR	NR	[redacted]	[redacted]	129 (32%)	21 (21%)
IGVH mutation, N (%)	**Missing**	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR	NR
	Mutated	[redacted]	[redacted]	NR	NR	(15%)	NR	NR	NR	NR
	Unmutated	[redacted]	[redacted]	45 (78%)	50 (75%)	(85%)	NR	NR	NR	NR
TP53 mutation, N (%)	**Missing**	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR	NR
	No	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR	NR
	Yes	[redacted]	[redacted]	55 (71%)	29 (33%)	NR	NR	NR	NR	NR
17p deletion N (%)	**Missing**	NR	NR	NR	NR	NR	NR	NR	NR	NR
	No	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Yes	NR	NR	NR	NR	(28%)	NR	NR	NR	NR
Baseline ALC	**Mean (SD)**	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR	NR
Bulky disease, N (%)	**Missing**	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR	NR
	Nodes < 5CM	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR	NR
	Nodes >= 5CM	[redacted]	[redacted]	76 (48%)	36 (40%)	NR	NR	NR	NR	NR
	Nodes >= 10CM	NR	NR	21 (13%)	9 (10%)	NR	NR	NR	NR	NR
Rai stage at screening, n (%)	**0**	NR	NR	1 (1%)	NR	(1%)	NR	NR	NR	NR
	1 or 2	NR	NR	84 (53%)	NR	(27%)	NR	NR	NR	NR
	3 or 4	NR	NR	73 (46%)	NR	(65%)	NR	NR	NR	NR
	Missing	NR	NR	0 (0%)	NR	(7%)	NR	NR	NR	NR

						Without 17p deletion or TP53 mutation	**17p deletion or TP53 mutation**	**Total**		

Median Treatment duration (months)	NR	NR	23.1	NR	NR	NR	19.4 (95% CI: 12.3, not reached)	22.3 (95% CI: 20.0, 28.1)	17.9 (95% CI: 11.5, 25.6)	21.2 (95% CI: 18.6, 24.7)	19.1 (95% CI: 11.7, 27.0)
Median PFS (months)	NR	NR	27.2 (95% CI, 21.9 – not reached)	24.7 (95% CI 19.2–not reached)	8.1	4.0	6.5 (95% CI: 4.0, 7.3)	NR	NR	NR	NR
Median OS (months)	NR	NR	Not reached	Not reached	20.8	14.8	20.8 (95% CI: 14.8, not reached)	Not reached	33	43.1	32.5 (95% CI: 20.3, 41.8)
Median OS Follow-up (months)	NR	NR	NR	NR	NR	NR	NR	15.5	20.6	18.9	33.1

Footnotes: Mean and median age with CI for SACT data were not available in the PHE report but provided by NHS Digital following the ERG's request (clarification latter A11&12). Patients age within SACT data is age at the start of treatment. SACT OS by mutation was provided by NHS Digitial (clarification letter, appendix A). The ERG had to assume SACT performance data was the same as ECOG status. M14 data included main cohort and expansion cohort.

Abbreviations: CDF: Cancer Drugs Fund, CI: Confidence Interval, EAMS: Early Access to Medicines Scheme, ECOG: Eastern Cooperative Oncology Group, NR: Not Reported, PFS: Progression-free Survival, OS: Overall Survival, SACT: Systemic Anti-Cancer Therapy.

3.1.2 Data collected through CDF

At the conclusion of TA487, the NICE appraisal committee recommended that real-world treatment effectiveness should be collected to inform the use of venetoclax in the UK population due to the clinical uncertainties (particularly the generalisability) with M12-175, M13-982, and M14-032 trials. The primary source of data in the current CS is the Systemic-Anti-Cancer Therapy (SACT) dataset to evaluate venetoclax treatment through the Cancer Drugs Fund (CDF) – commissioned by NHS England and NHS Improvement and carried out by Public Health England (PHE). The SACT dataset provides real-world information on venetoclax treatment for CLL in England, during the period of managed access (October 2017 to December 2020). The "SACT CDF cohort" is the relevant group in the SACT dataset used in the economic evaluation. The SACT data has not previously been published and data are presented in the CS and the PHE Report Commissioned by NHS England and NHS Improvement for the NICE Appraisal Committee (Review of TA487) [5] (known hereafter as the PHE SACT report), provided to the ERG. Patient characteristics and efficacy outcomes information for the SACT CDF cohort is summarised in Table 14.

3.1.2.1 SACT CDF vs EAMS

Within the SACT dataset, data from additional patients (N = 105) were combined from either an Early Access to Medicine (EAMS) cohort from 23 August 2016 to 5 December 2016 or other compassionate access programmes and were established as any venetoclax treatment for chronic lymphocytic leukaemia recorded in the SACT dataset before 5 October 2017. 102/105 patients receiving venetoclax were included in the SACT EAMS analyses. Of the three patients excluded from the EAMS cohort, two patients were not currently in SACT, and one patient died before treatment. Patient characteristics and efficacy outcomes for the EAMS cohort are presented in the PHE SACT report provided to the ERG and summarised in Table 14.

The SACT CDF and EAMS cohorts appear to be similar in age. However, the ERG notes that the EAMS cohort may be slightly healthier than the SACT CDF cohort when comparing the Eastern Cooperative Oncology Group (ECOG) performance status. This must be interpreted with caution given the SACT CDF cohort had more missing performance data compared to the EAMS cohort.

The ERG found that the EAMS data shows slightly worse efficacy outcomes compared to the SACT CDF cohort data (Figure 1). The ERG's clinical advisor hypothesised that the EAMS cohort may have been a higher risk group with clinicians motivated to get them on venetoclax through an early access scheme. The EAMS cohort had a longer median follow-

up for OS (33.1 months) compared to SACT CDF (18.9 months), and so potentially contains more information on the long-term efficacy of venetoclax.

Patient characteristics and efficacy outcomes information for the EAMS cohort is presented in the PHE SACT report and summarised in Table 14. The company noted that "although SACT data were provided for both the SACT CDF and EAMS cohorts, only the SACT CDF cohort data is split by del(17p)/TP53 mutation status as required for the economic model. As such, only data from the SACT CDF cohort are presented within this submission". ERG agrees with this statement. In addition, the ERG notes that the eligibility of the EAMS patients were noted in the PHE SACT report; however, the eligibility for patients in the other compassionate access programmes are unknown. Due to this uncertainly in patient eligibility in the EAMS cohort, it is likely appropriate to prioritise the SACT CDF cohort for consideration in this submission. If the EAMS OS data were broken down by deletion/mutation status and pooled with the CDF data, it is likely that the efficacy of venetoclax would decrease.

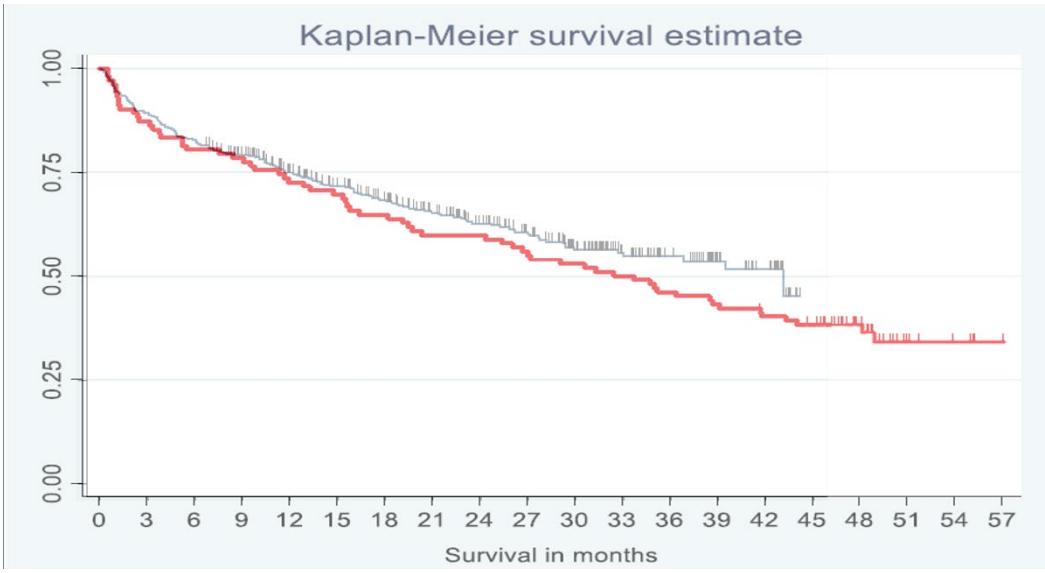


Figure 1: Comparison of SACT CDF (blue) and SACT EAMS (red) overall survival data

A comprehensive report on the efficacy and safety outcomes of a similar EAMS cohort have been published by Eyre and colleagues (2019).[6] The ERG found some discrepancy between the patient characteristics and efficacy outcomes reported in the PHE SACT report and the Eyre et al (2019)[6] paper, suggesting the populations are not identical. There is unclear rationale for such inconsistency between both reports, thus the ERG do not consider the Eyre report to be more reliable than the SACT report. If it were, there would be the potential to extract information from Eyre and utilise it within the economic model. The ERG did

however use the Eyre et al (2019)[6] paper as a reference point to compare the modelled post-progression survival of venetoclax patients in section 4.1.2.2, as no alternative sources were available.

3.1.2.2 SACT CDF Data

3.1.2.2.1 SACT CDF Overview

Between 5 October 2017 and 4 December 2020, 454 applications for venetoclax were identified in NHS England and NHS Improvement's Blueteq system. Following appropriate exclusions, 429 unique patients were identified. This cohort included the following:

- patients with confirmed diagnosis of chronic lymphocytic leukaemia or small lymphocytic lymphoma that requires treatment
- patients with performance status of 0-2
- patients with prospectively assessed for the risk of the development of tumour lysis syndrome following the start of venetoclax
- patients tested for mutation status
- patients without 17p deletion or TP53 mutation who have never received venetoclax before or has been previously treated with the combination of venetoclax and rituximab in which case the patient must not have progressed during treatment with venetoclax
- patients without 17p deletion or TP53 mutation who have progressive disease on or after chemoimmunotherapy and B-cell receptor pathway inhibitor
- patients with 17p deletion or TP53 mutation who have progressive disease on or after B-cell receptor pathway inhibitor or there must be a contraindication to the patient receiving both a BTKi and a PI3Ki.

Detailed patient eligibility criteria can be found in the PHE SACT report (pages 10 to 11).

The ERG notes that for patients with 17p deletion or TP53 mutation, the inclusion of "patients who had never received venetoclax before or has been previously treated with the combination of venetoclax and rituximab in which case the patient must not have progressed during treatment with venetoclax" was not reported in the PHE SACT report. It is unclear how exactly this imbalance in eligibility criteria might affect baseline prognosis at the start of

the venetoclax monotherapy treatment. The ERG's clinical advisor highlighted that the National CDF list [7] was updated in December 2021 to bring all recommendations in line and the omission regarding previous venetoclax monotherapy or combination treatment has been included for those with 17p deletion or TP53 mutation.

3.1.2.2.2 SACT CDF Results

Of the 429 patients identified through CDF funding, seven patients did not receive treatment and 16 patients died before treatment. No further information on the seven patients who did not receive treatment was noted in the PHE SACT report. 406 patients were identified as the SACT CDF cohort for the main analysis. Venetoclax was administered orally, and treatment was generally prescribed in a healthcare facility. The ERG notes that the dosage and frequency of venetoclax treatment were not reported in the CS and PHE SACT report. The median OS follow-up time of patients in the SACT CDF dataset was 18.9 months. The ERG considered this a relatively short follow-up duration. The key patient flow of the CDF cohort data is provided in CS Appendix B.1 Table 13 and the PHE SACT Report (Table 8 and 12). The most common reason for treatment discontinuation in the SACT CDF cohort is death.

Baseline characteristics of the SACT CDF cohort (N = 406) were reported by the company (CS Table 4) and summarised by the ERG (Table 14). The ERG verified these data using the tables reported in the PHE SACT report. Baseline characteristics stratified by deletion/mutation status for patients in the SACT CDF cohort was provided in response to clarification question A21. The ERG notes that there was a lack of presentation of key prognostic baseline characteristics (e.g., prior lines of treatment, disease stage). The clinical advisors consulted for the ERG deemed the SACT CDF cohort to be generally representative of UK patients.

The ERG notes that the company did not use the median age (71 years) reported for the SACT CDF cohort in its economic analyses, instead the company used the median age (65 years) from the pooled trials presented in the original appraisal (see Table 14), which is potentially lower than the average age of UK patients receiving venetoclax. The ERG's clinical advisors highlighted that the median age of the SACT CDF cohort is representative of the UK population, given most patients needing treatment being in their 70's which is around the peak age for CLL diagnosis and treatment in the UK according to national statistics.[8]

The key efficacy outcomes (treatment duration (also referred to as time on treatment (TOT) in this submission) and overall survival) for all patients in the SACT CDF cohort are described in the PHE SACT Report (Tables 9-11 and Figure 7 for TOT and Tables 26-28

and Figure 10 for OS) and summarised in Table 14. TOT was used as a proxy for progression-free survival (PFS) for the SACT CDF cohort within the economic model due to lack of progression information within the SACT database. In response to clarification question A5, the company provided evidence to assess the similarity of the PFS and TOT from one of the venetoclax trials – M13-982 and reported that TOT was 4 months shorter than PFS. The ERG was not assured by this, and notes that there is uncertainty around the robustness of this proxy measure and anticipates that using TOT as a proxy for PFS may favour venetoclax treatment. As SACT CDF dataset is a single armed study, the statistical assessment of outcomes was descriptive. Kaplan-Meier methods were used to estimate TOT and OS.

TOT and OS by mutation status were presented in CS section A.6.2.2 to A.6.2.3 and summarised in Table 14. The ERG verified these data using the tables reported in the PHE SACT report. For patients with deletion/mutation the median TOT was 17.9 months. The median OS was 33 months. The 95% confidence interval was not reported for median OS. For non-deletion/mutation patients the median TOT was 22.3 months, and the median OS was not reached. As expected, median TOT and OS were lower for deletion/mutation patients compared to non-deletion/mutation patients. The ERG's clinical advisor highlighted that such patterns are consistent with experience in the clinical settings.

Safety outcome measures for venetoclax were not reported for the SACT CDF cohort.

3.1.2.2.3 Treatment switchers

The ERG notes that following the original appraisal, other combination treatments with venetoclax have been routinely commission in the NHS. NICE guidance recommending venetoclax with rituximab (VenR) for routine use for relapsed/refractory patients was published in February 2019 (TA561).[9] Similarly, venetoclax with obinutuzumab entered routine commissioning as a first-line treatment for selected CLL populations, and was recommended into the CDF for other CLL populations, with NICE guidance published in December 2020 (TA663).[10] 80 out of 406 patients within the SACT CDF cohort and 32 out of 102 EAMS patients received rituximab on or after the earliest venetoclax treatment start date (known as treatment switchers). The ERG notes that patients who received rituximab may have received additional benefit relative to if they had received only venetoclax. The NHS England and NHS Improvement rules stated patients were allowed to switch from venetoclax monotherapy to VenR therapy within the titration period (~5 weeks) of beginning venetoclax, as VenR was approved for routine use after the CDF recommendation was received for

venetoclax. However, the SACT report states only 30/112 of these switching patients started their rituximab within 8 weeks.

The PHE SACT report stated that it is uncertain if the 112 patients are true treatment switchers because some may have received rituximab as a subsequent treatment instead of combination. Whilst it is possible that rituximab was given after termination of venetoclax monotherapy; it remains unclear why these patients received rituximab. The possible inclusion of patients who had rituximab after termination of venetoclax monotherapy impinges the generalisability of the SACT CDF data in the UK clinical practice.

The PHE SACT report presented sensitivity analyses where the patients who also received rituximab were excluded from the SACT CDF and EAMS populations, which the ERG presents in Figure 2 and Figure 3 respectively. In both plots, there is same pattern when the rituximab patients are removed, suggesting rituximab has had an effect.

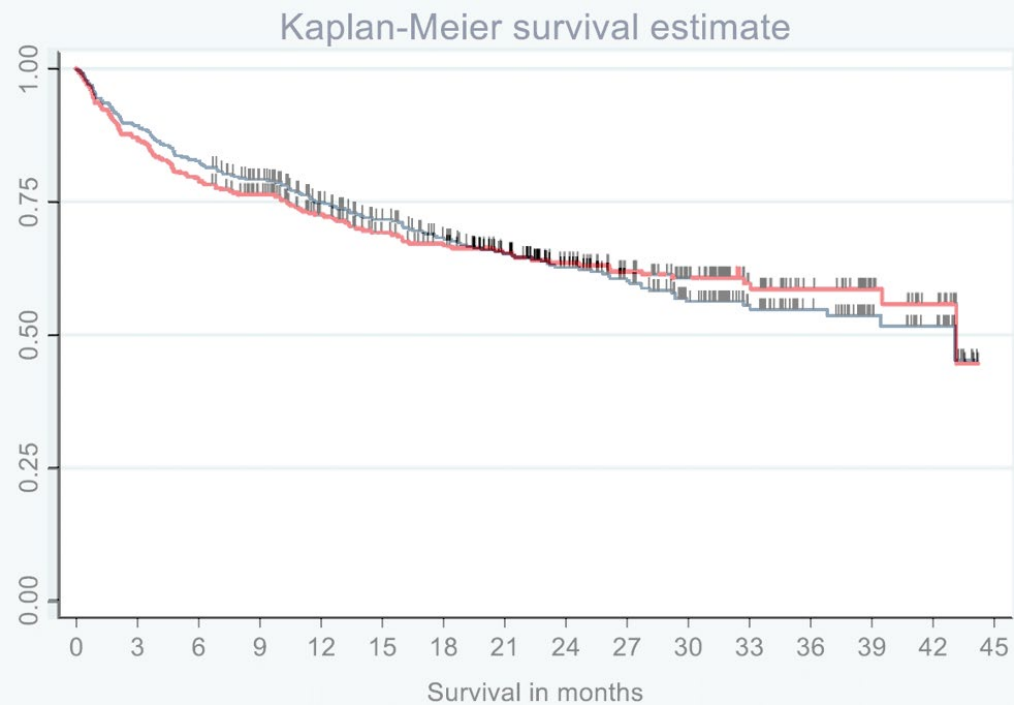


Figure 2: Comparison of CDF overall survival including (blue) and excluding (red) patients who received rituximab.

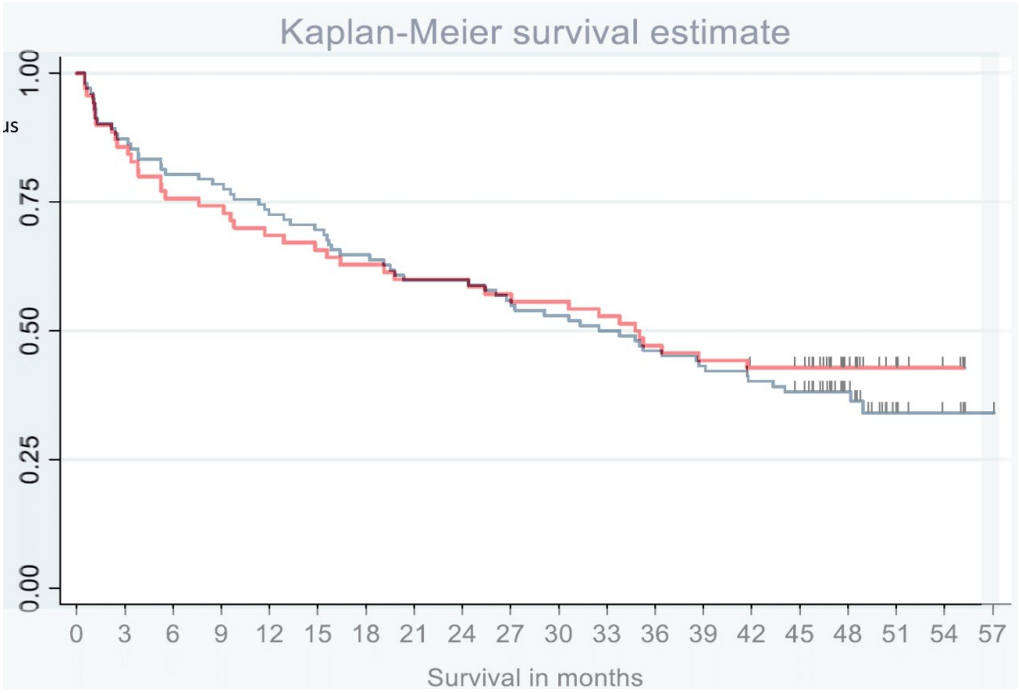


Figure 3: Comparison of EAMS overall survival including (blue) and excluding (red) patients who received rituximab.

In response to clarification question A14 to PHE, the patient characteristics and efficacy outcomes by deletion/mutation status were provided for the population excluding patients who are classed as treatment switchers. The ERG found no major differences between the patient characteristics of the SACT CDF cohort with treatment switchers and those without treatment switchers.

Figure 4 and Figure 5 contain updated SACT CDF information excluding the patients who received rituximab with or following their venetoclax therapy, overlayed onto the original plots. It is apparent that there is a difference between the TOT of the two populations. These data have not been incorporated into the economic model but doing so would likely influence the ICER.

The ERG conducted a scenario analysis adding the costs of rituximab therapy for some patients in the venetoclax population (section 6.1.3).

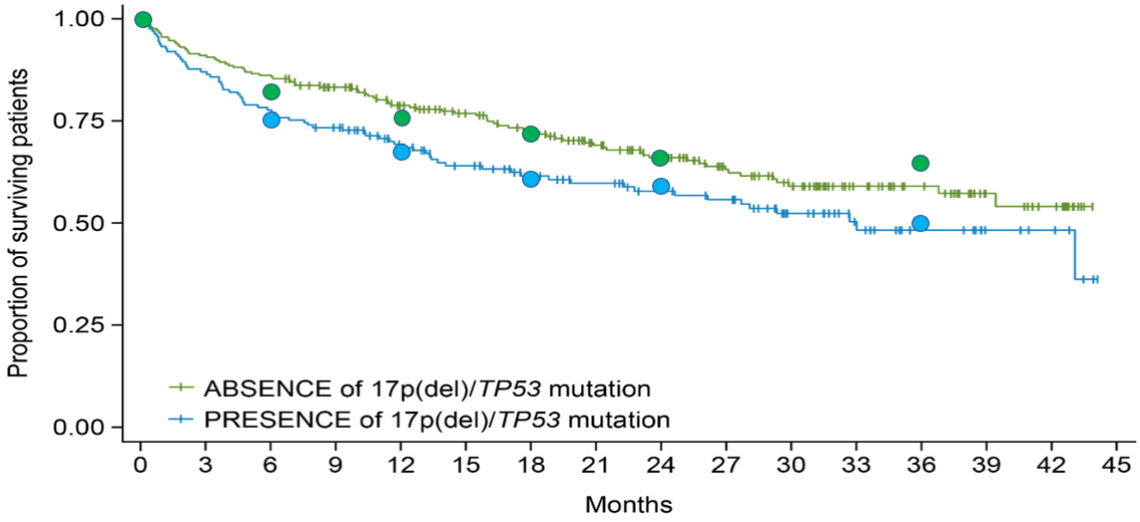


Figure 4: Overall survival for venetoclax patients from CDF SACT, comparing the effect of removing patients who received rituximab (dots) from the wider population (lines).

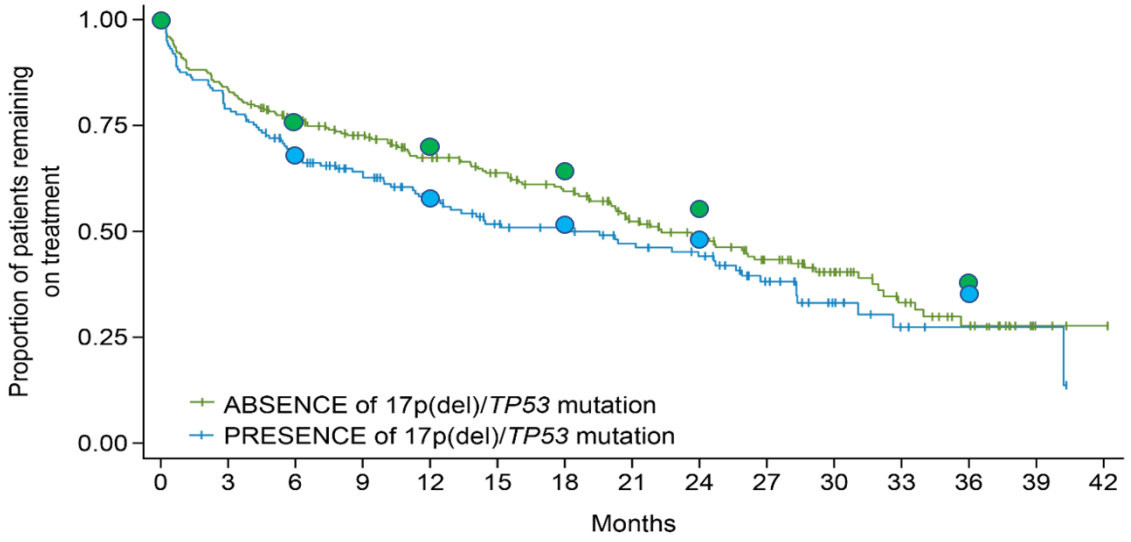


Figure 5:Time on treatment for venetoclax patients from CDF SACT, comparing the effect of removing patients who received rituximab (dots) from the wider population (lines).

3.2 Overview of BSC evidence

In the original appraisal (TA487), the company used the rituximab arm of the 116 trial as the main comparative evidence for BSC. This was recommended by the company's clinical experts to inform for BSC during an advisory board, where it was indicated that rituximab is used in the post-BCRi setting. Study 116 was a phase III, double-blind, randomised controlled trial conducted in the US, France, UK, Italy and Germany in which idelalisib with

rituximab was compared with rituximab monotherapy (N=220 total sample, and n=110 in the rituximab arm) in people with chronic lymphocytic leukaemia.[1] This rituximab population was selected by the company as an appropriate comparator group for venetoclax and was used in the economic model. The NICE Appraisal committee highlighted that the comparator group was eligible for a B-cell receptor inhibitor, whereas to be offered venetoclax under this indication patients must have disease progression after a B-cell receptor inhibitor. An alternative data source from the 116 trial (rituximab plus idelalisib which comprised patients with disease which has progressed after a B-cell receptor pathway inhibitor) was proposed by the ERG. The committee agreed that the alternative data source was appropriate; however, there were concerns around the plausibility of the extrapolations generated from models fitted to this data.

In the current CDF submission, the company's approach is unchanged, and the 116 trial (rituximab arm) is the main evidence source for BSC used in the economic model. The survival outcomes (PFS and OS) for the 116 trial were extracted directly from the idelalisib NICE appraisal (TA359) [1] because adjustments for treatment switching were taken into account due to the availability of patient level data in the Gilead NICE manufacturer's submission. No updated information on the 116 trial was presented by the company in the current submission (clarification question A6) nor was a systematic search for an alternative source of BSC data performed (clarification question A8). The ERG notes that extended follow-up from trial 116 is now available,[11] however, it was not publicly reported to the detail necessary for inclusion in this appraisal. The company did not make any attempt to obtain useable information from the authors. Patient characteristics and efficacy outcomes measures for the rituximab arm are included in Table 14.

In line with the committee's comments above, for current submission, the ERG's clinical advisor highlights that the 116 trial is not a suitable comparator because the patients in the trial had other treatment options (such as BTKi and venetoclax) which may have improved their survival post study, whereas patients who receive venetoclax monotherapy have few options for further therapy (such as trials of new agents or allogeneic transplant if fit enough (where most are not).

It was hoped that the SACT dataset would provide data on BSC in clinical practice to represent a comparator arm to venetoclax due to uncertainty regarding the appropriateness of the comparator study cohort from the original submission. Public Health England (PHE) reported that no meaningful data was captured on BSC within SACT during the period of managed access (due to under reporting of haematological malignancies in the SACT dataset at the time the BSC treatment option was available). PHE conducted a feasibility

assessment of the SACT CDF dataset that determined that a matched cohort analysis of the BSC data would not provide meaningful analyses. The PHE feasibility assessment was provided following request from clarification question A18. Consequently, BSC treatment from the SACT data was not used in the economic model. The ERG considers that BSC data from SACT would have been beneficial for the CDF review had it been available.

3.3 Comparison of SACT CDF and trial 116

The eligibility criteria of the SACT CDF cohort study and trial 116 [1, 12] have been considered by the ERG. The ERG notes that these criteria are difficult to compare because they mostly provide different categories of patient eligibility; however, a few similarities and differences were found. The differences with potential relevance are:

- In the SACT CDF cohort study, patients were required to have never received venetoclax before or had been previously treated with the combination of venetoclax and rituximab in which case the patient must not have progressed during treatment with venetoclax. In the 116 trial, the requirement was that previous treatment must have included either a CD20 antibody– based regimen or at least two previous cytotoxic regimens. It is unclear how the differences in the prior lines of therapy may impact the benefit of venetoclax over BSC.

- In the SACT CDF cohort study, patient must either have relapsed on or after a B-cell receptor pathway inhibitor (a Bruton's tyrosine kinase inhibitor [BTKi] e.g. ibrutinib or a PI3K inhibitor [e.g. idelalisib]) or there must be a contraindication to the patient receiving both a BTKi and a PI3Ki; this was not stated in the eligibility criteria for the 116 trial. It is unclear how the differences in the prior lines of therapy may impact the benefit of venetoclax over BSC.

- In the 116 trial, patients had chronic lymphocytic leukaemia (CLL) that had progressed within 24 months after their last treatment; this was not stated in the eligibility criteria for the SACT CDF cohort study. It is unclear how any differences in the progression during treatment interval may impact the benefit of venetoclax over BSC.

- In the 116 trial, patients were excluded if they had history of prior allogenic bone marrow progenitor cell or solid organ transplant; this was not stated in

the eligibility criteria for the SACT CDF cohort. This may have led to the selection of fitter patients into the SACT CDF cohort study.

The company did not provide a matched population based on the eligibility criteria from both studies. The lack of matching of the patients means there is considerable uncertainty towards the similarity of the two populations later used as sources of information for the economic model.

Table 9Limited patient characteristics information presented for the SACT CDF cohort in the CS makes comparison with the 116 trial characteristics challenging. The ERG notes that some of the patient characteristics appear to be similar, including: age and gender. The 116 trial (rituximab arm) had significantly smaller number of participants (n=110) compared to N=406 in the SACT CDF cohort. Insufficient information on prognostic patient characteristics factors in the SACT CDF cohort prevented any meaningful comparisons of the two populations.

Differences in the PFS definition between the SACT CDF cohort and the 116 trial rituximab population were also observed by the ERG. Treatment duration (TOT) was used as a proxy for PFS due to lack of progression information within the SACT database. The ERG anticipates using treatment duration as a proxy for PFS may favour venetoclax treatment. The ERG notes that there is uncertainty around the robustness of this proxy measure.

The ERG note that the company have not presented a statistical model demonstrating clinical superiority of venetoclax over BSC. The ERG requested (clarification A2) a naïve comparison be performed however the company stated this was not possible due to a lack of access to available data. The ERG accepts any comparison would be flawed given challenges around treatment switching and differences in baseline characteristics, but since there is a complete lack of alternatives, the ERG maintain that a crude comparison would still be valuable. Instead, the company rely solely on economic modelling based on the assumption of clinical superiority.

3.4 Additional work on clinical effectiveness undertaken by the ERG

3.4.1 Comparison of venetoclax to BSC

The ERG sought to do a statistical comparison of venetoclax to BSC, as the company failed to provide one. Such a comparison was only possible if the two main patient populations were pooled, i.e., ignoring deletion/mutation status. For venetoclax the ERG digitised the data from the sensitivity analysis in the PHE report which excluded patients who received

rituximab and pooled together the EAMS and CDF datasets. The number of death and censoring events made it difficult to accurately capture the venetoclax data. For BSC, the ERG digitised post-progression survival plots from Rigolin[13] and Aarup,[14] and combined the data together.

Fitting a Cox proportional hazards model to the recreated data, with a fixed effect for treatment, produced a hazard ratio of 0.57 (0.44, 0.73). Whilst this figure is not robust estimate of treatment effect, it is some indicator of the potential of the magnitude of benefit in the lack of any alternative.

This analysis has numerous weaknesses, including inaccuracy of data in the analysis, and differences between patients, both in terms of their baseline characteristics and the later therapies they received. It also does not distinguish between deletion/mutation and non-deletion/mutation, however as this is thought to be a prognostic factor, the hazard ratio is unlikely to differ significantly across these groups. The ERG conducted scenario analyses in the cost-effectiveness section applying this hazard ratio to the Weibull extrapolations of BSC for the two main populations (section 6.1.6).

3.4.2 Potential effect of the changing treatment pathway

The target population at the time of entry of venetoclax into the CDF was for patients proceeding along the following treatment pathway as shown in Figure 6**Error! Reference source not found.**. The data in the CDF SACT population deviates slightly from this as it allowed patients who received prior venetoclax therapy. Judging by the timing of the outcomes of venetoclax for the other CLL indications, the ERG predicts the number of these patients to be small, however it is not stated in the SACT report. No patients in trial 116 had prior venetoclax therapy.

A potentially bigger issue is that of the evolving treatment pathway. Earlier courses of venetoclax are available routinely or through the CDF since the time of the original appraisal. This means that patients eligible to receive venetoclax under this indication moving forward will have followed a different treatment pathway to that of most CDF patients. The ERG's clinical expert supported this view, as does the updated treatment pathway provided in their response to ERG clarification (Figure 7).

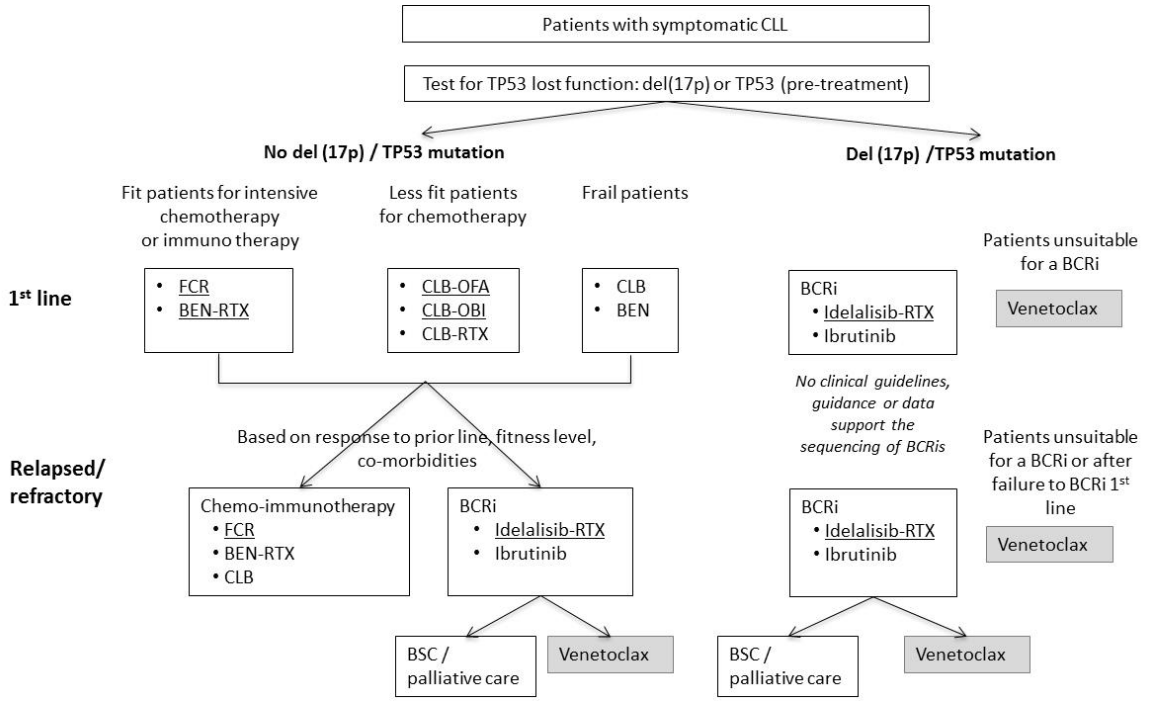
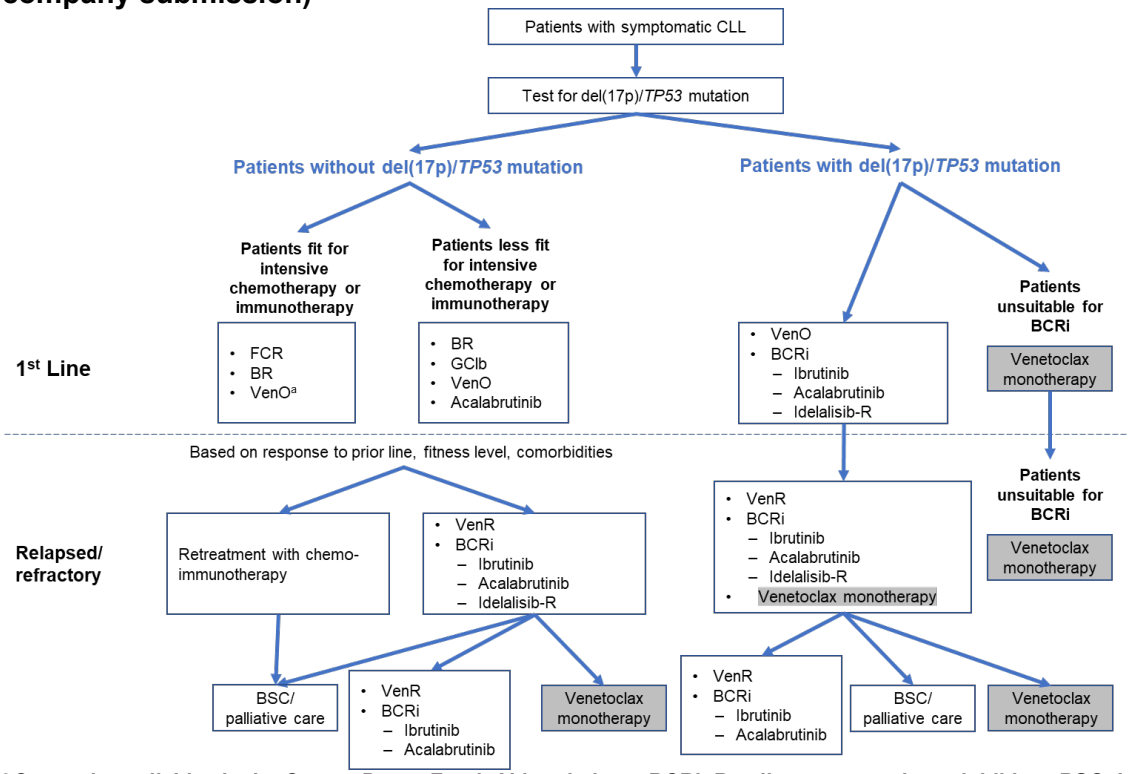


Figure 6: Treatment pathway at point of original appraisal (taken from original company submission)



[a] Currently available via the Cancer Drugs Fund. Abbreviations: BCRi: B-cell receptor pathway inhibitor; BSC: best supportive care; BR: bendamustine with rituximab; CLL: chronic lymphocytic leukaemia; FCR: fludarabine, cyclophosphamide and rituximab; GClb: obinutuzumab with chlorambucil; R: rituximab; VenG: venetoclax with obinutuzumab; VenR: venetoclax with rituximab.

Figure 7: Updated treatment pathway at representing currently approved treatments (taken from company clarification response)

Evidence is still emerging over the extent of the efficacy of repeated venetoclax therapy. The ERG briefly examined some of this emerging evidence, and in discussion with our clinical expert conclude that venetoclax is likely to be efficacious after previous exposure to venetoclax therapy, though uncertainty remains over the degree of efficacy.

The ERG was unable to find useful data for the efficacy of venetoclax monotherapy following previous venetoclax therapy. However, information is available from the MURANO trial which retreated patients with venetoclax rituximab (VenR). The overall response rate (ORR) for retreatment was 55% compared to 75% for those in the control arm who received VenR for the first time [15] and 92% ORR for the venetoclax arm for its initial course [16]. A presentation at the American Society Haematology Conference (ASH) 2020 combined data from MURANO and CLL14, and reported an ORR of 72.2% for retreatment compared to 88% ORR to initial VenR therapy.[17] A similar report using MURANO data quoted a best overall response rate of 72.2% for second course of venetoclax compared to 80% for those who switched to receive venetoclax therapy for the first time.[18]

Furthermore, there is emerging evidence to suggest some patients may become resistant to venetoclax therapy, particularly when the duration does not have a fixed endpoint, as in this appraisal.[19] Whilst resistance could potentially be screened for, the ERG understands this is not routinely performed. The ERG's clinical expert reported venetoclax is unlikely to be given to patients who have responded poorly to prior venetoclax therapy, but the decision would be made on a case-by-case and this possibility cannot be ruled out.

The ERG concludes that whilst venetoclax monotherapy will probably still have a strong and significant positive effect in a population who have already received prior venetoclax therapy, the effect of venetoclax monotherapy is likely to be reduced relative to what was observed in the CDF SACT data (a suspected largely venetoclax naïve population). This reinforces the ERG's concerns around the generalisability of the CDF SACT data to routine venetoclax usage moving forward.

According to the ERG's clinical expert, additional evidence on this issue may be presented at ASH 2021; however, the ERG has not been able to incorporate this into their report.

3.5 Conclusions of the clinical effectiveness section

The new main source of evidence for venetoclax, the SACT PHE study, improves upon the issue of generalisability to UK clinical practice, which was a major limitation of the pooled venetoclax trials used in the original appraisal, but has its own limitations.

Clinical outcomes from the PHE SACT study suggested a positive response to treatment with venetoclax; however, the real-world study of venetoclax has a relatively short follow-up time frame, and survival outcomes for patients without 17p deletion or TP53 mutation do not have enough data to be fully informed. In the absence of a comparator group within the PHE SACT report, the magnitude of the benefit of venetoclax over treatment with best supportive care is uncertain. The main limitations of the SACT CDF data are the influence of patients who also received rituximab, and the representativeness of UK care given the approval of venetoclax therapy for earlier lines.

Evidence for the comparator (BSC) was taken from the rituximab arm of the 116 trial. The company did not identify or present alternative sources of BSC data as recommended in the scope. The patient population in the comparator trial do not represent those for whom venetoclax could be considered under this indication. There are known differences in setting and case definitions between the SACT CDF population and the 116 cohort, and potentially many more unknown differences. The company did not perform any form of matching analysis to account for the identified differences, nor any statistical comparison demonstrating the clinical benefit of venetoclax over BSC.

4 COST EFFECTIVENESS

4.1 Summary and critique of the company's economic evaluation

4.1.1 Model structure

There have been no changes to the model structure, population, intervention and comparators, perspective, time horizon or discounting of the model submitted by the company, which were previously accepted by the Committee in TA487.

4.1.2 Treatment effectiveness and extrapolation

4.1.2.1 BSC data and extrapolation

The company did not discuss in detail the data and extrapolations for BSC in their CDF submission. The ERG presents a summary of this information as it of high importance to the CDF review.

4.1.2.1.1 Summary of previous BSC data and extrapolation

Briefly, the company selected the placebo plus rituximab arm of study 116, a randomised trial comparing idelalisib plus rituximab to placebo plus rituximab in patients with relapsed

CLL disease. In the NICE appraisal of idelalisib for CLL, the company fitted parametric curves to the PFS and OS data from this arm, simultaneously for patients with and without deletion/mutation.[1] The OS data was adjusted for treatment switching whilst PFS was not. They selected the Weibull model as it yielded the most plausible extrapolation for both populations according to the company's clinical expert. It was also among best fitting curves according the information criteria assessing the goodness-of-fit. The Weibull model included a parameter for deletion/mutation status, giving hazard ratios of 0.677 for PFS and 0.543 for OS.[1] In this CDF review, the company opted to use the shape and scale parameters from the Weibull model to estimate PFS and OS for the deletion/mutation population. But for the non- deletion/mutation population they apply a hazard ratio for this difference estimated using pooled data from the venetoclax trials (0.585 for PFS, 0.524 for OS).

The limitation with the study 116 data was that the patients were eligible for idelalisib therapy, whereas the relevant population for this CDF review are patients who have progressed after B-cell receptor inhibitor, such as idelalisib. Furthermore, comparing the patients from study 116 to those in the venetoclax trials suggested that the patients in the venetoclax trials were much healthier and it was unlikely to be a fair comparison. Reliance on an adjustment for treatment switching is also a weakness, as these adjustments can be associated with considerable uncertainty.

The ERG previously explored alternative methods and attempted to utilise the data for post-progression survival from the idelalisib arm of the 116 trial. Whilst the data may be more applicable, it had limitations and was associated with implausible extrapolations for the deletion/mutation population.

4.1.2.1.2 Current situation

In their CDF submission, the company did not identify or present any alternative approaches to modelling for the BSC arm and maintained their original modelling approach.

In review, the ERG note that the company have not explored any other sources of information, despite a number of years passing since the previous appraisal. The ERG searched for alternative sources of data for the BSC, constrained by the short duration of a CDF review. A summary of results can be found in Table 15, which shows a wide variety of overall survival outcomes for populations following discontinuation of ibrutinib or idelalisib therapy. Factors associated with post-progression survival include the number of prior therapies, the reason for discontinuation and the subsequent therapy received.

Table 15:Summary of potential reference points or alternative sources for BSC

Study	Relevant Sample Size (Location)	Post-progression survival details	Most common post-progression treatments
Jain 2015 [20]	33 (USA)	Med OS = 3.1 months (all patients) Med OS = Not reached (untransformed)	Chemoimmunotherapy or no treatment
Jain 2017 [21]	90 (USA)	Med OS = 20.6 months (all patients) Med OS = 33 months (intolerance/toxicities) Med OS = 16 months (progression)	No treatment (n=8) Idelalisib (n=6) Venetoclax (n=6)
UK CLL Forum 2016 [22]	72 (UK)	Med OS = 3.1 months (all patients)	NR
Iskierka-Jażdżewska 2019 [23]	37 (Poland)	Med OS = 2.0 months (all patients)	Palliative care
O'Brien 2019 [24]	82 (RESONATE trial)	Med OS = 9.3 months (1-2 prior therapies) Med OS = Not reached (0 prior therapies)	Chemoimmunotherapy
Aarup 2020 [14]	86 (Denmark)	Med OS = 18.2 months	Venetoclax (n=22) Idelalisib (n=10)
Maddocks 2015 [25]	76 (USA)	MED OS = 9.1 months (other AE/reason) Med OS = 3.4 months (transformed) Med OS = 17.5 months (progression)	NR
Rigolin 2021 [13]	~99 (Italy)	Med OS = 15.5 months (progression) Med OS = Not reached (toxicities) Med OS = (pooled)	NR
Company modelling - deletion/mutation population	-	Med OS = 18 months	-
Company modelling - non-deletion/mutation population	-	Med OS = 24 months	-
AE, adverse event; Med OS, median overall survival; NR, not reported			

The ERG judge that the sources with the most relevant populations are Rigolin [13] and Aarup,[14] as they both contain real world data. Both contained a combination of patients with and without deletion/mutation and did not breakdown results for these subgroups, but there is still the potential for the company to conduct a pooled analysis for comparison and validation purposes. A comparison of the unadjusted OS Kaplan-Meier plots showed that

patients in study 116 had a better survival than patients in Aarup, but were similar to worse than patients in Rigolin who received therapy following progression, though the ERG is unable to determine the impact of the magnitude of the adjustment for treatment switching implemented within the idelalisib appraisal.

In addition, extended follow-up from study 116 is available [11] but is not mentioned by the company. The majority of results reported from this extended follow-up include data for patients who switched to additional idelalisib therapy, from either the placebo or idelalisib arms, as allowed in the trial, making it of little or no relevance to this appraisal. However, some information is available for PFS that reduces this problem since the majority of the switching occurred after disease progression. The ERG present the updated follow-up in Figure 8, contrasted to the follow-up used for the original idelalisib modelling. The company do not appear to have attempted to use or obtain this extended follow-up (clarification A6).

The publicly available information pools together patients regardless of their deletion/mutation status and so cannot be incorporated into the economic model. It is important to highlight that the updated data suggests a slightly better performance of rituximab than the data the company originally used, though it is not possible to infer whether this applies to one or both of the deletion/mutation populations. The ERG conclude that had the company obtained and modelled the latest survival data from study 116, it is likely that BSC would perform better than is currently modelled in the company base case.

The FAD also highlights differences between study 116 and the venetoclax patients. Given the lack of evidence for the CDF SACT patients, it is difficult to conclude whether they are comparable to the Trial 116 patients.

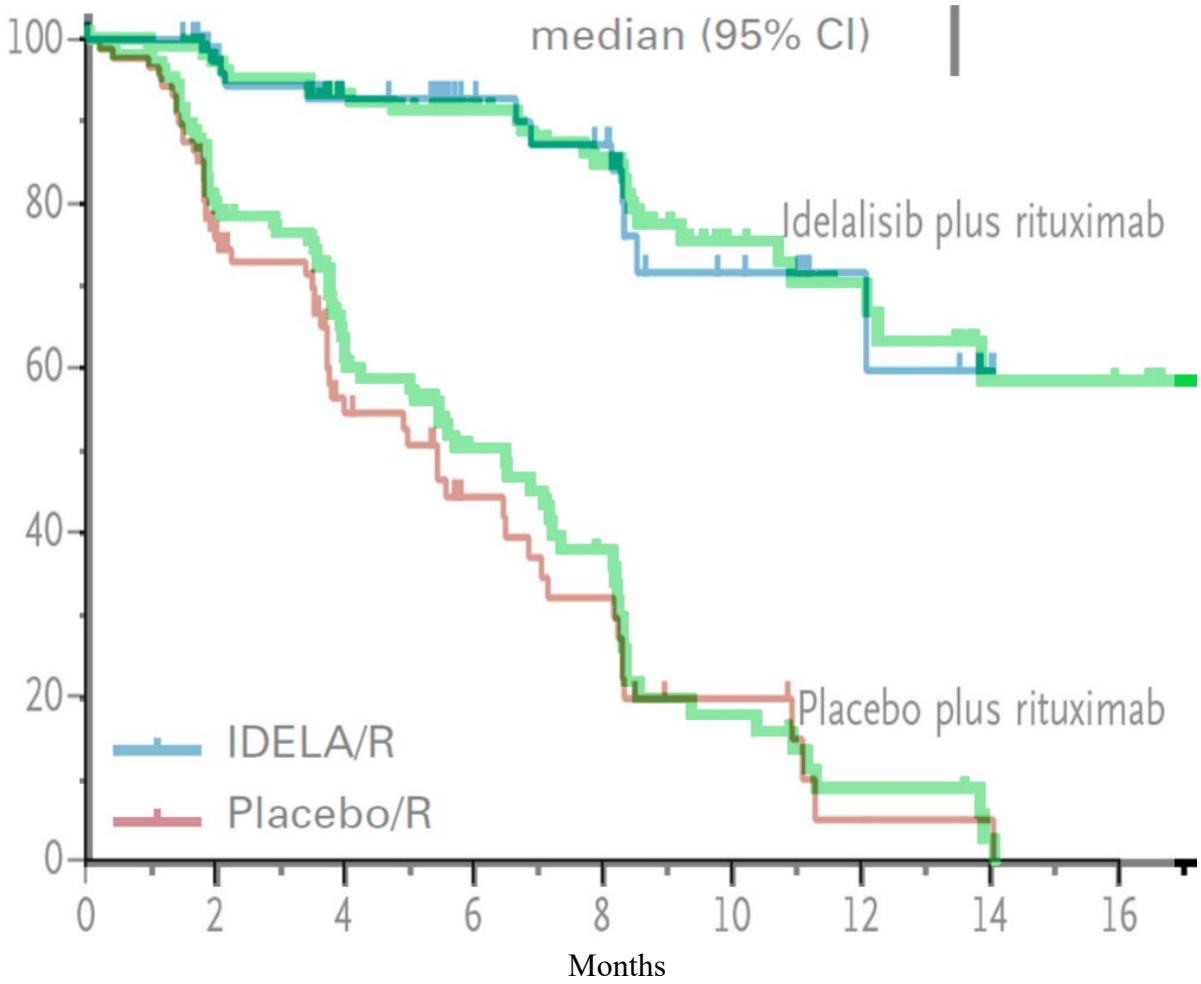


Figure 8: Updated (green) vs old follow-up of progression-free survival from Trial 116 demonstrating slightly improved PFS for the placebo arm. (Overlayed figures from Furman et al. 2014 [12] and Sharman et al. 2019 [11]).

The issue of applying a hazard ratio estimated from venetoclax data onto a BSC model was raised in the ERG report of the original appraisal (TA487).[5] Combining parameters from different models in this way is not usually a sensible or robust statistical approach. Furthermore, the parameters estimated from the venetoclax trials suggest a more negative effect of deletion/mutation than was estimated in the idelalisib appraisal.[1] The approach taken by the company slightly overestimates survival for the non-deletion/mutation BSC population, relative to what would have been predicted had the hazard ratio from the BSC data been used.

Potentially a bigger issue is that there is now an inconsistency in the survival modelling for each arm. For BSC, a single model is fitted simultaneously to data for those with and without deletion/mutation, with an external hazard ratio applied to generate a survival curve for each population. This assumes that the hazard rates for these two groups are proportional.

Meanwhile, for venetoclax, separate curves are fitted to each arm, meaning there is no assumption of proportionality, nor any hazard ratio estimated or applied. Given the company present no assessment of potential violation of the proportional hazards assumption, the ERG have identified that fitting one model to both groups of the venetoclax data would be more appropriate and consistent with the modelling of BSC. This would increase the information contributing to the models and parameter estimates used to extrapolate the survival curves for venetoclax and be consistent with the modelling for the BSC. The company should consider modelling all the data together in one model, unless there is evidence that the hazard rates are not proportional.

The company incorporated the ERG's previous base case modelling for BSC from the original appraisal, when requested (clarification B3), but not implemented any alternative modelling for BSC or conducted any systematic searching of literature (clarification A8).

Overall, the company have not sufficiently addressed the issue of uncertainty in the BSC arm, and the ERG recommend exploring alternative sources of data for modelling purposes.

4.1.2.2 Venetoclax extrapolation

The company now use SACT CDF data to model and extrapolate venetoclax outcomes with rather than the pooled trial data that was used previously. The SACT CDF data is an improvement over the previous trials in terms of its generalisability to NHS care, but still has limitations as detailed in section 3.1.2.

The company fitted parametric survival models to the data they recreated from the SACT report. As the CDF data were presented by deletion/mutation status, the company used these instead of the EAMS data which was not broken down this way. The company fitted separate models to each deletion/mutation status group, and so did not assume proportionality between the groups, unlike their modelling for BSC.

In the original appraisal (TA487), the company used PFS data to fit and extrapolate PFS. However, PFS data were not available for the CDF SACT population and so the company use time-on-treatment (TOT) for the same purpose. This has strengths and weaknesses compared to the using PFS data. The company assign costs and utilities to the progression-free health state. Using PFS data means the utility values reflect the correct stage of disease. However, it's possible that patients may stop venetoclax therapy prior to disease

progression due to toxicity, meaning the modelled costs of venetoclax are too high. The opposite is true if TOT data are used.

The ERG requested that the company estimate a hazard ratio of effect between the PFS and TOT from their venetoclax trials to demonstrate the similarity of the outcomes (clarification A5) but the desired analyses were not provided to support this assumption. The ERG are concerned at the possible differences, and the need for an adjustment to be applied to the TOT data in order for it to better represent PFS. The ERG also requested a visual comparison of the TOT data from the company's venetoclax trials and the SACT CDF data, to examine the consistency between the sources (clarification A4). The company also failed to provide this.

The main limitation of using the TOT data is that it is inconsistent with the modelling for BSC.

From the candidate curves considered by the company, the Weibull is among the best fitting and is the only model to produce plausible extrapolations, both for PFS/TOT and OS across both deletion/mutation populations. Hence the company use the Weibull model throughout their base case analyses.

The selection of the Weibull model appears sensible, however is not without limitation. The company provided detailed survival information, including survival, hazard and cumulative hazard plots.

A visual inspection of the OS and TOT hazard plots for patients with deletion/mutation suggest a Weibull curve may not be representative of the observed data. The hazard rates for both outcomes begin increasing part-way through the follow-up. The increase occurs at ~24 months for OS where 58 patients are still at risk (Figure 9), and for TOT it is at ~15 months where 61 patients remain at risk outcomes (Figure 10). Yet the Weibull extrapolations model a continuously decreasing hazard rate. Whilst such an upward trend could be considered 'noise', given the substantial numbers of patients remaining at risk at the points of increase, and the fairly consistent increase beyond this point, the ERG conclude the Weibull extrapolation does not capture the data well and could be improved upon. The same upward trend was not observed in the population without deletion/mutation, however this may be because these patients have a better prognosis, and so their data may be effectively less mature. The ERG consider it highly plausible that hazard rates for both populations will increase in the future as the treatment effect wears off.

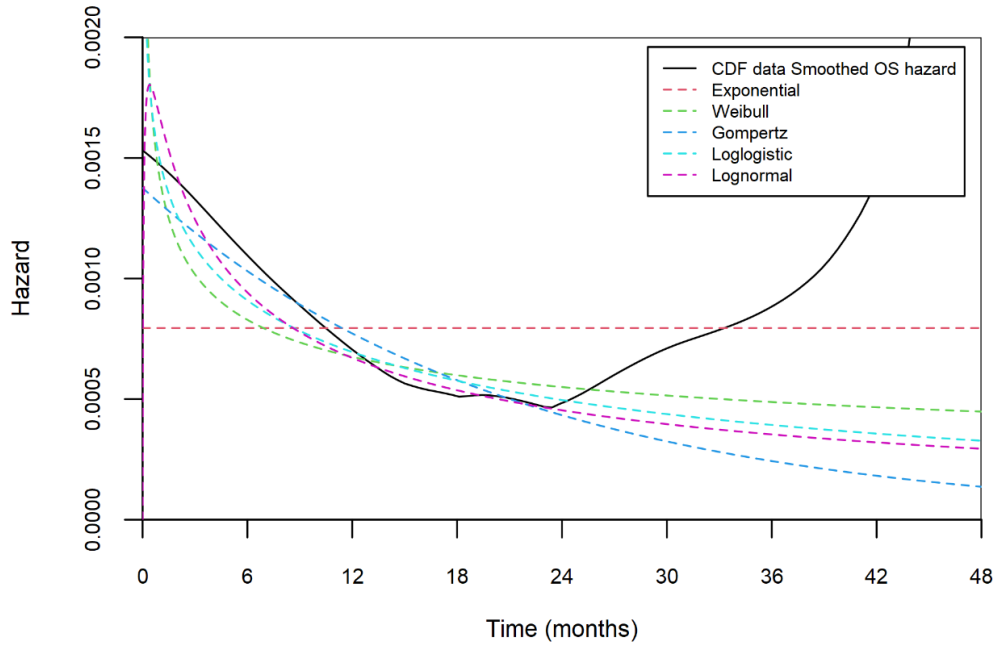


Figure 9: OS hazard rate for deletion/mutation population (from CS Figure 8)

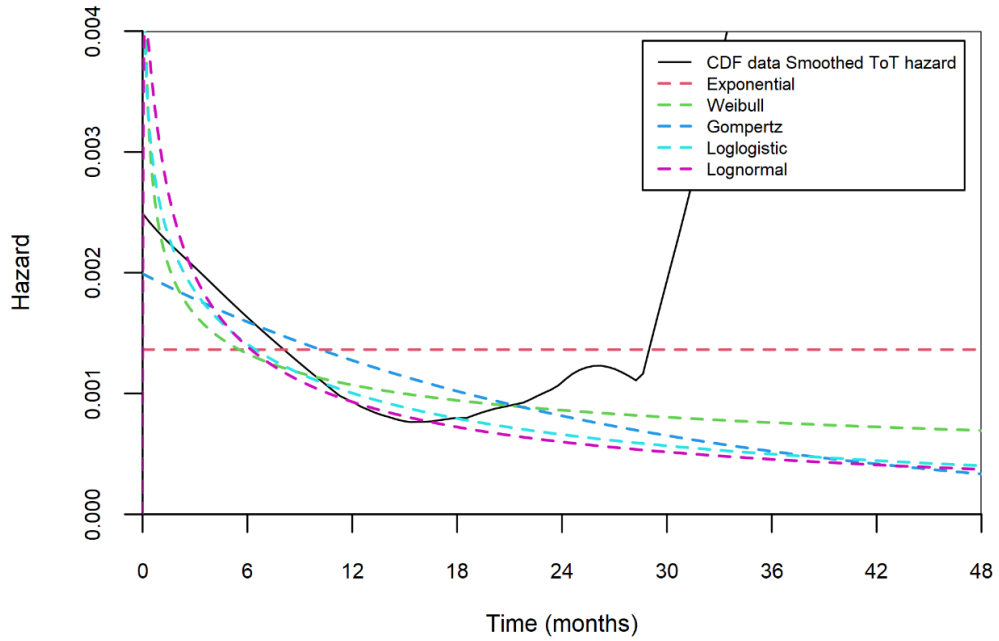


Figure 10: TOT hazard rate for deletion/mutation population (from CS Figure 11)

The decreasing hazard rate is inconsistent with the results reported by Jones et al. in their study of venetoclax after ibrutinib therapy.[26] Their Kaplan Meier plot for duration of response shows an increasing hazard rate over time (Figure 11**Error! Reference source not found.**), with longer OS follow-up likely to follow a similar trend due to the correlation between the outcomes. A similar trend can be found in Figure 31 of the company submission reporting the duration of response for M14-032 trial of venetoclax.

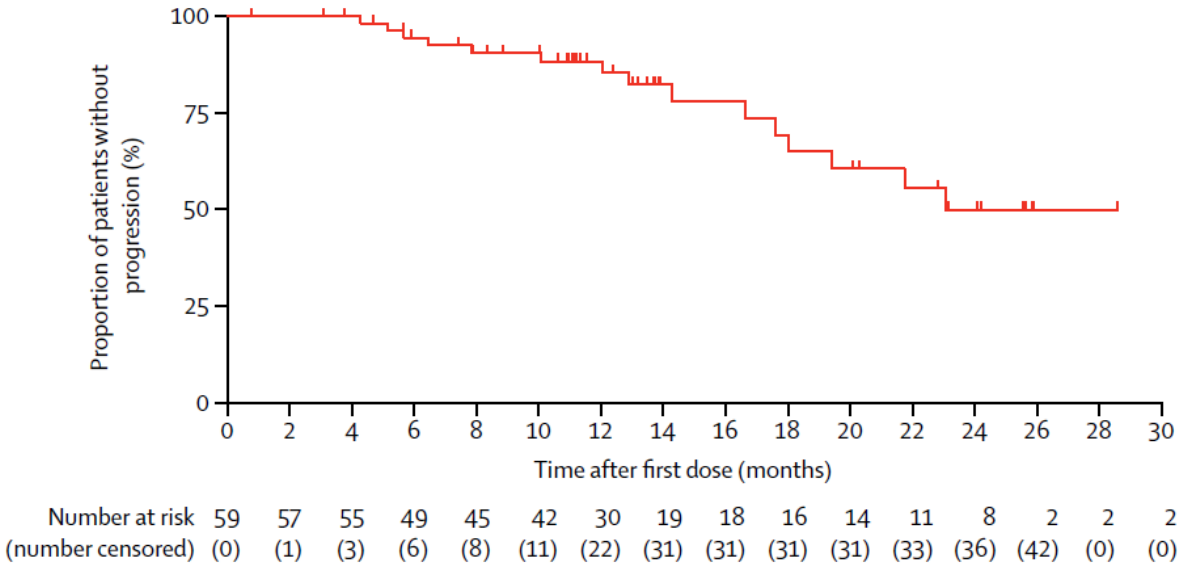


Figure 11: Duration of response for venetoclax, taken from Jones 2018.[26]

The ERG requested the company fit generalised gamma and spline curves as part of their clarification requests, in an attempt to find more plausible extrapolations than the Weibull. These may better fit the deletion/mutation data and provide plausible alternatives to the Weibull.

Unfortunately, the company were unable to provide these more flexible models within the time frame, and so the ERG is unable to confidently improve on the company's extrapolations despite concerns over their clear limitations.

Whilst no treatment effect is explicitly modelled, a hazard ratio is implied based on the extrapolations used for each arm. Unfortunately, due to different units of time used by the company to model each arm, the ERG was unable to calculate a hazard ratio from the economic model, but were able to extract transition probabilities. Figure 12 and Figure 13 show the transition probabilities for the deletion/mutation and non-deletion/mutation populations respectively. It shows how the implied transition ratio gets stronger in favour of venetoclax for the duration of the model, with ratio of transition probabilities falling below [redacted] for both populations suggesting an incredibly large treatment benefit. Whilst this is different to a hazard ratio, it is clearly a magnitude of difference away from the hazard ratio of 0.57 calculated by the ERG in Section 3.4.

[redacted]

Figure 12: OS transition probabilities for deletion/mutation population

Figure 13: OS transition probabilities for non-deletion/mutation population

When validating the company's modelling, the ERG also note a limitation of the company's Weibull extrapolations for both deletion/mutation venetoclax subgroups. When extrapolated and combined, the extrapolations estimate of 1.81 and 3.10 post-progression life-years for deletion/mutation and non- deletion/mutation populations respectively.

The ERG identified a paper by Eyre et al who report PPS for UK patients who received venetoclax monotherapy, as per this appraisal.[6] The ERG excluded the PPS times of patients who continued to receive venetoclax after their progression, giving a sample size of 22 patients.

The ERG fitted parametric curves to the remaining data, the best fitting of which were log-normal, log-logistic and generalised gamma. The ERG compared the restricted mean survival times (i.e. life-years, capped at 20 years) of these best fitting models to the estimates from the company analyses (Table 16, Figure 14).

The post-progression survival of venetoclax modelled by the company exceeds their entire modelled survival of BSC. It also far exceeds the life-estimates produced by the ERG when fitting models to data recreated from Eyre.[6] Whilst the Eyre data contains both patients with and without deletion/mutation, the life-year estimate coming from it is far below what the company model for the prognostically worse off deletion/mutation population. The company's PPS modelling comes from their selection of the Weibull model, which supports the ERG's view that the Weibull extrapolation with its decreasing hazard rate is implausible.

Table 16: Estimates of life-years for different models and data.

Source	Percentage with deletion/mutation	Percentage without deletion/mutation	Post-progression life years	Total life years
Company BSC modelling	100%	0%	0.51 (Weibull OS)	0.95 (Weibull OS)
Company BSC modelling	0%	100%	1.06 (Weibull OS)	1.80 (Weibull OS)
Company Ven modelling	100%	0%	1.80 (Weibull OS)	-
Company Ven modelling	0%	100%	2.44 (Weibull OS)	-
ERG modelling of	48% (of entire study	50% (of entire study	0.35 (Log-normal OS)	-

Eyre 2019 [6]	population at baseline)	population at baseline)	0.48 (Log-logistic OS) 1.27 (Gen gamma OS)	
ERG Ven Scenario otherwise using company base	100%	0%	0.40 (Weibull OS)	-
ERG Ven Scenario otherwise using company base	0%	100%	0.96 (Weibull OS)	-
BSC, best supportive care; ERG, evidence review group; OS, overall survival; Ven, venetoclax				

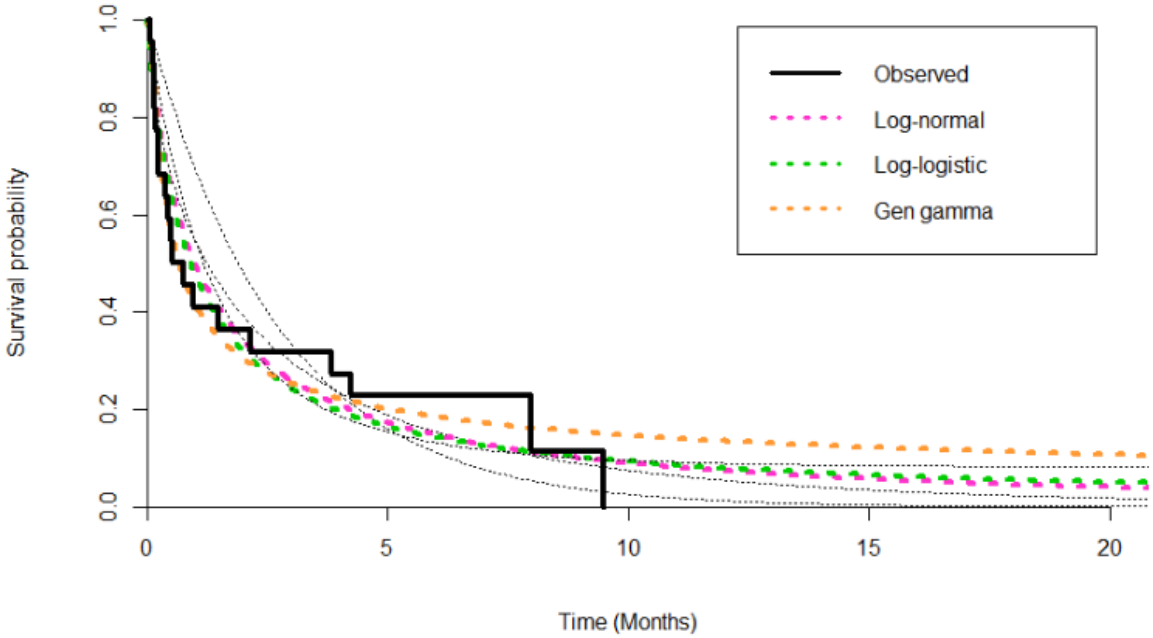


Figure 14: Observed survival from Eyre[6], and the best fitting ERG-fitted parametric curves

As no other candidate curves are available, the ERG maintains the use of the Weibull curves for TOT/PFS and OS in both populations, despite their concerns that post-progression survival for venetoclax patients is overestimated.

The ERG suggests exploration of modelling using pooled data from the SACT CDF and EAMS populations, if the deletion/mutation status of EAMS patients can be identified, whilst excluding those who received rituximab. This would maximise the size and relevance of the venetoclax data but would still be limited by the shifting treatment pathway. What is currently presented are analyses based on only the SACT CDF data for patients regardless of

whether they received rituximab at some point following their initial dose of venetoclax monotherapy.

To explore the impact of alternative modelling for venetoclax, the ERG will perform a scenario analysis where the OS transition probability in each cycle for venetoclax is obtained using a combination of the transition probabilities estimated for both BSC and venetoclax (Section 6.1.4). The ERG estimates the proportion of patients alive after disease progression, out of those modelled alive. We then generate a weighted transition probability, where the original venetoclax OS transition probability is weighted by the proportion of patients either progression-free plus 90% of those in post-progression. This is combined with the 10% of post-progression patients whose overall proportion weight the BSC OS transition probability. For example, when all alive patients are progression-free, the transition probability is identical to the company's venetoclax transition probability. But when 10% of alive patients are in the post-progression health state, the new venetoclax transition probability would estimated by 0.99*old venetoclax transition probability + 0.01*old BSC transition probability, where 0.99 is the sum of 0.9 of alive patients being in the PFS health state plus 0.9*0.1 of the post-progression health state. The ERG selected this proportion as it generated post-progression survival estimates more consistent with the ERG's extrapolations of Eyre, accounting for prognostic differences depending for deletion/mutation status[6]. The ERG was not able to adjust the PFS extrapolations using any model or evidence based reference point, and so these results should only be used as a rough indicator of the effect of using more plausible extrapolations for venetoclax, which do not have decreasing transition probabilities for the full model duration. The company could allow the calculation of a hazard ratio assumed within the model by converting their CDF SACT data to use the same units of time as the BSC data (months) and refitting their models accordingly.

4.1.3 Health related quality of life

Utility estimates remain unchanged from the original CS and are in line with the committee and ERG's preferences.

4.1.4 Resources and costs

Resource use and costs were unchanged from the original company submission. The ERG has checked and is satisfied that costs have been updated from 2017 price year to 2019/20 prices using the appropriate inflation index (NHS Cost Inflation Index).

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The original CDF CS base-case model produces incremental cost-effectiveness ratio (ICER) of £43,201 for patients with deletion/mutation (Table 17) and £49,104 for patients without deletion/mutation (Table 18) when venetoclax is compared to BSC. This is achieved when the model is updated to incorporate SACT CDF data to model venetoclax outcomes in line with the committee's recommendations. At clarification, ERG identified an error in the censoring of the digitised survival data which resulted in incorrect censoring of observations at the tail ends of the survival curves (Clarification A3). This was corrected by the company and the model updated to reflect the amended data. The new ICER from the updated company's model was £43,239 for patients with deletion/mutation (Table 19) and £49,213 for patients without deletion/mutation (Table 20) when venetoclax is compared to BSC. Unless otherwise stated, the updated company's model that corrected for the error in censoring will be used to generate ICERs based on the ERG assumptions and data sources in the remainder of this report. All ICERs presented in this report include a confidential PAS discount for venetoclax. The ERG have produced separately a confidential appendix containing key ICERs that include discount for other relevant treatments in this appraisal.

Table 17: New company deterministic base case for patients with deletion/mutation (CS Table 9)

Technology	Total		Incremental: venetoclax vs BSC		ICER / QALYs, £
	Costs, £	QALYs	Costs, £	QALYs	
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	£43,201
BSC	[redacted]	0.627			

BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; QALY: quality-adjusted life year

Table 18: New company deterministic base case for patients without deletion/mutation (CS Table 9)

Technology	Total		Incremental: venetoclax vs BSC		ICER / QALYs, £
	Costs, £	QALYs	Costs, £	QALYs	
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	£49,104
BSC	[redacted]	1.160			

Table 19: Company deterministic base case for patients with deletion/mutation (censoring amended)

Technology	Total		Incremental: venetoclax vs BSC		ICER / QALYs, £
	Costs, £	QALYs	Costs, £	QALYs	
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	£43,239
BSC	[redacted]	0.627			

Table 20: Company deterministic base case for patients without deletion/mutation (censoring amended)

Technology	Total		Incremental: venetoclax vs BSC		ICER / QALYs, £
	Costs, £	QALYs	Costs, £	QALYs	
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	£49,213
BSC	[redacted]	1.160			

5.2 Company's sensitivity analyses

The company's probabilistic sensitivity analyses (PSA) produced ICERs of £44,652 and £50,966 at venetoclax PAS price for populations with and without deletion/mutation respectively. The ICER values are marginally higher than the deterministic ICERs of £43,201 for patients with deletion/mutation and £49,104 for patients without deletion/mutation. The corresponding average ICERs, following probabilistic simulations, at venetoclax list price were £[redacted] /QALY gained vs BSC for the patient population with deletion/mutation and £[redacted] /QALY gained for the patient population without deletion/mutation (full details in CS Appendix C). The scatterplots generated by these results are shown below in Figure 15 and

[redacted]

Figure 16, reproduced from the CS.

Figure 15 Scatterplot of probabilistic results for the patient population with deletion/mutation at venetoclax PAS price - CS Figure 21

[redacted]

Figure 16: Scatterplot of probabilistic results for the patient population without deletion/mutation at venetoclax PAS price - CS Figure 22

The company conducted several one-way sensitivity analyses to explore impact of parameter variation on the ICER. The sensitivity analyses results in the CS were generated based on the company's original model and not the updated model that corrected for the error in censoring of the digitised survival curves. The results of 6 of the most influential parameters are presented as tornado diagrams in the CS (Figures 23 and 24). The input values and resulting ICERs for these are tabulated in Table 21 and Table 22 below. Low and high values used in the one-way sensitivity analyses for some of the model parameters (e.g. VEN OS hazard rate, BSC OS hazard rate multiplier, etc.) have not been directly specified in the model excel workbook. It would appear these have been derived from a combination of other parameters in the modelling but the ERG was unable to verify the formulae used to derive the values used due to time constraints.

Table 21: Company one way sensitivity analyses- patient population with *deletion/mutation*

	Low value		High value	
	Value[1]	**ICER**	**Value**	**ICER**
VEN OS hazard rate		52,866		34,473
BSC OS hazard rate multiplier		57,399		39,916
VEN PFS hazard rate		38,043		50,423
BSC: proportion receiving HDMP + R	0.402	43,795	0.598	42,606
BSC PFS hazard rate multiplier		43,379		43,843
Starting age	65.216	42,888	67.292	43,614

[1]Low/High parameter values not directly specified in the model workbook

Table 22: Company one way sensitivity analyses- patient population without *deletion/mutation*

	Low value		High value	
	Value[1]	**ICER**	**Value**	**ICER**
BSC OS hazard rate multiplier		87,589		42,716
VEN OS hazard rate		63,521		38,242
VEN PFS hazard rate		43,830		55,873
BSC PFS hazard rate multiplier		50,908		48,918
Starting age	64.396	48,445	66.472	49,830
BSC: proportion receiving HDMP + R	0.402	49,697	0.598	48,512

[1]Low/High parameter values not directly specified in the model workbook

The results for the one-way sensitivity analyses for the six parameters ranged from £34,473 per QALY to £57,399 per QALY for venetoclax versus BSC for patient population with deletion/mutation. The results for patient population without deletion/mutation ranged from £38,242 per QALY to £87,589 per QALY for venetoclax versus BSC. The major drivers of variation were venetoclax OS and PFS hazard rate and the BSC OS hazard rate multiplier.

The company also presents a range of scenarios exploring uncertainty in OS and TOT extrapolations (see Table 11 of CS for full details). Table 23 presents a summary of the ICERs resulting from the company scenario analyses.

Table 23: Company scenario analyses

Scenario	**Patients with deletion/mutation**	**Patients without deletion/mutation**
	ICER	**ICER**
CS Base case (original CDF model)	*£43,201*	*£49,104*
CS Base case (corrected model)	*£43,239*	*£49,213*
Uncertainty in OS extrapolations		
OS log-normal extrapolation	£36,134	£39,755
OS log-logistic extrapolation	£37,379	£42,307
OS Gompertz extrapolation	£29,314	£36,049
OS Exponential extrapolation	£54,708	£61,239
Uncertainty in TOT extrapolations		
TOT log-normal	£54,791	£63,100
TOT log-logistic	£54,038	£61,553
TOT Gompertz	£53,743	£51,960
TOT Exponential	£34,225	£41,203

5.3 Model validation and face validity check

The ERG conducted a face validity check of the model submitted by the company and found that the company have largely adhered to the Appraisal Committee's preferred assumptions from the terms of engagement. The only exception is the modelling of BSC arm because of the company failed to fully explore alternative sources of BSC data. The ERG noted that the Weibull is the best fitting survival function for extrapolating long-term survival benefit of venetoclax for this patient population. Table 24 presents undiscounted life-years generated by the company's economic model based on the Weibull extrapolations for venetoclax and BSC.

Validating the model's predictions is problematic due to lack of suitably published external information for comparison and model validation of treatment under venetoclax and BSC. The best the ERG could come up with is a paper Eyre et al that post-progression survival for UK patients who received venetoclax monotherapy, as per this appraisal.[6] Eyre et al is not stratified by mutation status. The ERG modelling of the Eyre et al data described in detail in section 4.1.2.2 generated post progression life-years ranging from 0.35 to 1.27 (Table 5, Figure 12) for the combined population of patients with and without del(17p)/TP53 mutation.

The ERG fitted parametric curves to the remaining data, the best fitting of which were log-normal, log-logistic and generalised gamma. The ERG compares the restricted mean survival times (i.e. life-years, capped at 20 years) of these best fitting models to the estimates from the company analyses (Table 5, Figure 12). It also far exceeds the life-estimates produced by the ERG when fitting models to data recreated from Eyre.[6] Whilst the Eyre data contains both patients with and without deletion/mutation, the life-year estimate coming from it is far below what the company model for the prognostically worse off deletion/mutation population. Whilst acknowledging the limitations of using the Eyre data to validate the model, the company's post progression life-years generated by the Weibull extrapolations when compared to the ERG modelling of the Eyre data supports the ERG's view that the Weibull extrapolation with its decreasing hazard rate is implausible.

Table 24: Predicted life-years stratified by del(17p)/TP53 mutation status and disease progression for venetoclax and BSC

		Undiscounted Life Years		
Subgroup	**Treatment**	**Pre-Progression**	**Post-Progression**	**Total**
del(17p)/*TP53* mutation	Venetoclax	2.7	1.8	4.5
	BSC	0.4	0.5	0.9
	Incremental	2.3	1.3	3.4
Non del(17p)/*TP53* mutation	Venetoclax	3.1	2.4	5.5
	BSC	0.7	1.1	1.8
	Incremental	2.4	1.3	3.7

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

The ERG identified a number of key areas of uncertainty that warranted exploration through additional analyses, with some of the assumptions being carried forward into the ERG base

case. Other assumptions were not based on sufficiently robust data for the ERG to carry into their base but are still highly relevant and should be considered carefully.

6.1.1 Age at start of treatment

For the cost-effectiveness results to reflect NHS patients, the baseline characteristics of the modelled population should closely match the characteristics of CDF cohort at start of treatment. However, the company did not change the average age of the modelled population from that used in the original submission which was based on the venetoclax trials to the mean age observed in the SACT CDF data (71 years). Implementing this change worsens the company's base-case ICERs from £43,239 to £46,355/QALY in the population with deletion/mutation and from £49,213 to £53,273/QALY in the population without deletion/mutation.

6.1.2 Gender distribution

Similarly to baseline age mentioned above, the gender distribution of the modelled population should closely much that of the CDF cohort for the cost-effectiveness results to be generalizable to NHS patients. The sex distribution (proportion male) in the modelled population remained the same as in the original submission (i.e. based on the venetoclax trials rather than the SACT CDF data). Pragmatically, this has a relatively modest impact on ICERs. Changing the proportion male in the modelled population from 68.17% to 64% for the deletion/mutation population improved the ICER marginally from £43,239 to £43,219. Changing the proportion male in the modelled population from 73.86% to 70% for the population without deletion/mutation marginally improved the ICER from £49,213 to £49,175.

6.1.3 Patients switching to (or receiving) rituximab

The ERG considers that benefits of rituximab are captured within the SACT CDF data (section 3.1.2.2.3) hence costs need to be equally captured. The ERG undertook additional analysis incorporating rituximab costs in the venetoclax arm to account for a proportion of the CDF cohort who received rituximab. Bearing the uncertainties around treatment switching and the lack of information on duration of rituximab treatment, the ERG conservatively assumes that rituximab is given over 6 months, consistent with its use in VenR, for 20% of the patient population, consistent with the SACT CDF data. The ERG assumes that for the proportion of patients on VenR, Rituximab 375 mg/m2 is given intravenously on day 1 of cycle 1, followed by 500 mg/m2 on day 1 of cycles 2 to 6. Rituximab is stopped after cycle 6. This is consistent with NICE Technology appraisal guidance [TA561].[9]

Implementing this change marginally increases the company's base-case ICERs from £43,239 to £44,110 in the population with deletion/mutation and from £49,213 to £50,123 in the population without deletion/mutation.

6.1.4 Correction for over-optimistic post-progression survival estimates for venetoclax

The ERG considers that post-progression survival modelled for venetoclax is unexpectedly high and potentially inconsistent with clinical evidence (4.1.2.2). The ERG explores the impact of alternative modelling for venetoclax, by performing a scenario analysis where the transition probabilities applied for venetoclax are estimated using weighted average of the transition probabilities of venetoclax and BSC. Implementing this change worsens the company's base-case ICERs from £43,239 to £61,135 in the population with deletion/mutation and from £49,213 to £68,408 in the population without deletion/mutation.

6.1.5 Application of correct BSC hazard ratio for deletion/mutation effect

The ERG identified what it considers to be an error in the implementation of hazard ratios for the BSC group in the economic model for patients with deletion/mutation (section 4.1.2.1.2). The error has a relatively modest impact on survival predictions. The ERG updated the PFS and OS values from 0.585 and 0.524 (PFS and OS respectively) to 0.677 and 0.543 (PFS and OS respectively).[1] Implementing this change marginally lowers the ICER from £49,213 to £48,329 in the population without deletion/mutation. The change is not applicable to the deletion/mutation ICER.

6.1.6 Application of venetoclax OS hazard ratio to BSC extrapolation

The company's economic model used different datasets to generate survival extrapolations for venetoclax and BSC. The two comparators were not directly compared in one survival analysis model to adjust patient characteristics likely to confound the treatment effect hazard ratio estimate for venetoclax relative to BSC. The ERG therefore conducted additional exploratory analyses of the available data and estimated a naïve hazard ratio for venetoclax relative to BSC (section 3.4.1). These exploratory analyses have several limitations include lack of suitable data stratified by deletion/mutation status and differences between patients, both in terms of their baseline characteristics and the later therapies they received. However, in the absence of comparative effectiveness evidence for treatments indicated in this appraisal, the ERG thinks the naïve analyses conducted could be useful for decision making. The results in Table 25 and Table 26 present cost-effectiveness results for the populations with and without TP53 mutations based on show that applying a hazard ratio of 0.57

estimated from the ERG additional analyses (section 3.4.1) to the Weibull extrapolations of BSC. The results suggest a substantial worsening of the ICER for venetoclax relative to BSC in both populations.

Table 25: Applying OS hazard ratio to BSC extrapolation for patients with deletion/mutation (censoring amended)

Technology	Total		Incremental: venetoclax vs BSC		ICER / QALYs, £
	Costs, £	QALYs	Costs, £	QALYs	
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	£73,753
BSC	[redacted]	0.627			

Table 26: Applying OS hazard ratio to BSC extrapolation for patients without deletion/mutation (censoring amended)

Technology	Total		Incremental: venetoclax vs BSC		ICER / QALYs, £
	Costs, £	QALYs	Costs, £	QALYs	
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	£77,265
BSC	[redacted]	1.160			

6.1.7 Previous ERG base case modelling

The results in Table 27 and Table 28 show that applying the previous ERG's base case for the BSC arm to the company model (updated to incorporate SACT CDF data to model venetoclax outcomes), led to an increase to the company's ICER in both groups.

Table 27: Previous ERG's base case model for BSC arm with updated SACT CDF data to model venetoclax outcomes for patients with deletion/mutation (censoring amended)

Technology	Total		Incremental: venetoclax vs BSC		ICER / QALYs, £
	Costs, £	QALYs	Costs, £	QALYs	

Technology	Total		Incremental: venetoclax vs BSC		ICER / QALYs, £
	Costs, £	QALYs	Costs, £	QALYs	
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	£63,973
BSC	[redacted]	1.058			

Table 28: Previous ERG's base case model for BSC arm with updated SACT CDF data to model venetoclax outcomes for patients without deletion/mutation (censoring amended)

Technology	Total		Incremental: venetoclax vs BSC		ICER / QALYs, £
	Costs, £	QALYs	Costs, £	QALYs	
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	£103,370
BSC	[redacted]	2.087			

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The impact of additional clinical and economic analyses undertaken by the ERG on the ICER are incorporated in the ERG's preferred assumptions and described in detail in section 6.3 below.

6.3 ERG's preferred assumptions

The ERG prefers to use the updated model (which adjusted for censoring in the digitised data) as the company base case. The ERG's preferred assumptions are to use the SACT CDF data to model (i) average age at start of treatment, (ii) proportion of males in the modelled population rather than the venetoclax trials data. (iii) For the population without deletion/mutation, the ERG also prefer to apply the hazard ratio for the effect of the deletion/mutation as calculated from the BSC data, rather than the venetoclax data. The ERG has not been able to robustly improve the accuracy of the venetoclax extrapolations in regard to the post-progression survival, however exploratory modelling performed by the ERG (sections 6.1.4 and 6.1.6) suggests that the ICER for both subgroups is likely to be considerably higher than as presented in the ERG base case (Table 29**Error! Reference source not found.**).

Table 29: ERG's preferred model assumptions

ERG preferred assumption	Brief rationale and section in ERG report	ERG Report Section	Results (Impact to base-case ICER): deletion/ mutation	Results (Impact to base-case ICER): non-deletion/ mutation
Base case (model updated for censoring)			£43,239	£49,213
ERG-01: Change baseline age at start of treatment to 71.4 years for patient population with a del(17p)/TP53 mutation and to 71.2 years for patient population without a del(17p)/TP53 mutation	The ERG considers that the patients in the venetoclax trials are younger than venetoclax trials and may have higher burden of disease. The company also notes this in the CS (Section A.6.2.1)	6.1.1	£46,355 (+£3,116)	£53,273 (+£4,060)
ERG-02: Base the proportion male on SACT CDF data	The ERG considers that since the effectiveness of venetoclax is now modelled on SACT CDF data, the sex distribution should be based on the same population. The sex distribution from the venetoclax trials differ from SACT CDF data and are therefore not reflective of current NHS population.	6.1.2	£43,219 (-£20)	£49,175 (-£38)
ERG-03: Correct error in application of hazard rates in BSC arm of patients without deletion/ mutation.	The ERG considers that the same approach used to estimate PFS and OS in the BSC arm of the deletion/mutation population should be used for the BSC arm of the non-deletion/mutation population	4.1.2.1.2	-	£48,329 (-£884)
ERG-04: ERG base-case: use the baseline characteristics (age and proportion males) from	The ERG implemented these changes simultaneously to assess the cost-effectiveness of venetoclax compared to BSC based on the ERG's preferred assumptions.	As above	£46,325 (+£3,086)	£52,169 (+£2,956)

SACT CDF data and apply changes to model with adjusted censoring.				

Implementing the ERG's preferred assumptions increases the company ICER by £3,086 to an ERG preferred deterministic ICER of £46,325 in the population with deletion/mutation (Table 30). The ICER increases by £2,956 to an ERG preferred deterministic ICER of £52,169 in patients without deletion/mutation (Table 31).

Table 30: ERG preferred deterministic base case results (deletion/mutation population)

Technology	Total		Incremental: venetoclax vs BSC		ICER / QALYs, £
	Costs, £	QALYs	Costs, £	QALYs	
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	£46,325
BSC	[redacted]	0.605			

Table 31: ERG preferred deterministic base case results (non-deletion/mutation population)

Technology	Total		Incremental: venetoclax vs BSC		ICER / QALYs, £
	Costs, £	QALYs	Costs, £	QALYs	
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	£52,169
BSC	[redacted]	1.068			

The ERG performed a PSA on their base-cases, with the mean values shown in Table 32 and Table 33 for the deletion/mutation and non-deletion/mutation populations respectively. Both are higher, but generally consistent with their deterministic counterparts.

Table 32: ERG's preferred probabilistic base case results for deletion/mutation population

Technology	Total		Incremental: venetoclax vs BSC		ICER, £/ QALY
	Costs, £	QALYs	Costs, £	QALYs	
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	£47,900
BSC	[redacted]	0.611			

Table 33: ERG's preferred probabilistic base case results for non-deletion/mutation population

Technology	Total		Incremental: venetoclax vs BSC		ICER, £/ QALYs
	Costs, £	QALYs	Costs, £	QALYs	
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	£53,526
BSC	[redacted]	1.077			

6.4 Conclusions of the cost effectiveness section

The company addressed one of the two key issues highlighted by the committee in the ToE, namely the generalisability of venetoclax trials to the NHS population. SACT CDF data, rather than updated venetoclax trials data are now used to inform clinical effectiveness of venetoclax in the models, in line with the committee's preference. The ERG considers that the SACT CDF data that informed the company's CDF submission is a major improvement over the previous submission in terms of the generalisability to the NHS population, despite having limitations. The company's modelling of venetoclax benefit appears to overestimate post-progression survival and exploratory modelling by the ERG suggests this has a large effect on the ICER. The use of venetoclax TOT data as a surrogate for PFS, and inconsistent survival modelling of the two arms are additional concerns that the ERG was unable to fully consider due to insufficient information.

The company did not address the second issue of relative effectiveness of venetoclax as no data were collected within the SACT cohort to inform a suitable comparator arm. The ERG could not separately identify data to inform a suitable comparator arm. Therefore, the magnitude of the clinical and cost-effectiveness benefit of venetoclax over treatment with best supportive care remains uncertain.

The ERG considers that the company ICERs are likely to be higher, mainly due to the patient age of those who will be treated with venetoclax (based on SACT CDF data) being higher than the mean age of the trials as used in the company base case. Addressing this issue and incorporating the ERG's other preferred assumptions increased the ICERs by £3,086 and £2,956 in patients with and without deletion/mutation respectively.

7 END OF LIFE

The committee previously concluded that venetoclax met the end-of-life criteria for the two main deletion/mutation populations, and no new evidence has been presented for the ERG to discuss.

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