NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Venetoclax for treating chronic lymphocytic leukaemia (CDF review of TA487) [ID3886]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Venetoclax for treating chronic lymphocytic leukaemia (CDF review of TA487) [ID3886]

Contents:

The following documents are made available to consultees and commentators:

Link to TA487 on the NICE website

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from AbbVie

2. **Clarification questions and company responses**

3. **NICE CDF team/NHS Digital Clarification questions and responses**
   a. Response
   b. Appendix A – Patient characteristics, excluding treatment switchers
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4. **Patient group, professional group and NHS organisation submission** from:
   a. Leukaemia Care-Chronic Lymphocytic Leukaemia Support
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5. **Evidence Review Group report** prepared by Warwick Evidence

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7. **Technical engagement response** from AbbVie

8. **Technical engagement response & expert statement from experts:**
   a. Professor Adrian Bloor – clinical expert, nominated by UK CLL Forum
   b. Professor Peter Hillmen – clinical expert, nominated by AbbVie

9. **Technical engagement response from consultees and commentators:**
   a. Leukaemia Care-Chronic Lymphocytic Leukaemia Support
   b. UK CLL Forum
   c. National Cancer Research Institute-Association of Cancer Physicians-Royal College of Physicians-Royal College of Radiologists

10. Evidence Review Group critique of company response to technical engagement prepared by Warwick Evidence

a. ERG critique

b. ERG addendum

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund Review of TA487

Venetoclax for treating chronic lymphocytic leukaemia (CDF review of TA487) [ID3886]

Company evidence submission for committee

November 2021

File name	Version	Contains confidential information	Date
ID3886 Venetoclax_CLL_NICE_CDF Review_Redacted	Final	No	25th November 2021

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This submission should not be longer than 25 pages, excluding the pages covered by this template. If it is too long it will not be accepted.

If applicable provide any supportive and detailed methodological or investigative evidence (additional to the clinical trial and/or Systemic Anti-Cancer Therapy data) in an appendix to this submission.

When cross referring to evidence in the original submission or appendices, please use the following format: Document, heading, subheading (page X).

For all figures and tables in this summary that have been replicated, cross refer to the evidence from the main submission or appendices in the caption in the following format: Table/figure name – document, heading, subheading (page X).Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

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Abbreviations

Abbreviation	Definition
AIC	Akaike information criterion
AML	Acute myeloid leukaemia
BIC	Bayesian information criterion
BNF	British National Formulary
BSC	Best supportive care
CDF	Cancer Drugs Fund
CEM	Cost effectiveness model
CLL	Chronic lymphocytic leukaemia
DCO	Data cut-off
DOR	Duration of Response
EAMS	Early Access to Medicine
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERG	Evidence review group
FAD	Final appraisal document
GP	General practitioner
HCHS	Hospital and community health services
HDMP	High-dose methyl-prednisolone
HRG	Health resource group
ICER	Incremental cost-effectiveness ratio
IQR	Interquartile range
ITC	Indirect treatment comparison
IV	Intravenous
LDH	Lactose dehydrogenase
LYG	Life years gained
NHS	National Health Service
NHSCII	National Health Service cost inflation index
NHSE	NHS England
NHSI	NHS Improvement
NICE	National Institute of Health and Care Excellence
OS	Overall survival
PAS	Patient access scheme
PFS	Progression-free survival
PHE	Public Health England
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
RCT	Randomised control trial
SACT	Systemic Anti-Cancer Therapy
TLS	Tumour lysis syndrome
ToT	Time on treatment

uMRD	Undetectable minimal residual disease
VEN	Venetoclax

Cancer Drugs Fund review submission

A.1 Background

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

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

During the appraisal of TA487, the committee concluded that venetoclax met both end-of-life criteria. Incremental cost-effectiveness ratios (ICERs) presented to the committee included a simple patient access scheme discount of [redacted]. The committee noted that the company base case ICERs (with the patient access scheme [PAS] applied) were £39,940 per quality-adjusted life-year (QALY) gained for adults with a del(17p)/*TP53* mutation and £47,370 QALY gained for adults without a del(17p)/*TP53* mutation. The corresponding Evidence Review Group (ERG) ICERs (using a different data source for best supportive care [BSC]) were £57,476 and £77,779 per QALY gained respectively.

The committee considered that the ERG estimates for overall survival (OS) in the BSC arm could be too high, particularly for the population without a del(17p)/*TP53* mutation. If the estimates were closer to the company's, then the committee acknowledged that venetoclax would have "plausible potential" to be cost-effective.[1]

The committee's key uncertainties were the OS for people on venetoclax as those in the trials had less advanced disease and the committee did not feel that the results were generalisable to UK practice. In addition, because the trials were all single arm, the relative effectiveness of venetoclax was uncertain.

Systemic Anti-Cancer Therapy (SACT) has collected data on treatment duration, OS and baseline characteristics of those having venetoclax in UK clinical practice. It was anticipated that SACT could also provide data on BSC in clinical practice to form a comparator arm. Public Health England (PHE) investigated collecting this data and the SACT Operational Group considered that no meaningful data could be captured on BSC within SACT during the period of managed access; AbbVie were informed of this decision on 2nd March 2021. NICE and NHS England and NHS Improvement (NHSE&I), in partnership with the committee chair, considered that the ongoing data collection would still provide useful information for the purpose of the guidance update, and the technology continued to be available through the CDF.

A.2 Key committee assumptions

The committee's preferred assumptions from TA487 are detailed in Table 1. The requests for the CDF review (highlighted bold in Table 1) are subsequently discussed and addressed in this submission. All of the committee's other preferred assumptions remain unchanged from TA487.

Table 1: Key committee assumptions

	Committee preferred assumptions

Population	The marketing authorisation includes three populations:
	• adults with a 17p deletion or *TP53* mutation and:
	  o whom a B-cell receptor pathway inhibitor is unsuitable (population 1a),
	  o whose disease has progressed after a B-cell receptor pathway inhibitor (population 1b)
	• adults without a 17p deletion or *TP53* mutation and whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor (population 2).
	
	A clinical expert explained that although 17p deletion or *TP53* mutation can be a prognostic factor, clinical decisions on progressed disease are based on length of response rather than deletion or mutation response. The committee concluded they should follow the marketing authorisation which split the populations by the presence or absence of the 17p deletion or *TP53* mutation.
	The committee heard there are few, if any, people who are intolerant to both of the B-cell receptor pathway inhibitors recommended by NICE at the time of the original appraisal (idelalisib and ibrutinib) because of their different safety profiles. The committee were not persuaded of the relevance of population 1a but concluded that venetoclax should be recommended in the populations defined in the marketing authorisation.
	
	Adults with a 17p deletion or *TP53* mutation whose disease has progressed after a B-cell receptor pathway inhibitor or a B-cell receptor pathway inhibitor is unsuitable and adults without a 17p deletion or *TP53* mutation whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor are the relevant populations for the CDF review.

Comparators	The company presented comparisons with BSC (rituximab and high-dose methylprednisolone) and palliative care (no active treatment). The clinical expert explained than in practice, most people would be offered active therapy (which may include rituximab monotherapy) and very few would be offered palliative care. The committee concluded that BSC was a more appropriate comparator and used this for decision-making. **The company should present clinical and cost-effective evidence for venetoclax compared to BSC.**

Generalisability of the trial data.	Three single arm trials provided the evidence base for venetoclax: M12-175 (phase 1, with or without del(17p)/*TP53* mutation; NCT01328626), M13-982 (phase 2, with deletion in relapsed or refractory CLL; NCT01889186) and M14-032 (phase 2, with or without del(17p)/*TP53* mutation in relapsed or refractory CLL after a B-cell receptor pathway inhibitor; NCT02141282).[2-4] Neither M12-175 or M14-032 included any UK centres. The committee also understood that the patients in the trials were younger and fitter (by ECOG status) than those in UK clinical practice. In addition, the pooled health related quality of life collected in the venetoclax trials was higher than the age matched general population and the committee agreed this was further evidence that people in the trials did not reflect people with advanced CLL seen in clinical practice. The committee concluded that patients enrolled in the venetoclax trials were likely to have a lower burden of disease than the people for whom venetoclax would be an option in UK practice and the treatment benefit for these people were uncertain. **SACT data should inform the generalisability of the trial data.**
Survival data	Given the mix of deletion and mutation status, and number of previous therapies across the trials, the committee found it hard to interpret the trial results based on the populations specified in the marketing authorisation. Additional challenges were the small patient numbers and lack of direct comparator data due to the single-arm trial design. In the economic model the company pooled the survival data across the trials and extrapolated both the OS and PFS with a Weibull distribution. The committee was aware that the different potential curves diverged greatly after 4 years and understood that the Gompertz distribution could fit the data equally well to the Weibull, and this resulted in lower progression free and OS estimates. Clinical experts explained that the 10-year progression free survival rate using the Gompertz curve was less clinically plausible than the Weibull. Overall, the committee concluded that despite the uncertainty, the Weibull distribution was justifiable. **The company should explore the most appropriate extrapolation method given the more mature trial data and SACT data collected during the period of managed access.**
Source of BSC data	As the venetoclax trials were single arm, data for the BSC arm needed to come from a different source. The company used the rituximab arm of the 116 RCT (NCT01539512) which compared idelalisib with rituximab for previously treated CLL patients.[5] However, the ERG said this was not appropriate because these people did not have relapsed or refractory disease after having a B-cell receptor pathway inhibitor, they had been randomised to have either rituximab or a B-cell receptor pathway inhibitor, so represented an earlier point in the treatment pathway. The committee agreed that the people in the idelalisib arm of the 116 trial, after disease progression, more closely matched the population who would be offered venetoclax in practice compared to the rituximab arm of the 116 trial.

	However, the committee did acknowledge that using this approach for the population without a 17p deletion or *TP53* mutation suggested that the post-progression survival was much longer than progression-free survival (4.02 and 1.62 years respectively), and the clinical expert stated that 4 years of post-progression survival did not reflect (i.e. were longer than those seen in) clinical experience in England. The company highlighted the lack of face validity of the ERG's survival estimates, along with the small patient numbers of the 116 trial (only 11 patients had progressive disease following treatment by idelalisib in combination with rituximab) and the fact that some patients had received a second, additional, post-progression dose of idelalisib (at a higher dose than the first) and as such was not comparable to the BSC comparator in this appraisal. The company provided an alternative approach to estimating outcomes for the BSC arm, based on the end-of-life expectancy criterion (i.e. maximum 24 months survival), but the committee did not consider it to be acceptable because it was based on assumptions only and not on any clinical trial evidence. Overall, the committee were concerned that all comparisons were naïve and subject to bias but accepted that the ERG's approach and source of BSC data was the most appropriate, despite not giving full weight to the estimates of post-progression survival, particularly for the population without a 17p deletion or *TP53* mutation. **The company should fully explore the most appropriate source of BSC based on data collected during the period of managed access.**
Indirect comparison	The company used pooled progression-free and OS outcomes for venetoclax from the M12-175, M13-982 and M14-032 trials, and the rituximab arm of the 116 RCT for BSC to conduct an indirect comparison. The ERG stated that pooling was not appropriate considering the different baseline characteristics and the variation in treatment duration for venetoclax. However, the committee concluded that although imperfect this method produced similar results to the ERG's preferred method of pooling through a meta-analysis and therefore thought it was acceptable. The company showed that OS with venetoclax was much higher than BSC. The committee had concerns with their comparison due to the generalisability of the 116 trial rituximab arm population and because there had been no matching on baseline characteristics. This was important because disease stage data suggested that people in the 116 trial had more advanced disease than the venetoclax trials and therefore were likely to have lower OS than would be expected if the patients in the venetoclax trials had received BSC. The committee concluded that the relative survival benefit from the company's ITC was biased in favour of venetoclax. **The company should fully explore the most appropriate comparison based on data collected during the period of managed access, with particular focus on SACT data to establish the relative effectiveness of venetoclax compared to BSC.**
Utility values	The PFS health state utility value based on the pooled data from the venetoclax trials was 0.853. The ERG explained that this was higher than the age-matched general population value and chose 0.71 based on PFS in the 2nd line treatment setting from the literature.

	The company felt this was too low and argued that 0.80 had been accepted by the committee during the appraisal of idelalisib. The committee noted this value had actually been 0.75. The committee agreed that the ERG's value was too low but did not think the value from the venetoclax trials was appropriate because the population did not reflect clinical practice. They concluded that the utility value of 0.748 from the idelalisib appraisal was the most appropriate. The committee also agreed with the ERG's disutility for adverse events (and updated costs of some adverse events) in its base case. Although the committee noted that this didn't have a large impact on the ICER. **The company should use a utility value of 0.748 for the progression-free health state, unless SACT data informing the generalisability of the trial data provides a strong justification to deviating from the committee's preferred assumption.**
Most plausible ICER	The company revised its base case in response to consultation by incorporating the committee's preferred utility and adverse event cost assumptions. The deterministic ICERs were £39,940 per QALY gained for adults with a 17p deletion or *TP53* mutation whose disease has progressed after a B-cell receptor pathway inhibitor or for whom a B-cell receptor pathway inhibitor is unsuitable, and £47,370 per QALY gained for adults without a 17p deletion or *TP53* mutation and whose disease had progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor. The ERG used post-progression data after idelalisib from the 116 trial to inform BSC and the ICERs were £57,476 and £77,779 per QALY gained for adults with and without 17p deletion or *TP53* mutation respectively. The committee considered that the OS for BSC could be lower than the ERG estimates, particularly for the population without a 17p deletion or *TP53* mutation and this would decrease the ICERs. They felt that plausible ICERs were around £50,000 and £60,000 for with and without deletion, respectively. They recognised the uncertainty around the relative effectiveness of venetoclax and acknowledged that if the estimates were closer to the company's then venetoclax would have plausible potential to be cost-effective.
End of life	Venetoclax does meet the end-of-life criteria.

Abbreviations: BSC: best supportive care; CDF: Cancer Drugs Fund; CLL: chronic lymphocytic leukaemia; ECOG: Eastern cooperative oncology group; ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; ITC: indirect treatment comparison; OS: overall survival; PFS: progression-free survival; RCT: randomised control trial; SACT: Systemic Anti-Cancer Trust.

A.3 Other agreed changes

In accordance with the NICE process for CDF review, no additional changes or evidence have been included in this submission other than detailed above.

A.4 The technology

A description of venetoclax is provided in Table 2.

Table 2: Technology being reviewed

UK approved name and brand name	Venetoclax (Venclyxto®)
Mechanism of action	Venetoclax is a first in class orally available, selective small molecule inhibitor of B-cell lymphoma-2 (Bcl-2), an anti-apoptotic protein overexpressed in approximately 95% of CLL cases.[6-9] Venetoclax restores apoptosis independently of the P53 protein.[7, 9] As venetoclax is thought to act downstream of *TP53*, its mechanism of action provides a rationale for targeting Bcl-2 irrespective of del(17p)/*TP53* status.[9]
Marketing authorisation/CE mark status	Venetoclax was first granted conditional approval by the EMA on 5th December 2016.[10] Full marketing authorisation was subsequently granted on 20 November 2018.[11]
Indications and any restriction(s) as described in the summary of product characteristics	Venetoclax monotherapy has marketing authorisation in the indication of interest for this appraisal, for CLL:[10] • 'in the presence of 17p deletion or *TP53* mutation in adults unsuitable for or who have failed a B-cell receptor pathway inhibitor' • 'in the absence of 17p deletion/*TP53* mutation in adults who have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor' Venetoclax also has marketing authorisations for the following indications: • in combination with obinutuzumab for the treatment of adult patients with previously untreated CLL • in combination with rituximab for the treatment of adult patients with CLL who have received at least one prior therapy • in combination with a hypomethylating agent for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy
Method of administration and dosage	Venetoclax is administered orally as a film coated tablet. For patients with CLL, the daily regimen is initiated with a 5-week dose ramp-up (one week each of 20, 50, 100, and 200 mg, then 400 mg daily for one week), thereafter continuing at 400 mg daily until disease progression or no longer tolerated by the patient.[10]
Additional tests or investigations	No additional tests or investigations are required to identify the population for whom venetoclax is indicated beyond those that are already part of current clinical practice, including the testing of the 17p deletion prior to treatment indication
List price and average cost of a course of treatment	Confirmed list price of venetoclax: • 14-tab pack (10 mg) = £59.87 (Week 1, 20 mg per day) • 7-tab pack (50 mg) = £149.67 (Week 2, 50 mg per day)

	• 7-tab pack (100 mg) = £299.34 (Week 3, 100 mg per day) • 14-tab pack (100 mg) = £598.68 (Week 4, 200 mg per day) • 112-tab pack (100 mg) = £4,789.47 (Week 5 onwards, 400 mg per day [28 days pack]) At list price, the average cost of venetoclax for year 1 when assuming 100% treatment compliance is £58,752.23 and for year 2 and subsequent years is £41,126.56.
Commercial arrangement (if applicable)	There is a simple discount PAS for venetoclax which entails providing a discount of [redacted] on the list price for venetoclax. The average cost of venetoclax for the course of 1-year, assuming 100% treatment compliance and accounting for this PAS is [redacted]. The average cost of venetoclax for year 2 and subsequent years, assuming 100% treatment compliance and accounting for this PAS is [redacted].
Date technology was recommended for use in the CDF	November 2017[12]
Data collection end date	December 2020[13]

Abbreviations: EMA: European Medicines Agency; CLL: chronic lymphocytic leukaemia; PAS: patient access scheme.

A.5 Clinical effectiveness evidence

The data collection agreement specified the terms of data collection during the period of managed access. In summary, real-world data was to be collected within the CDF by PHE (SACT data) to provide evidence of venetoclax OS data as well as a matched cohort analyses comparing real-world data on OS of BSC and venetoclax patients.

The final SACT report included data on both treatment duration and OS in patients treated with venetoclax. However, the report did not include data on the BSC cohort due to under reporting of haematological malignancies in the SACT dataset at the time the BSC treatment option was available (i.e. prior to the availability of venetoclax monotherapy). PHE also determined that a matched cohort analyses would not be able to provide a meaningful analysis, so these were not produced.

Table 3: Primary source of clinical effectiveness evidence (used in model)

Study title	**SACT data cohort study[13]**
Study design	SACT data cohort study
Population	Patients with CLL: • in the presence of del(17p)/*TP53* mutation in adults unsuitable for or who have failed a B-cell receptor pathway inhibitor • in the absence of del(17p)/*TP53* mutation in adults who have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor
Intervention(s)	Venetoclax
Comparator(s)	Not applicable

Outcomes collected that address the committee's key uncertainties	• Baseline characteristics • Treatment duration • Overall survival
Reference to section in appendix	Data are presented in Section A.6, with further supportive data in Appendix B

Abbreviations: CLL: chronic lymphocytic leukaemia; SACT: Systemic Anti-Cancer Therapy.

A.6 Key results of the data collection

A.6.1 Updated venetoclax trial data

In the original appraisal (TA487), data for the effectiveness of venetoclax in patients with CLL was based on three single-arm clinical trials: M12-175, M13-982, and M14-032.[2-4] Since venetoclax's entry to the CDF, updated data from the M13-982 (data cut-off [DCO] 4th April 2017) and M14-032 (DCO 30th June 2017) trials are now available.[3, 4] Full details of both trials can be found in TA487 Document B, Section 4.11. The updated venetoclax data is consistent with the pooled data submitted in the original appraisal.

As the generalisability of the venetoclax trial data was a key uncertainty of the original appraisal and SACT CDF data are more generalisable to NHS clinical practice (see section A.6.2.1), SACT CDF data rather than updated data from the venetoclax trials have been used to inform the model.

A.6.1.1 M13-982

As of the latest DCO, overall response rate was in line with data from the previous DCO at 77% (previously at 77.2%).[14] Median time on venetoclax was 23.1 months (range: 0–44.2 months) and median OS had still not been reached. 24 month estimates of OS were 73% (95% CI: 65%, 79%).[3] Further details on these results are presented in Appendix A.

A.6.1.2 M14-032

As of the latest DCO, 65% (95% CI: 53%, 74%) of patients had an overall response, this is in line with the original DCO which reported an overall response in 67.4% (95% CI: 51.5%, 80.9%). Median OS had not been reached, with an estimated 12 month survival of 91% (95% CI: 83%, 95%), which was higher than at the original DCO which had an estimated 12 month survival of 88.1% (95% CI: 73.6%, 94.9%).[4, 14] Further details on these results are presented in Appendix A.

A.6.2 SACT data

Key results from the SACT data collection are presented below, with additional results presented in Appendix B including the number of patients at risk as well as the number of censored patients and the number with events for both treatment duration and OS. The treatment outcomes and treatment status of patients in the SACT CDF cohort are also provided in Appendix B.

In total, PHE identified 454 applications for venetoclax between 5th October 2017 and 4th December 2020 through the CDF cohort and, following data cleaning, 406 unique patients were identified to receive treatment with venetoclax in the CDF cohort. Furthermore, 105 unique patients were identified as Early Access to Medicine (EAMS) patients that ran from 23rd August 2016 to 5th December 2016, of which 102 patients receiving venetoclax were included in the SACT analyses.

Although SACT data were provided for both the CDF and EAMS cohorts, only the CDF cohort data is split by del(17p)/*TP53* mutation status as required for the economic model. As such, only data from the CDF cohort are presented within this submission.

A.6.2.1 Baseline characteristics

A summary of the key baseline characteristics for patients treated with venetoclax in the SACT CDF dataset is presented in Table 4.

Table 4: Baseline characteristics of patients receiving venetoclax in the SACT CDF cohort

	CDF cohort, N=406	
	n	%
Sex		
Male	275	68
Female	131	32
Age		
<40	1	<1
40 to 49	7	2
50 to 59	44	11
60 to 69	109	27
70 to 79	165	41
80+	80	20
Performance Status		
0	84	21
1	146	36
2	40	10
3	7	2
4	0	0
Missing	129	32

Figures may not sum to 100% due to rounding.
Source: Public Health England SACT Data Review.[13]

As per the terms of engagement, in TA487, the committee considered that the patients included in the venetoclax trial may be younger and have a lower burden of disease compared with patients who would be expected to receive venetoclax in clinical practice.[12] Comparing the baseline characteristics of the SACT cohort to the venetoclax trials, patients are closer in age to the mean age at diagnosis in England (71 years, compared with a mean age of 65 years in the venetoclax trials).[2-4] Additionally, when excluding patients with missing Eastern Cooperative Oncology Group (ECOG) scores in the SACT cohort, there is a trend towards more advanced disease compared with the patients in the venetoclax trials, with a higher proportion of patients with a ECOG score of 2 or above (Table 5). [12] Data on prior lines of therapy received by each patient prior to treatment with venetoclax are not known for the SACT CDF dataset. The clinical data from these patients therefore addresses the committee's previous uncertainty surrounding

the generalisability of the venetoclax trial data, by providing an alternative source of efficacy data in a population of direct relevance to those who would receive venetoclax within the NHS.

Table 5: Table comparing ECOG score between the SACT CDF cohort and venetoclax trial data

	SACT CDF Cohort with known ECOG (n = 277*)	Pooled venetoclax trials	
		Non-del(17p)/*TP53* mutation population (n = 153)[a]	Del(17p)/*TP53* mutation population (n = 218)[b]
ECOG score n (%)			
0	84 (30)	[redacted]	[redacted]
1	146 (53)	[redacted]	[redacted]
2+	47 (17)	[redacted]	[redacted]

[a] Pooled from trials M14-032 and M12-175.
[b] Pooled from trials M14-032, M13-982 and M12-175.
*Percentages relate to SACT CDF cohort with known ECOG (n=277) rather than full CDF Cohort (n=406)
Abbreviations: CDF: Cancer Drugs Fund; ECOG: Eastern Cooperative Oncology Group; SACT: Systemic Anti-Cancer Trust.
Source: Public Health England SACT Data Review;[13] NICE TA487: Committee papers.[14]

Due the improved generalisability of the SACT CDF data compared to the venetoclax trial data, SACT CDF cohort data have been used to populate the economic model rather than the updated venetoclax trial data.

A.6.2.2 Treatment duration

In total, 220 patients (54%) were identified as no longer being on treatment at the latest date of follow up (28 February 2021) in the CDF cohort.[13] Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT CDF dataset or they have not received treatment with venetoclax in at least three months.[13] The median follow-up time in SACT CDF cohort was 14.6 months (445 days) amongst those without a del(17p)/*TP53* mutation and 10.6 months (322 days) amongst those with a del(17p)/*TP53* mutation.[13]

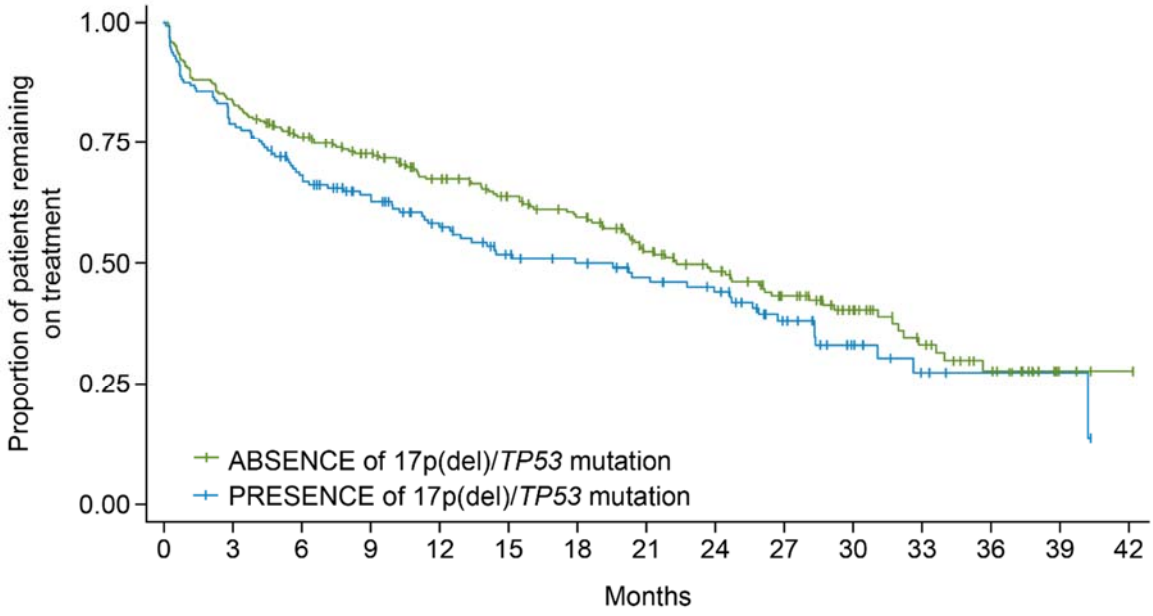
Figure 1 presents the Kaplan–Meier curve for treatment duration with venetoclax, with estimates at specific time intervals presented in Table 6. The median treatment duration for all patients without a del(17p)/*TP53* mutation was 22.3 months (95% CI: 20.0, 28.1; 678 days). For patients with a del(17p)/*TP53* mutation, median treatment duration was 17.9 months (95% CI: 11.5, 25.6; 544 days).[13]

Table 6: Treatment duration by mutation status at 6-, 12-, 18-, 24- and 36-month intervals

Time period	Patients remaining on treatment, % (95% CI)	
	Patients without del(17p)/*TP53* mutation (n=245)	Patients with del(17p)/*TP53* mutation (n=161)
6 months	76 (70, 81)	68 (60, 75)
12 months	67 (61, 73)	57 (49, 65)
18 months	59 (52, 66)	50 (41, 58)
24 months	48 (41, 55)	44 (35, 52)
36 months	28 (19, 37)	27 (17, 38)

Abbreviations: CI: confidence interval.
Source: Public Health England SACT Data Review.[13]

Figure 1: Kaplan–Meier treatment duration estimates for patients receiving venetoclax by mutation status



Source: Public Health England SACT Data Review.[13]

A.6.2.3 Overall survival

The median OS for all patients without a del(17p)/*TP53* mutation was not reached. The median OS for all patients with a del(17p)/*TP53* mutation was 33 months (1,004 days). OS at specific time intervals is shown in Table 7.

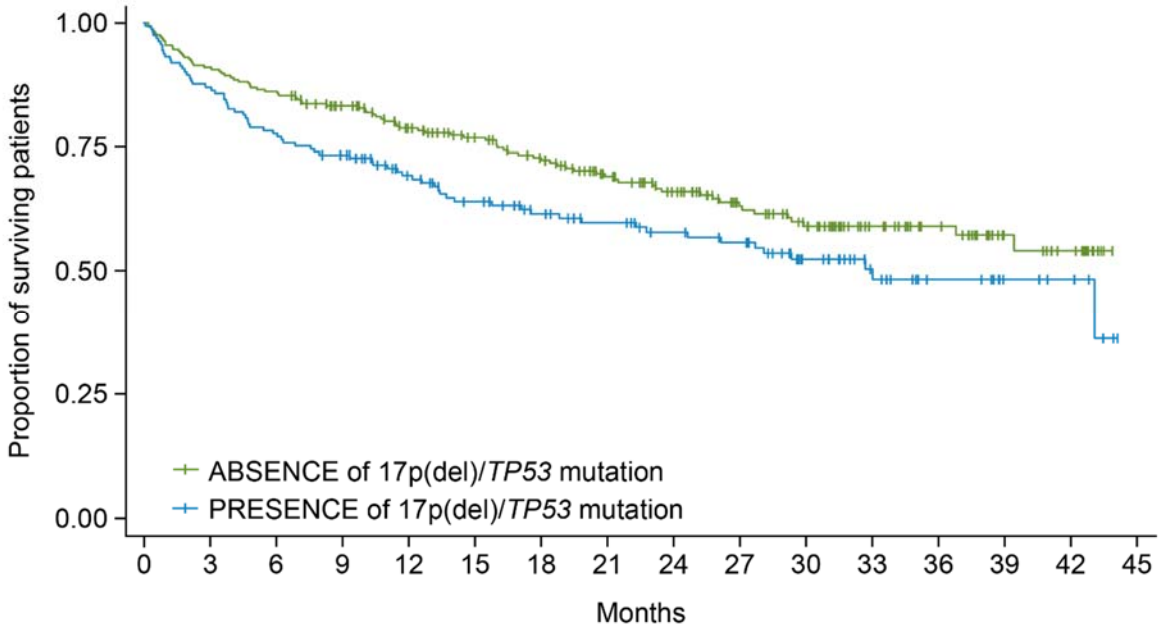
Table 7: Overall survival by mutation status at 6-, 12-, 18-, 24- and 36-month intervals

Time period	Patients remaining alive, % (95% CI)	
	Patients without del(17p)/*TP53* mutation (n=245)	Patients with del(17p)/*TP53* mutation (n=161)
6 months	86 (81, 90)	78 (70, 83)
12 months	79 (73, 83)	69 (61, 76)
18 months	73 (66, 78)	61 (53, 69)
24 months	66 (59, 72)	58 (49, 65)
36 months	59 (51, 66)	48 (38, 57)

Abbreviations: CI: confidence interval.
Source: Public Health England SACT Data Review.[13]

The median follow-up time in SACT was 20.6 months (627 days) amongst those without a del(17p)/*TP53* mutation and 15.5 months (471 days) amongst those with a del(17p)/*TP53* mutation. Figure 2 presents the Kaplan–Meier curve for OS.

Figure 2: Kaplan–Meier overall survival estimates for patients receiving venetoclax by mutation status



Source: Public Health England SACT Data Review.[13]

A.7 Evidence synthesis

No indirect/mixed treatment comparisons are included in this submission. As BSC data were not included in the SACT report, there are no updated comparator data available; the source of data for the comparator arm in the model remains therefore unchanged from the original appraisal.

A.8 Incorporating collected data into the model

The updated cost-effectiveness models (for both patients with and without del(17p)/*TP53* mutations) incorporate the results presented by PHE on the use of venetoclax in clinical practice in England, using the routinely collected SACT CDF dataset, as presented in Section A.6. The SACT CDF data, instead of the updated venetoclax trial data, have been used to inform the models due to the increased generalisability of the patient population to UK clinical practice.

The cost-effectiveness model (CEM) developed for the original appraisal, used a partitioned survival approach, with parametric survival curves fitted onto Kaplan–Meier plots from venetoclax trials to estimate PFS and OS beyond the trial period. In the absence of venetoclax PFS data from the SACT CDF dataset, the treatment duration (subsequently referred as Time on Treatment [ToT]) survival curves from the PHE data were used to inform PFS in the original model.

A.8.1 Overall Survival and Time on Treatment

As described in Section A.6, PHE analysed the data collected for the CDF cohort, the EAMS cohort, and a combined sample of the two. The CEMs developed in the original appraisal stratified between patients with and without a del(17p)/*TP53* mutation. However, PHE only presented a del(17p)/*TP53* stratified analysis for the CDF cohort. Therefore, the OS and ToT survival curves from the CDF cohort (N=406), split by mutation status, were used to inform OS and PFS survival in the CEMs.

Regarding the survival analysis of the CDF and EAMS cohorts, median treatment duration was 21.2 months (95% CI: 18.6, 24.7) amongst the CDF cohort, 19.1 months (95% CI: 11.7, 27.0) amongst the EAMS cohort and 21.2 months (95% CI: 17.9, 24.6) for the combined cohort (CDF and EAMS), indicating relatively small differences between the two cohorts in terms of treatment duration. Considering OS differences, the discrepancy is slightly higher with a median OS at 43.1 months[1] amongst the CDF cohort, 32.5 months (95% CI: 20.3, 41.8) amongst the EAMS cohort and 38.5 months (95% CI: 31.3, 44.1) for the combined cohort. The maximum follow-up period for survival was 44.9 months for the CDF cohort and 58.3 months for the EAMS cohort, with all patients being traced on 2nd July 2021. Despite these small differences, considering the availability of data split by mutation status, the CDF cohort was considered the most appropriate source of data for modelling the efficacy of venetoclax.

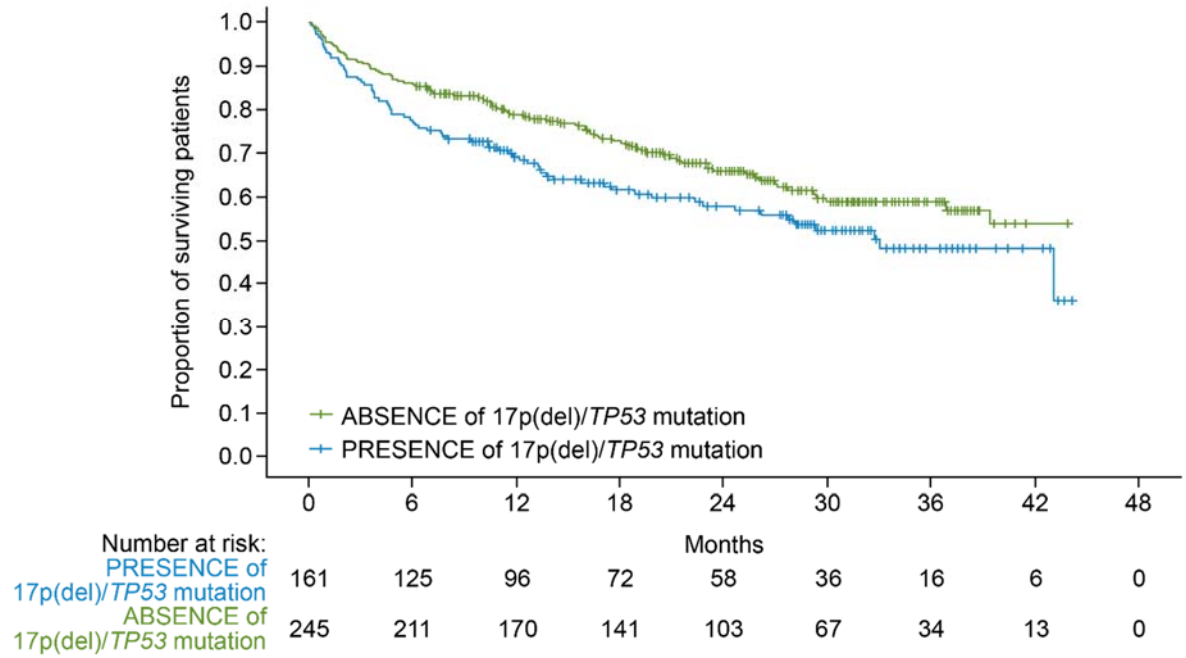
The OS Kaplan–Meier curves of the venetoclax treatment arm from the CDF cohort, split by del(17p)/*TP53* mutation status, were used to reconstruct pseudo patient-level data (median follow-up time in SACT in patients without a del(17p)/*TP53* mutation was 20.6 months [627 days] and in patients with a del(17p)/*TP53* was 15.5 months [471 days]). To this end, WebPlotDigitizer (Rohatgi 2015)[15] was used to digitise survival curves and reconstruct the Kaplan–Meier curves in the SACT report using the method developed by Guyot *et al* (2012).[16]

Aligned with the methodology developed for the survival analysis in the original appraisal,[17] parametric models were explored to estimate outcomes beyond the observed trial follow-up period. Five traditional parametric distributions, including exponential, Weibull, Gompertz, log-logistic, and log-normal, were fitted to the reconstructed OS data of the CDF cohort. Akaike information criterion (AIC) and Bayesian information criterion (BIC) values as well as visual inspection versus Kaplan–Meier data and smoothed hazards of the extrapolated models were evaluated to compare model fits. Additional clinical expert opinion for this CDF reappraisal was also sought from a UK-based Consultant Haematologist to confirm that the chosen base case extrapolations aligned with their expectations of UK clinical practice.

Figure 3 and Figure 4 present the Kaplan–Meier curves for venetoclax treatment based on the reconstructed patient-level data. The median OS for all patients without a del(17p)/*TP53* mutation (N=245) was not reached. The median OS for all patients with a del(17p)/*TP53* mutation was 33.03 months (N=161). It is upon the curves presented in Figure 3 and Figure 4 that parametric survival models were fitted independently for the patient population with a del(17p)/*TP53* mutation and the population without.

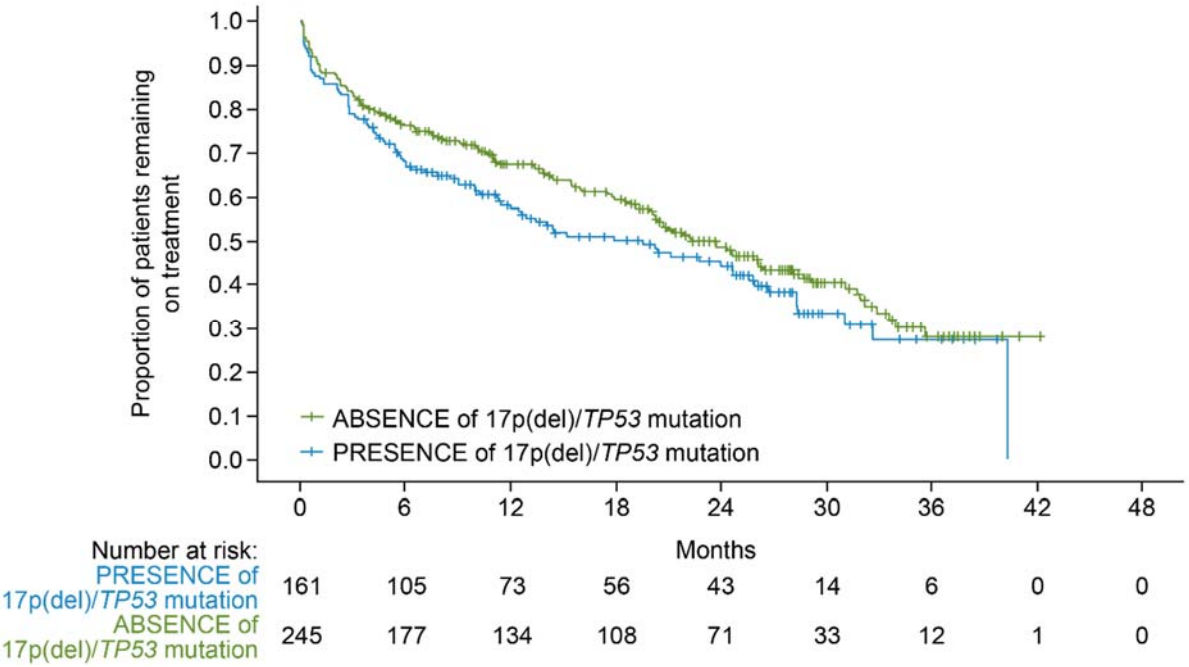
[1] Confidence intervals could not be produced as there was an insufficient number of events at the time the report was produced.

Figure 3: Kaplan–Meier OS plot for patients receiving venetoclax, by mutation status, based on the reconstructed patient-level data CDF cohort (N=406)



Abbreviations: CDF: cancer drugs fund; OS: overall survival.

Figure 4: Kaplan–Meier ToT plot for patients receiving venetoclax, by mutation status, based on the reconstructed patient-level data CDF cohort (N=406)



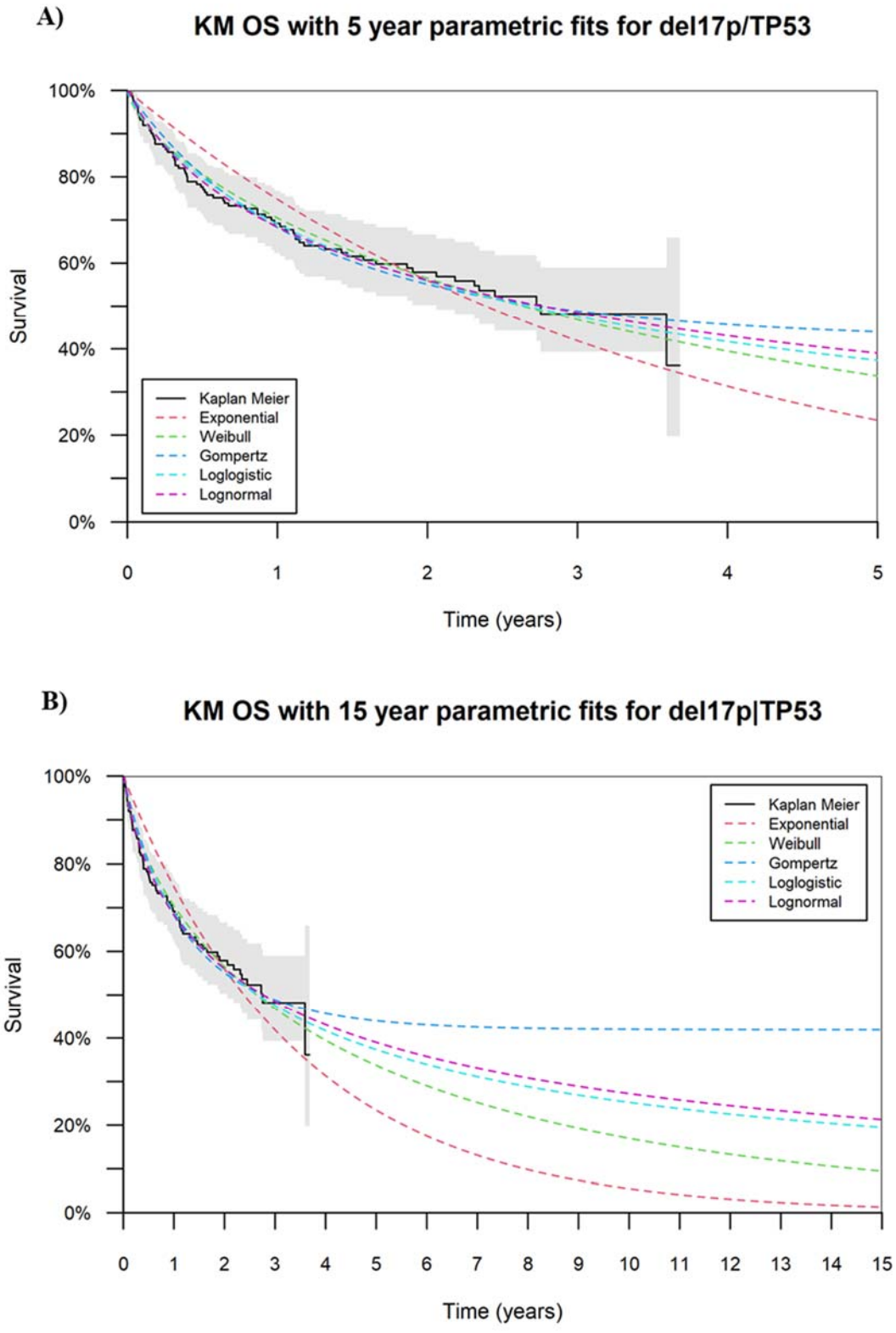
Abbreviations: CDF: cancer drugs fund; ToT: time on treatment.

A.8.1.1 OS and ToT – patient population with a del(17p)/*TP53* mutation

To visually assess fit, each parametric model was overlaid on the Kaplan–Meier curves. The choice of parametric function was further guided by the analysis of log cumulative hazard plots (to assess suitability of the proportional hazards models) and a smoothed hazard function plot (estimated using the R package Muhaz),[18] to determine whether hazards are likely to be increasing or decreasing, monotonically or otherwise.

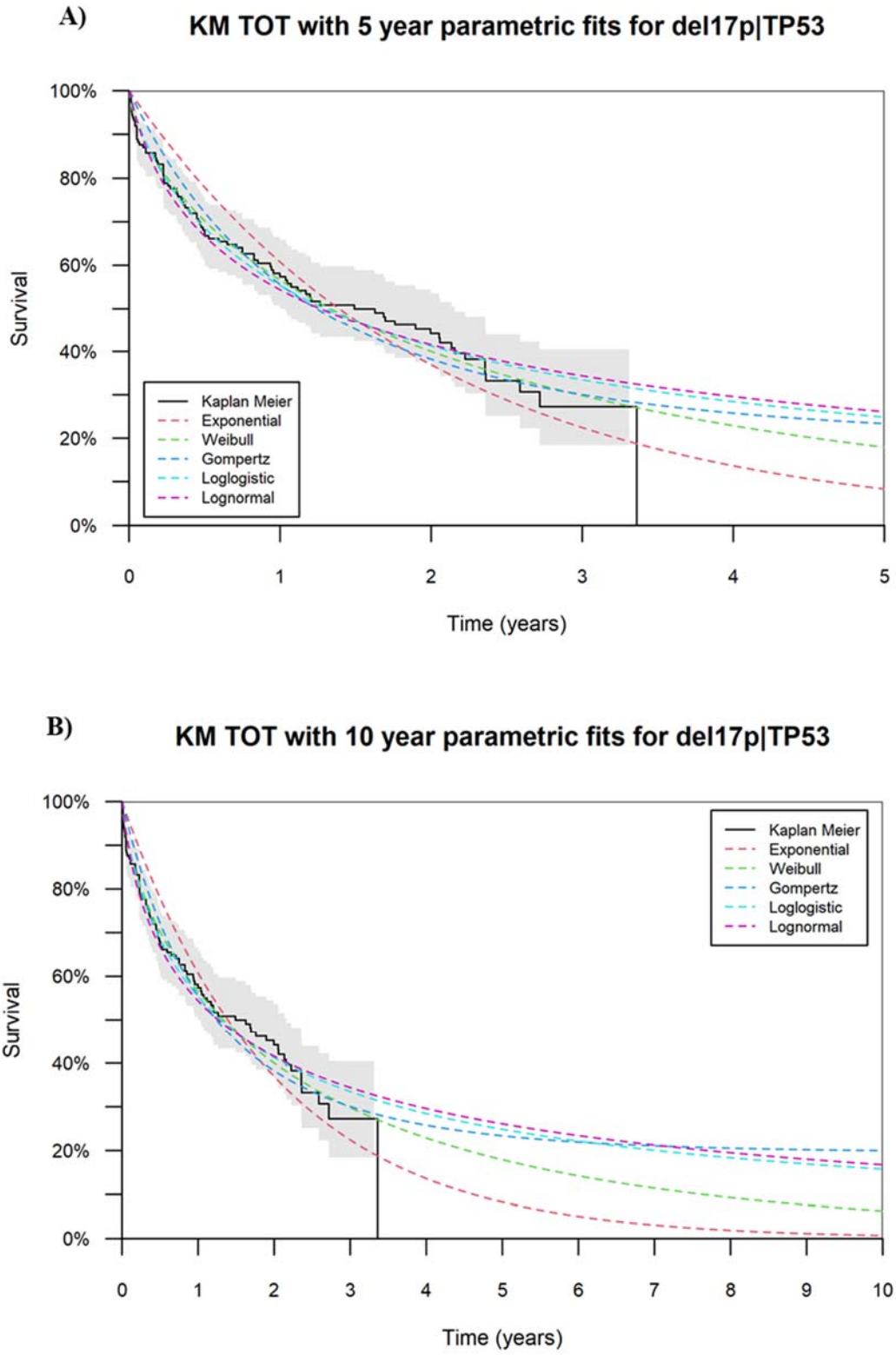
Figure 5 presents the reconstructed OS Kaplan–Meier curve for the patient population with a del(17p)/*TP53* mutation alongside exponential, log-logistic, Weibull, log-normal and Gompertz parametric fits, for a time horizon of 5 and 15 years. Figure 6 presents the reconstructed ToT Kaplan–Meier curve for the patient population with a del(17p)/*TP53* mutation alongside exponential, log-logistic, Weibull, log-normal and Gompertz parametric fits, for a time horizon of 5 and 10 years.

Figure 5: OS parametric fits – patient population with a del(17p)/*TP53* mutation using A) 5 and B) 15 years' time horizon



Abbreviations: OS: overall survival.

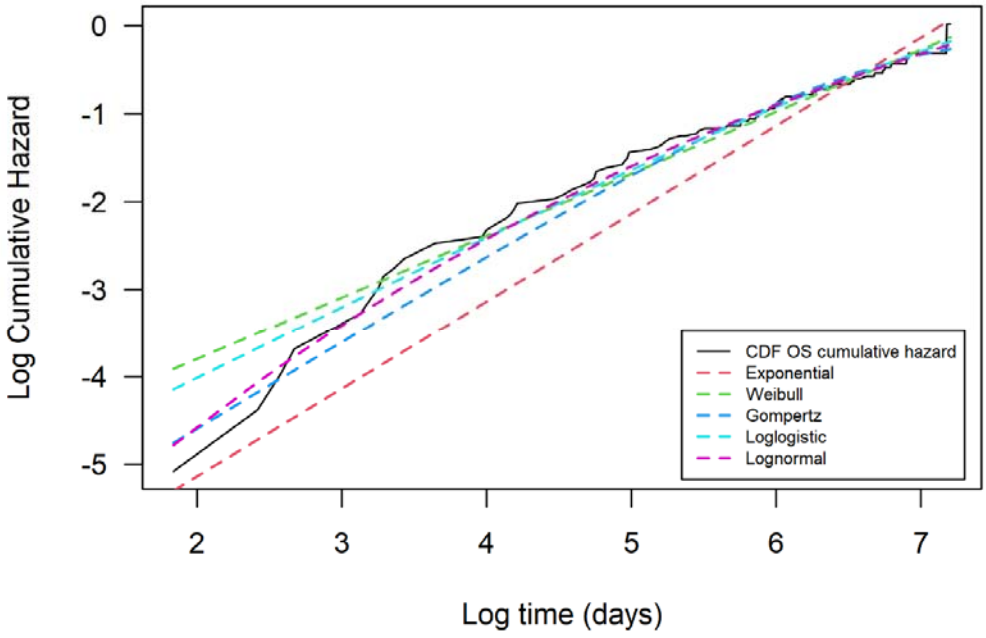
Figure 6: ToT parametric fits – patient population with a del(17p)/*TP53* mutation using A) 5 and B) 10 years' time horizon.



Abbreviations: ToT: time on treatment.

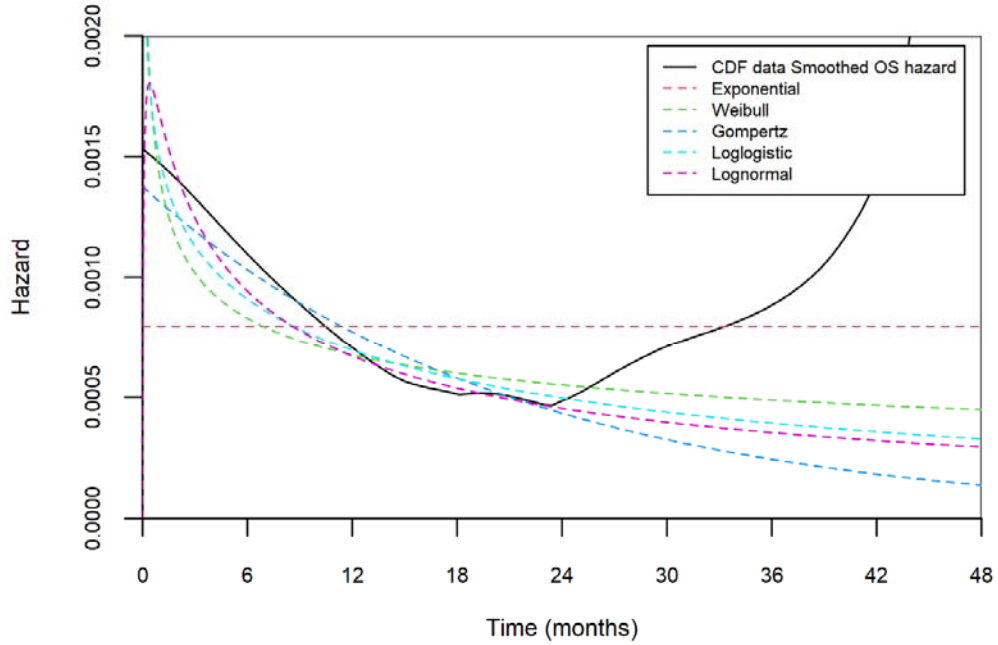
Figure 7 presents the log cumulative OS hazard plot for the CDF patient population with a del(17p)/*TP53* mutation and Figure 8 presents the smoothed OS hazard function over time.

Figure 7: OS log cumulative hazard with parametric fits for the patient population with a del(17p)/*TP53* mutation



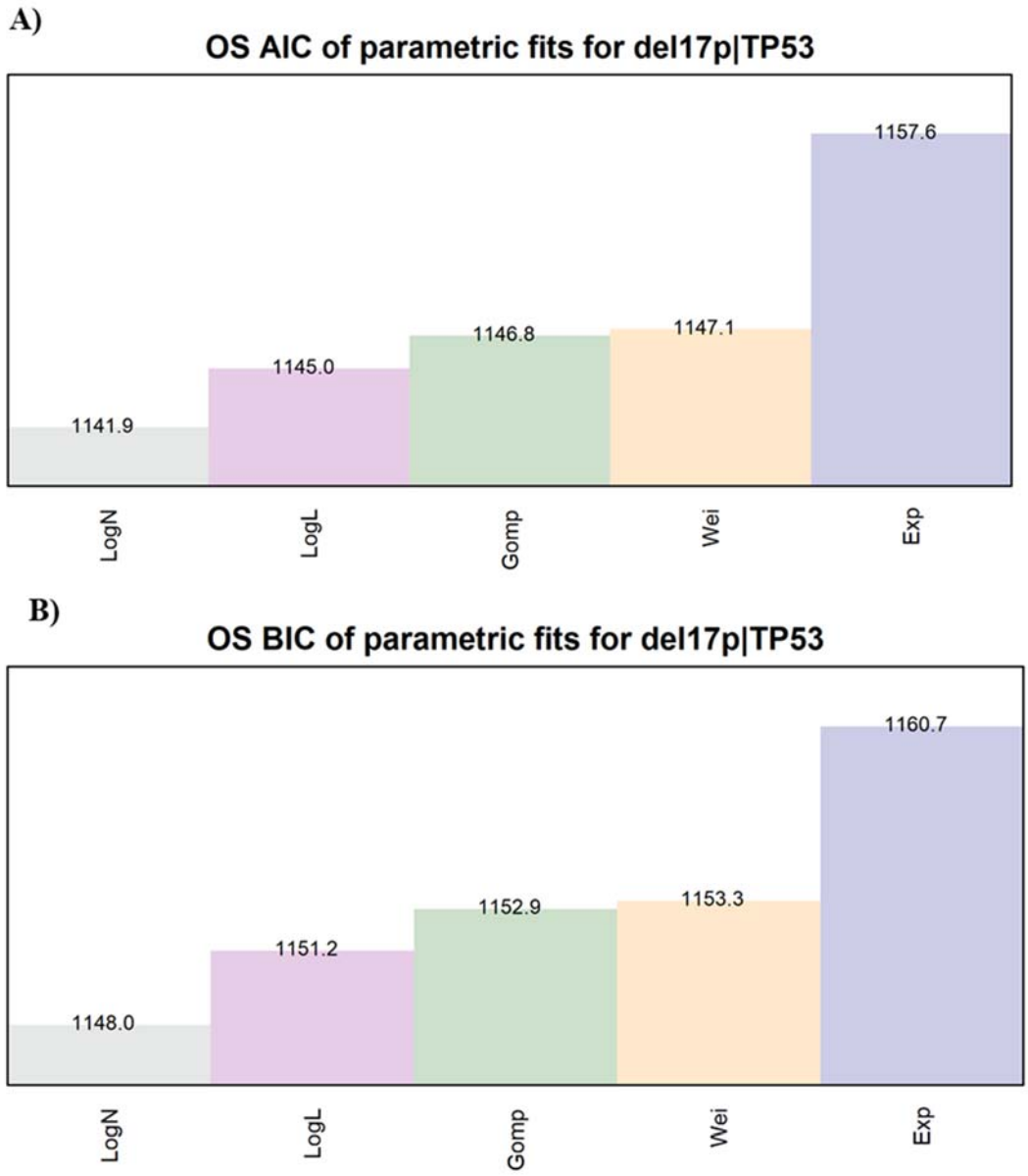
Abbreviations: CDF: cancer drugs fund; OS: overall survival.

Figure 8: OS smoothed hazard function with parametric fits for the patient population with a del(17p)/*TP53* mutation



Abbreviations: CDF: cancer drugs fund; OS: overall survival.

Figure 9: A) AIC and B) BIC values of parametric OS models for the CDF cohort: patient population with a del(17p)/*TP53* mutation



Abbreviations: AIC: Akaike's information criteria; BIC: Bayesian information criteria; CDF: cancer drugs fund; OS: overall survival.

The (broadly) linearity observed in the log cumulative hazard plot suggests that models allowing for hazards to increase or decrease monotonically, such as the Weibull, exponential or Gompertz, are an appropriate fit for the underlying data. Nonetheless, the observed smoothed hazard pattern for OS of the del(17p)/*TP53* mutation population is non-monotonic, decreasing up to 24 months and increasing thereafter, which is difficult to replicate by the exponential, Weibull, and Gompertz models. Nonetheless, it is worth mentioning that the smoothed hazard function becomes increasingly less reliable over time due to censoring, especially after about 2 years when the number at risk drops substantially (Figure 3). The other models seem to provide a better fit, as both the log-normal and log-logistic are non-monotonic functions and seem to replicate slightly better the observed smoothed hazard up to 24 months, which is also reflected on the lower AIC and BIC values (Figure 9). The hazards of the Gompertz curve are decreasing at an increasing rate, which is not particularly well supported by the log cumulative hazard plot and the smoothed hazard function. The hazards of the Weibull function are decreasing at a

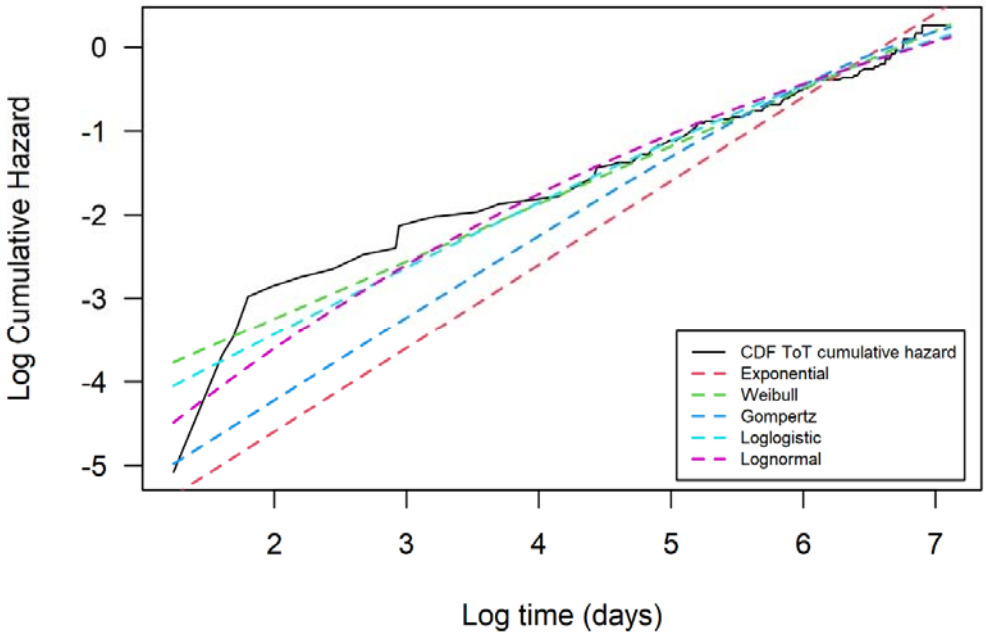
decreasing rate over time, which appears to provide a worse fit considering the AIC and BIC values.

Consultation with clinical experts in CLL by AbbVie during the original appraisal suggested that the 10-year OS of 12% (associated with the Weibull curve for the del(17p)/*TP53* mutation population in the original appraisal) is a reasonable estimate of longer-term OS outcomes. The 10-year OS estimates based on the CDF cohort with a del(17p)/*TP53* mutation were 5.5% for the exponential, 17.0% for the Weibull, 42.0% for the Gompertz, 25.2% for the log-logistic and 27.2% for the log-normal. Additional discussions with a clinical expert in CLL for this CDF reappraisal also supported the choice of Weibull; the clinical expert indicated that they would expect OS to be around 20% at 10 years in the del(17p)/*TP53* mutation population, and that Weibull would be the most appropriate curves for both OS and ToT in both populations.[19]

Overall, in terms of external validity, the 17% 10-year OS predicted by the Weibull model provides the closest estimate to the estimate that was validated in both the original appraisal and this CDF reappraisal and is therefore chosen as the most suitable parametric model of OS for the del(17p)/*TP53* population. The impact of using other parametric fits in the model, including the log-normal which presents the lowest AIC and BIC values, is investigated in the scenario analyses.

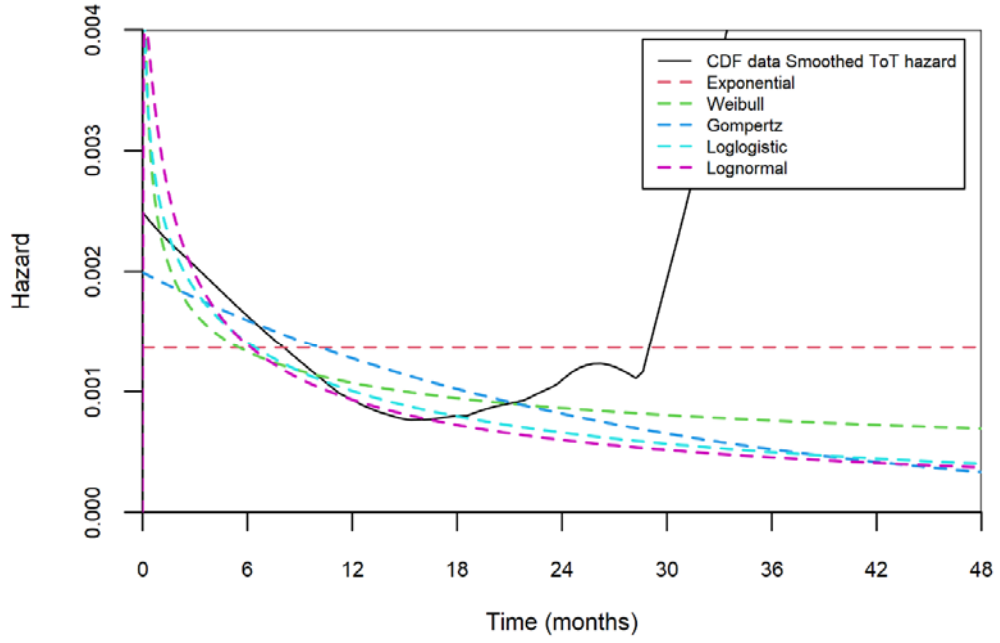
Figure 10 presents the log cumulative ToT hazard plot for the CDF patients with a del(17p)/*TP53* mutation and Figure 11 presents the smoothed ToT hazard function over time.

Figure 10: ToT log cumulative hazard with parametric fits for patients with a del(17p)/*TP53* mutation



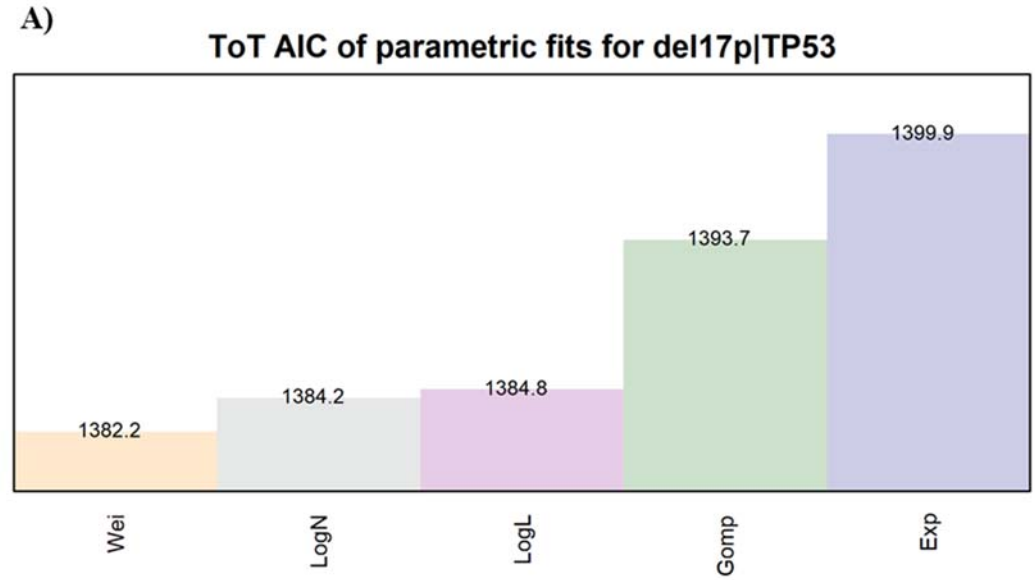
Abbreviations: CDF: cancer drugs fund; ToT: time on treatment.

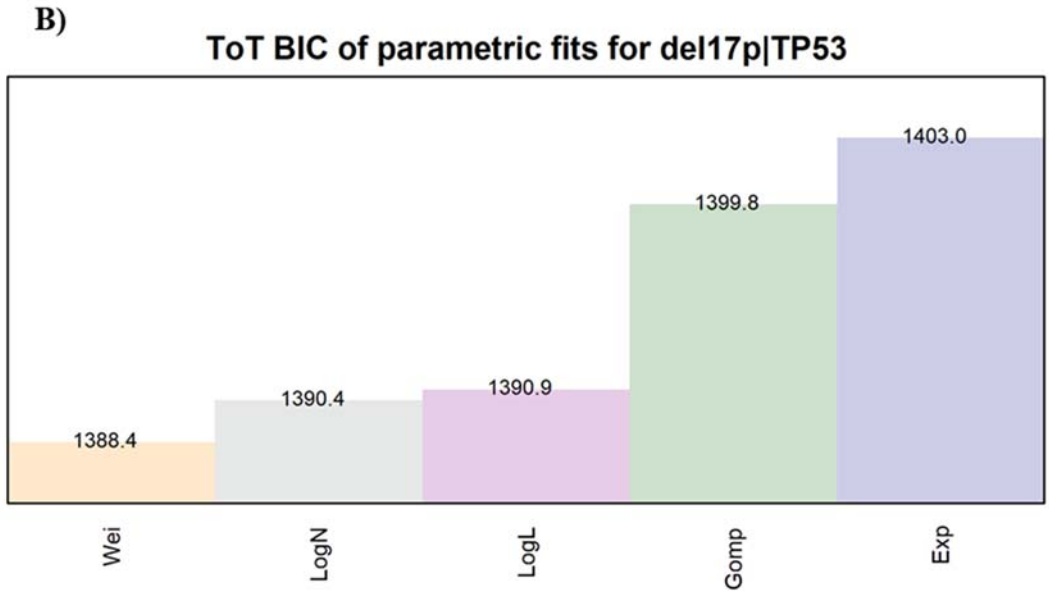
Figure 11: ToT smoothed hazard function with parametric fits for patients with a del(17p)/*TP53* mutation



Abbreviations: CDF: cancer drugs fund; ToT: time on treatment.

Figure 12: A) AIC and B) BIC values of ToT parametric models for the CDF patients with a del(17p)/*TP53* mutation





Abbreviations: AIC: Akaike's information criteria; BIC: Bayesian information criteria; CDF: cancer drugs fund; ToT: time on treatment.

For the base case ToT extrapolation of the del(17p)/*TP53* mutation population, the Weibull model was chosen as the most suitable function. The (broadly) linearity observed in the log cumulative hazard plot suggests that models allowing for hazards to increase or decrease monotonically, such as the Weibull, exponential or Gompertz are an appropriate fit for the underlying data. Nonetheless, the smoothed hazard function suggests that hazards are likely to be decreasing up to about 18 months and increasing thereafter (Figure 11). Although the hazards of the Weibull appear to plateau quickly towards a constant rate, which contrasts with the smoothed hazard function beyond around 18 months, it is important to note that the smoothed hazard function becomes increasingly less reliable over time due to censoring. The choice of the Weibull model is further supported by the measures of statistical fit (AIC and BIC values) and the visual inspection of the 10-year survival which leads to more realistic longer-term outcomes, 6.3% for the Weibull curve versus 0.7% for the exponential curve. Clinical expert consultation during the original appraisal suggested that due to the expected role of undetectable minimal residual disease (uMRD) in venetoclax patients (which was subsequently demonstrated in other randomised trials of venetoclax regimens), [20, 21] the 0% PFS associated with the Gompertz model at 10 years is perhaps an underestimation, and that the Weibull model, with an estimate of around 2%, led to more realistic longer-term outcomes. This was further confirmed by discussions with a clinical expert in CLL at the time of this CDF reappraisal.[19]

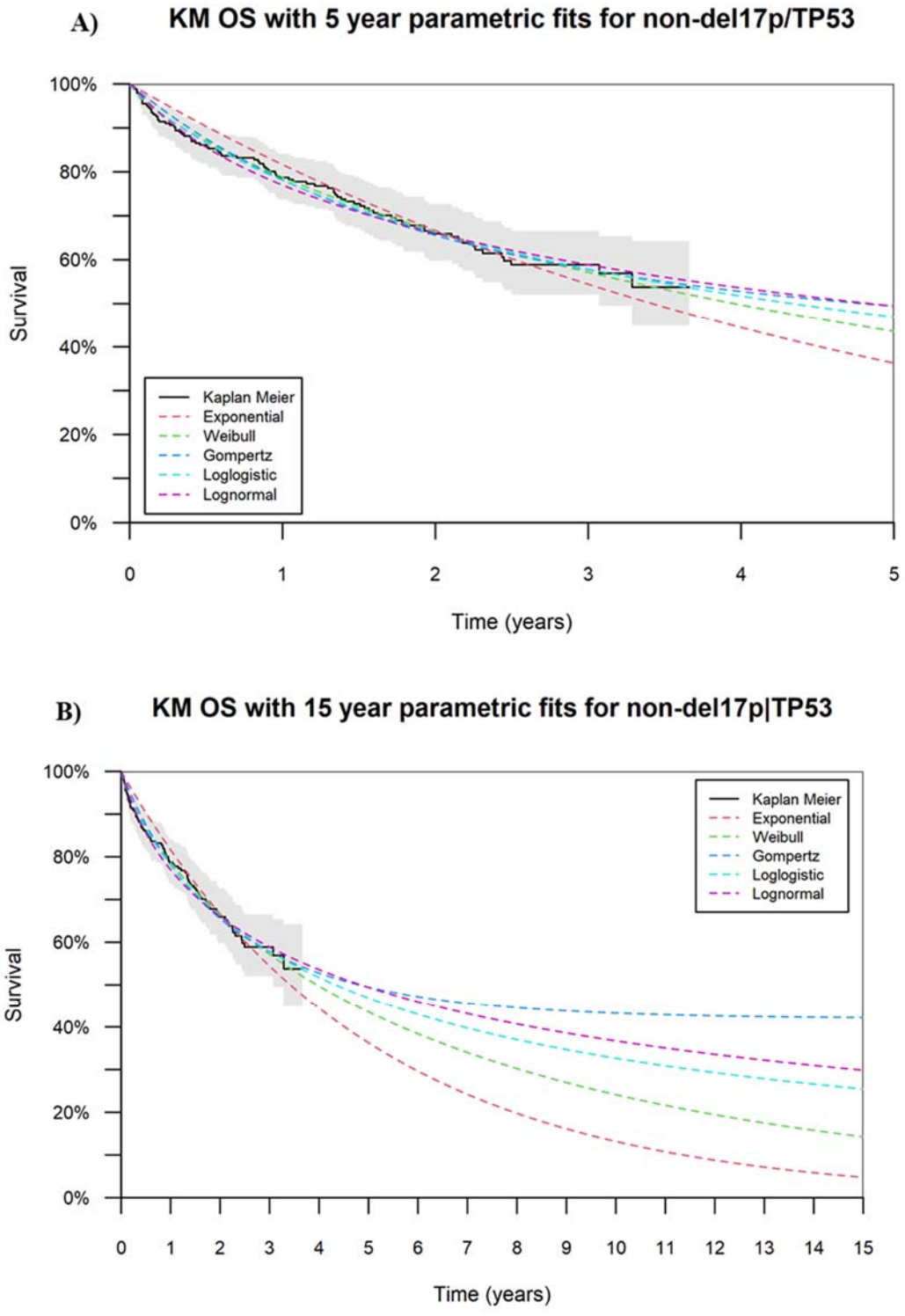
As a reflection of the uncertainty that surrounds the optimal curve choice, all ToT extrapolation parametric models were explored in a sequence of scenario analyses.

A.8.1.2 OS and ToT – patient population without a del(17p)/*TP53* mutation

Parametric fits were added on the Kaplan–Meier curves, based on the recreated patient-level data from the CDF patient population without a del(17p)/*TP53* mutation, at 5 and 15 years for OS and at 5 and 10 years for the ToT, to visually assess fit of parametric models and extrapolated outcomes. The choice of parametric function was further guided by the analysis of log cumulative hazard plots (to assess suitability of the proportional hazards models) and a smoothed hazard function plot (estimated using the R package Muhaz),[18] to determine whether hazards are likely to be increasing or decreasing, monotonically or otherwise. Figure 13 presents the reconstructed

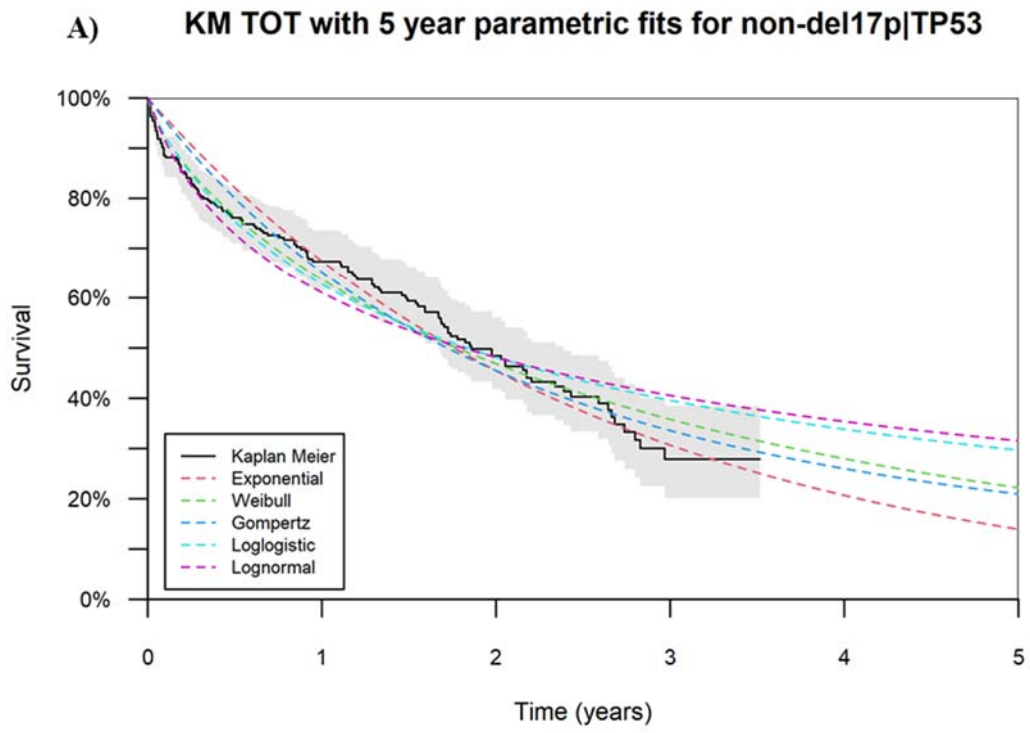
OS Kaplan–Meier curve for the patient population without a del(17p)/*TP53* mutation alongside exponential, log-logistic, Weibull, log-normal and Gompertz parametric fits, for a time horizon of 5 and 15 years. Figure 14 presents the reconstructed ToT Kaplan–Meier curve for the patient population without a del(17p)/*TP53* mutation alongside exponential, log-logistic, Weibull, log-normal and Gompertz parametric fits, for a time horizon of 5 and 10 years.

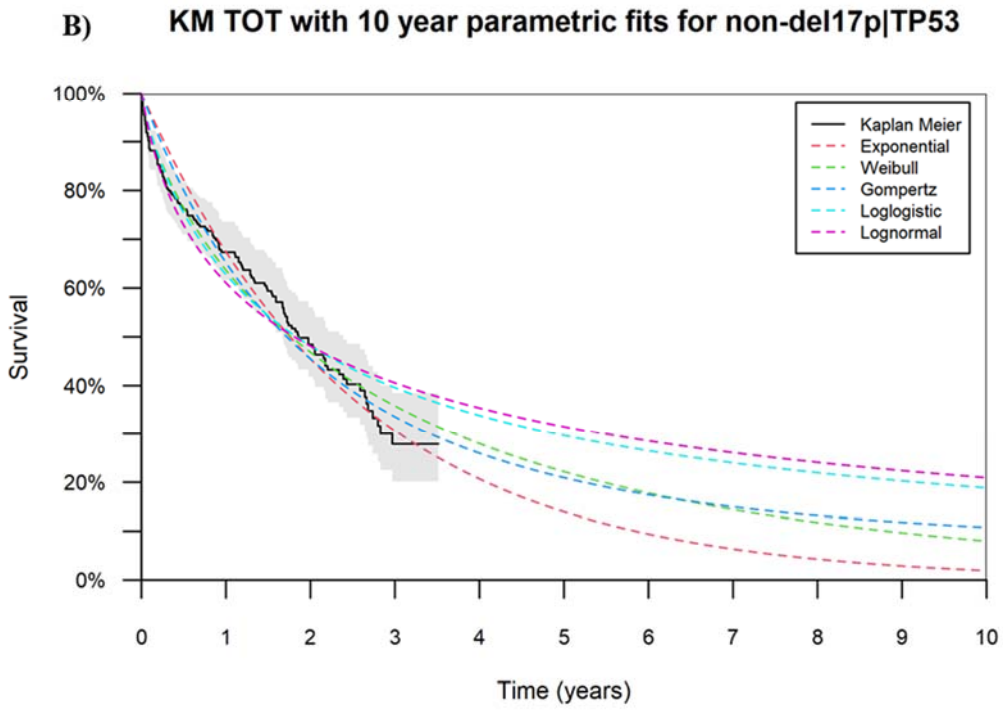
Figure 13: OS parametric fits – patient population without a del(17p)/*TP53* mutation using A) 5 and B) 15 years' time horizon



Abbreviations: OS: overall survival.

Figure 14: ToT parametric fits – patient population without a del(17p)/*TP53* mutation using A) 5 and B) 10 years' time horizon.

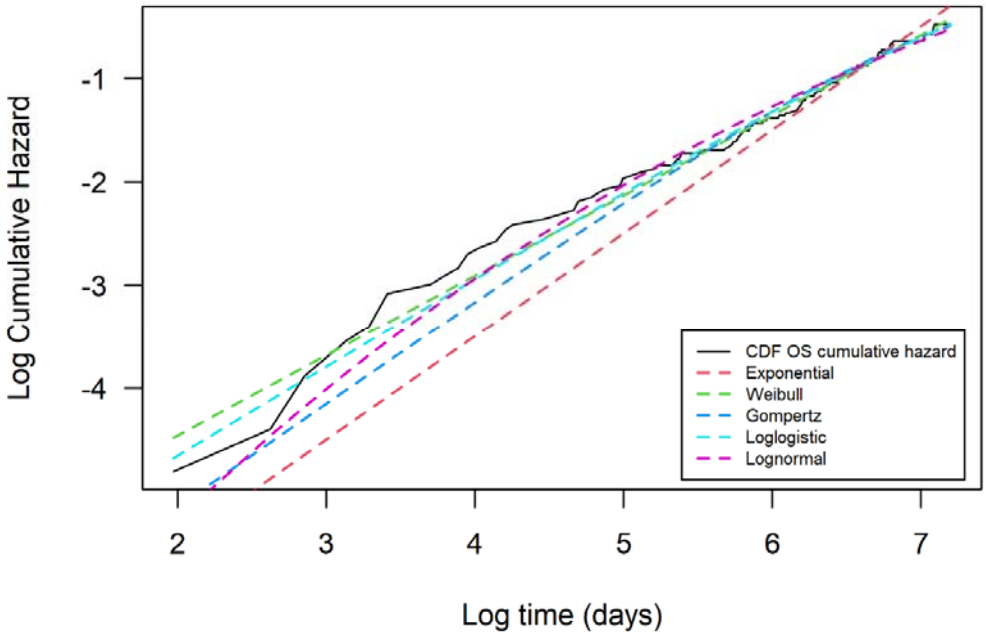




Abbreviations: ToT: time on treatment.

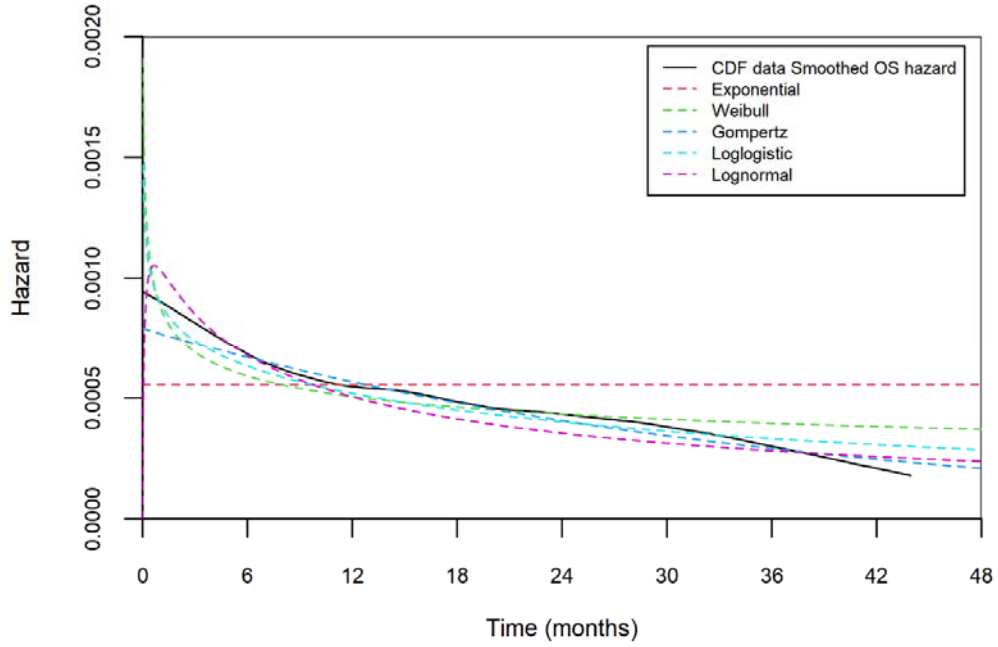
Figure 15 presents the log cumulative OS hazard plot for the CDF patient population without a del(17p)/*TP53* mutation and Figure 16 presents the smoothed OS hazard function over time.

Figure 15: OS log cumulative hazard with parametric fits for patient population without a del(17p)/*TP53* mutation



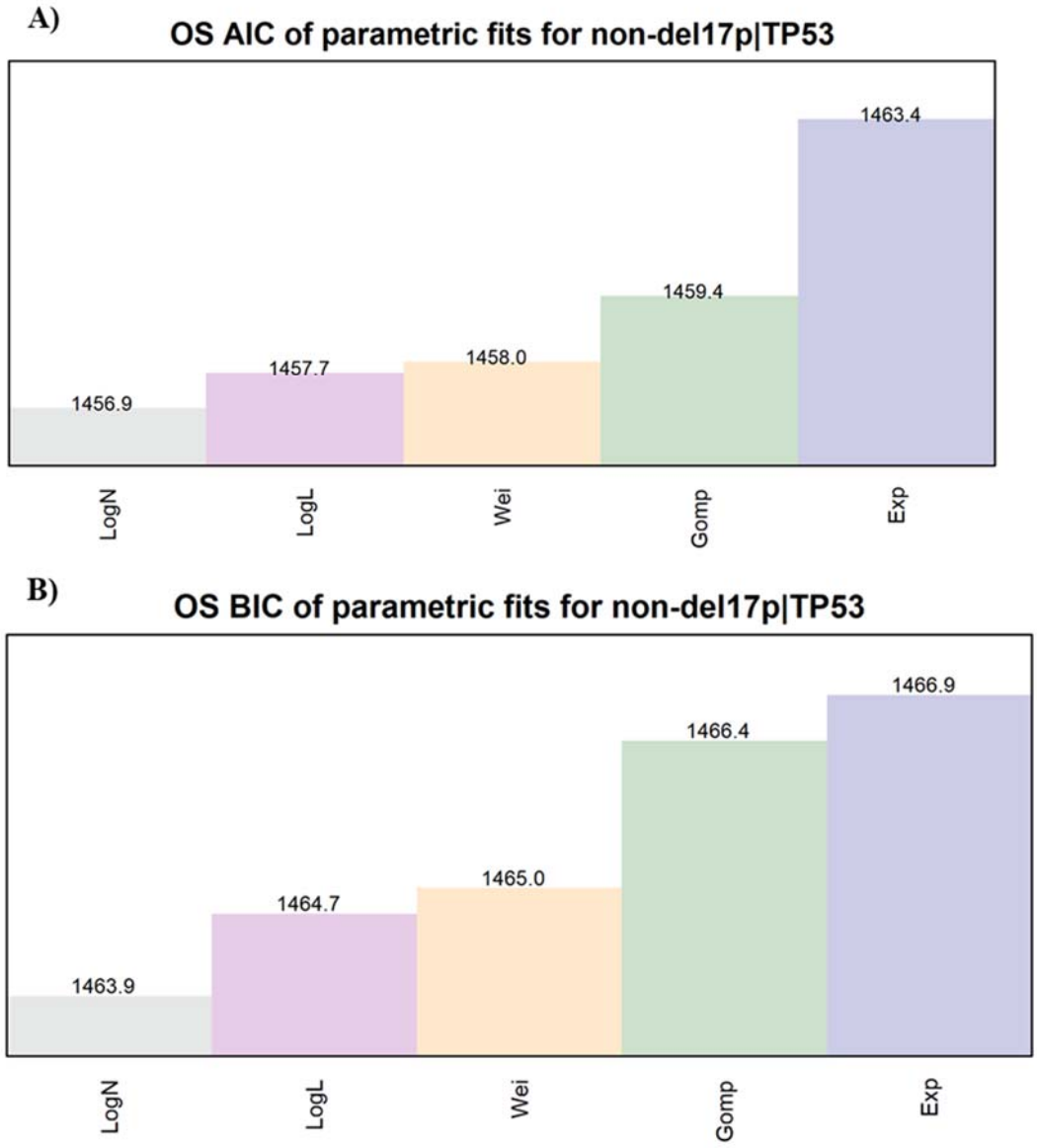
Abbreviations: CDF: cancer drugs fund; OS: overall survival.

Figure 16: OS smoothed hazard function with parametric fits for patient population without a del(17p)/*TP53* mutation



Abbreviations: CDF: cancer drugs fund; OS: overall survival.

Figure 17: A) AIC and B) BIC values of parametric OS models for the CDF patient population without a del(17p)/TP53 mutation



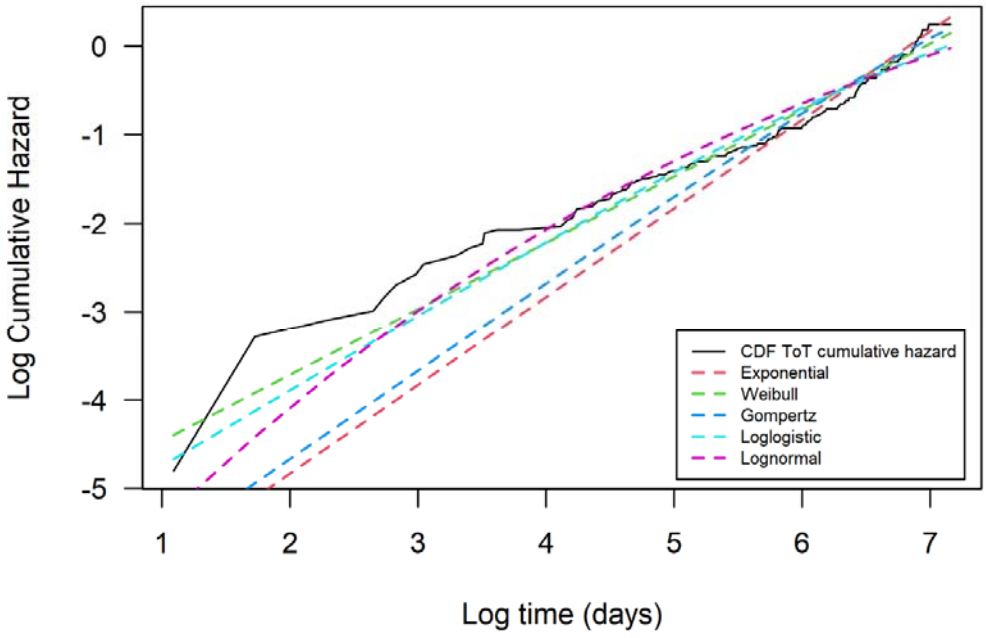
Abbreviations: AIC: Akaike's information criteria; BIC: Bayesian information criteria; CDF: cancer drugs fund; OS: overall survival.

The (broadly) linearity observed in the log cumulative hazard (Figure 15) and the observed smoothed hazard plot (Figure 16) suggests that models allowing for hazards to increase or decrease monotonically, such as the Weibull, exponential or Gompertz are an appropriate fit for the underlying data. The log-normal and log-logistic seem to replicate the observed smoothed hazard slightly better when considering the lower AIC and BIC values (Figure 17). The hazards of the Gompertz curve are decreasing at an increasing rate, which is not particularly well supported by the log cumulative hazard plot and the smoothed hazard function. The hazards of the Weibull function are decreasing at a decreasing rate over time, which appears to provide a worse fit considering the AIC and BIC values. However, considering both AIC and BIC values, the Weibull distribution seems to be the third best fitting distribution, after log-normal and log-logistic, and its deviation from the best fitting option (log-normal) in terms of both AIC and BIC values remains within 2.0 points. The 10-year OS estimates were estimated at 13.2% by the exponential, 24.0% by the Weibull, 43.3% by the Gompertz, 32.7% by the log-logistic and 36.8%

by the log-normal models. To align with the OS survival extrapolation choice for the patient population with a del(17p)/*TP53* mutation (Weibull see above) and the OS extrapolations in the original appraisal for the patient population without a del(17p)/*TP53* mutation (Weibull in original appraisal with a 10-year OS of 30%), the Weibull distribution is considered the most appropriate, but also conservative, choice when compared to the best fitting model based on AIC and BIC scores (log-normal). A clinical expert in CLL consulted by AbbVie for the CDF reappraisal agreed that the choice of Weibull was the most appropriate.[19] Therefore, combined with goodness of fit statistics and visual inspection, the Weibull curve is considered the best fitting extrapolation for OS in the CDF patient population without a del(17p)/*TP53* mutation. The impact of using other parametric fits in the model, including the log-normal which presents the lowest AIC and BIC values, is investigated in the scenario analyses.

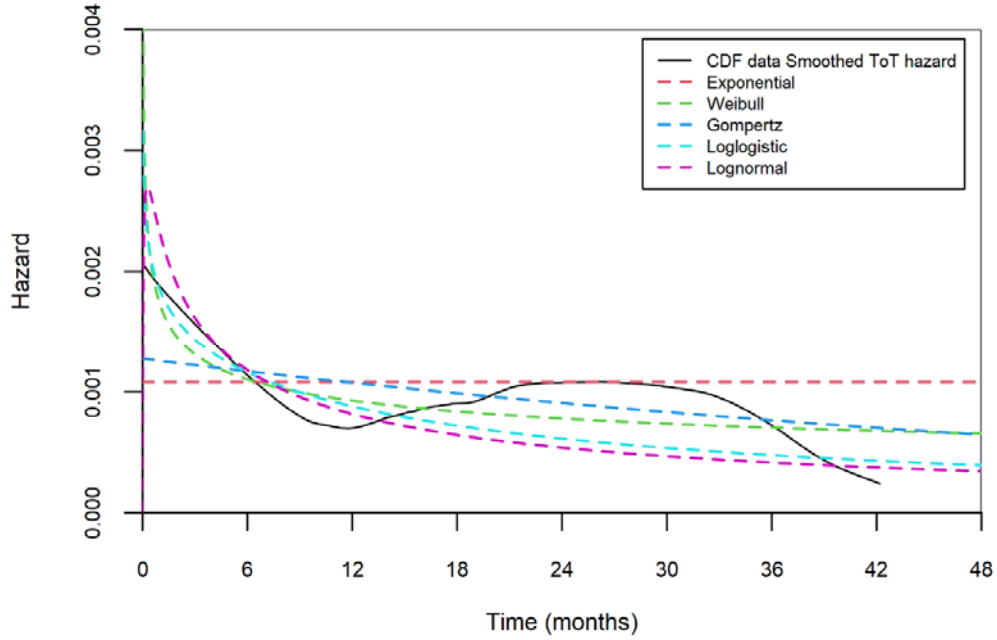
Figure 18 presents the log cumulative ToT hazard plot for the CDF patient population without a del(17p)/*TP53* mutation and Figure 19 presents the smoothed ToT hazard function over time.

Figure 18: ToT log cumulative hazard with parametric fits for patient population without a del(17p)/*TP53* mutation



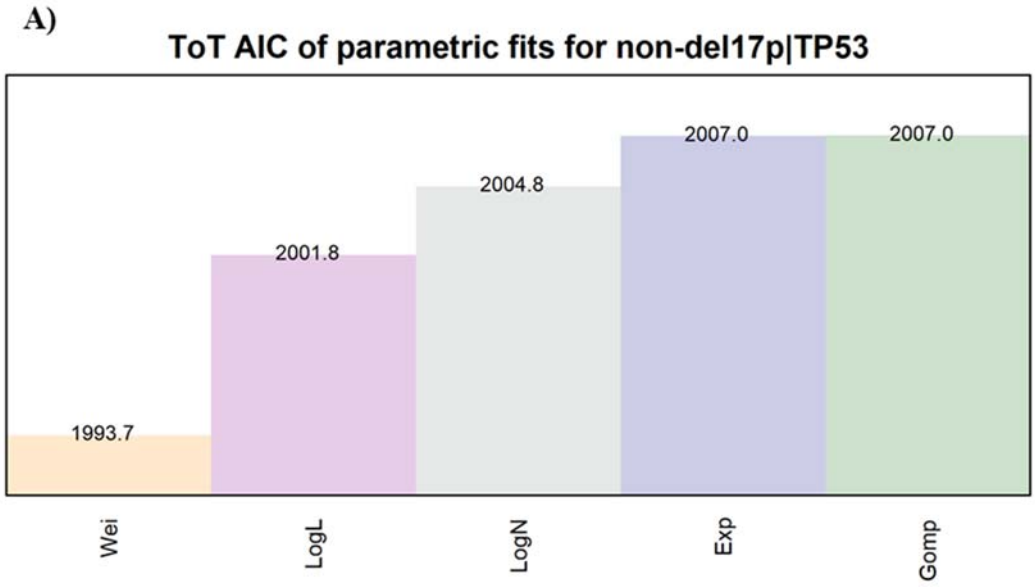
Abbreviations: CDF: cancer drugs fund; ToT: time on treatment.

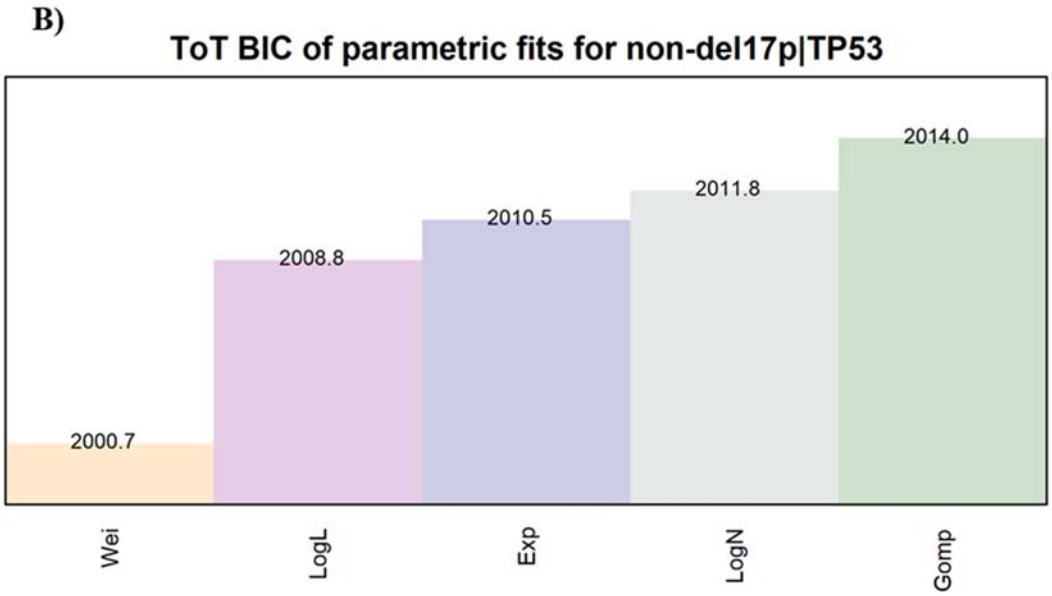
Figure 19: ToT smoothed hazard function with parametric fits for patient population without a del(17p)/*TP53* mutation



Abbreviations: CDF: cancer drugs fund; ToT: time on treatment.

Figure 20: A) AIC and B) BIC values of ToT parametric models for the CDF patient population without a del(17p)/*TP53* mutation





Abbreviations: AIC: Akaike's information criteria; BIC: Bayesian information criteria; CDF: cancer drugs fund; ToT: time on treatment.

For the base case ToT extrapolation of the patient population without del(17p)/*TP53* mutations the Weibull model was chosen as the most suitable function. The (broadly) linearity observed in the log cumulative hazard plot suggests that a proportional odds model such as the Weibull, exponential or Gompertz is an appropriate fit for the underlying data. Nonetheless, the smoothed hazard function suggests that hazards are likely to be decreasing up to about 12 months, increasing up to 24 months and decreasing from 30 months onwards (Figure 19). Although the hazards of the Weibull appear to plateau quickly towards a constant rate, which contrasts with the smoothed hazard function beyond 12 months, it is important to note that the smoothed hazard function becomes increasingly less reliable over time due to censoring. The choice of the Weibull model is further supported by the measures of statistical fit (AIC and BIC values) and the visual inspection of long-term ToT survival leads to more realistic longer term outcomes: 8% for the Weibull versus 1.9% for the exponential. Clinical expert opinion also supported the use of the Weibull extrapolation.[19]

As a reflection of the uncertainty that surrounds the optimal curve choice, all ToT extrapolation parametric models were explored in a sequence of scenario analyses.

A.9 Key model assumptions and inputs

The model is aligned with the assumptions of the model included in the previous appraisal as well as the committee's preferences at the time of entry into the CDF. Any variations or updates to this are outlined below.

Table 8: Key model assumptions and inputs

Model input and cross reference	Original parameter /assumption	Updated parameter /assumption	Source/Justification
PFS source [Section 5.3.4, page 129-140]	For the patient population with del(17p)/*TP53* mutations, OS data were pooled from trials M12-175, M13-982 and M14-032. For the patient population without del(17p)/*TP53* mutations, OS data were pooled from M12-175 and M14-032 trials	Treatment duration survival analysis in the SACT report, including data from 5th October 2017 to 4th December 2020, for the CDF cohort split by del(17p)/*TP53* mutation status	PHE did not collect data on PFS only on treatment duration. Using treatment duration to approach PFS assumes that patients remaining on venetoclax treatment are progression-free patients.
PFS extrapolation [Section 5.3.4, page 129-140]	Fully-fitted Weibull parametric curves	Fully-fitted Weibull parametric curves using the treatment duration survival analysis in the SACT report from patients of the CDF cohort with and without del(17p)/*TP53* mutations	Goodness of fit statistics and visual inspection suggests that the Weibull is the best fitting extrapolation for the SACT treatment duration data of the CDF cohort, split by del(17p)/*TP53* mutation status.
OS [Section 5.3.4, page 129-140]	For the patient population with del(17p)/*TP53* mutations, OS data were pooled from trials M12-175, M13-982 and M14-032. For the patient population without del(17p)/*TP53* mutations, OS data were pooled from M12-175 and M14-032 trials	OS SACT data collected during 5th October 2017 to 4th December 2020 for the CDF cohort split by del(17p)/*TP53* mutation status	OS for patients with and without del(17p)/*TP53* mutations were respectively extracted from the SACT report.
OS extrapolation	Fully-fitted Weibull and log-normal parametric models were used respectively for patient populations with and without del1p/*TP53* mutations	Fully-fitted Weibull parametric model based on SACT analysis of patients in the CDF cohort with and without del(17p)/*TP53* mutations	Refer to Section A.8.1. of the present document
Routine costs of care unit costs[1]			
Full blood count	£3.01	£2.53	National schedule of reference costs 2019/20: DAPS05-Haematology[22]

[Section 5.5.2.4 (page 163)]			
LDH [Section 5.5.2.4 (page 163)]	£1.19	£1.20	National schedule of reference costs 2019/20: DAPS04 – Clinical biochemistry[22]
Lymphocyte count [Section 5.5.2.4 (page 163)]	£3.01	£2.53	National schedule of reference costs 2019/20: DAPS05-Haematology[22]
Chest X-ray [Section 5.5.2.4 (page 163)]	£61.25	£84.59	National schedule of reference costs 2019/20: IMAGDA-DEXA scan[22]
Bone marrow exam [Section 5.5.2.4 (page 163)]	£497.23	£563.62	National schedule of reference costs 2019/20: SA33Z-Diagnostic Bone Marrow Extraction[22]
Haematologist visit [Section 5.5.2.4 (page 163)]	£154.05	£165.57	National schedule of reference costs 2019/20: Outpatient Attendances Data- 303- Clinical haematology[22]
Inpatient non-surgical/medical visit [Section 5.5.2.4 (page 163)]	£487.25	£679.31	NHS reference costs 2019/20[22]: Weighted average of day case SA32A, SA32B, SA32C and SA32D= £560.31 plus PSSRU 2020: Cost of medical consultant hour £119 [23]
Nurse home visit [Section 5.5.2.4 (page 163)]	£66.42	£99.30	National schedule of reference costs 2019/20: N10AF-Specialist Nursing, Cancer Related, Adult, Face to face[22]
Full blood transfusion [Section 5.5.2.4 (page 163)]	£498.75	£586.85	National schedule of reference costs 2019/20: N10AF-Specialist Nursing, Cancer Related, Adult, Face to face[22]
Platelet transfusion [Section 5.5.2.4 (page 163)]	£498.75	£586.85	National schedule of reference costs 2019/20: SA44A-Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over[22]
Costs of Adverse Events			

Abdominal pain [Section 5.5.2.2 (page 161)]	£752.10 NHS Reference Costs 2014-15: Total HRG's, weighted average of abdominal pain with interventions (FZ90A) and abdominal pain without interventions (FZ90B).	£649.11	NHS Reference Costs 2019-20: Total HRG's, weighted average of abdominal pain with interventions (FD05A) and abdominal pain without interventions (FD05B). [22]
Anaemia [Section 5.5.2.2 (page 161)]	£2,130.15 The ERG on 14th December 2016 suggested using the £2,088 (2012-2013) from Blommestein *et al* (2016) (page 108 in Appendix D of NICE committee papers document). This cost was inflated to 2014-2015 using the using the using the PSSRU HCHS index (2015).	£2,308.99	The ERG on 14th December 2016 suggested using the (2012-2013) from Blommestein *et al* (2016) [24] (page 108 in Appendix D of NICE committee papers document). The original cost of £2,088 (2012-2013) from Blommestein *et al* (2016) [24] was inflated to 2019-2020 using the using the NHS cost inflation index (NHSCII) (PSSRU 2020).[23]
Autoimmune haemolytic anaemia [Section 5.5.2.2 (page 161)]	£311.00 Zanella, A., & Barcellini, W. 2014 describe treatment as 'Corticosteroids, usually prednisone, are given at the initial dose of 1.0–1.5 mg/kg/day for 1–3 weeks until haemoglobin levels greater than 10 g/dL are reached.' Based on a body weight of 78kg and the midpoint of 1-3 weeks, the amount of prednisone required is 1228.5mg (1.5mg*78kg*10.5days). The cost of prednisone (BNF: Company evidence submission template for venetoclax in CLL 162 Lodotra 5mg modified-release tablets (Napp Pharmaceuticals Ltd)) is £89.00 for a pack of 100. Three packs, containing 1500mg in total, costs £267.00 (3*£89.00). Combined with the cost of a GP appointment lasting 11.7 minutes, including direct care staff costs and qualification costs (£44-PSSRU). The total cost is £311.00 (£267.00+ £44.00).	£386.10	Jäger, U., *et al*. (2020) [25] and Zanella *et al*. (2014)[26] describe that 'Most adult patients starting treatment should receive oral prednisone 1 mg/kg daily for 2-3 weeks'. The cost of prednisone (BNF 2021: 1.23 per unit (tablet of 5 mg)). Based on a body weight of 78kg and the midpoint of 2-3 weeks, the amount of prednisone required is 1365.0mg (1.0 mg*78kg*17.5days). Combined with the cost of a GP appointment lasting 11.7 minutes, including direct care staff costs and qualification costs (£4.30 per minute of patient contact -PSSRU Table 10.3b (General practitioner unit cost (incl. qualification costs)),[23] leads to the total cost of £386.1 (£335.79+ £50.31).
Dyspnoea	£366.25	£397.00	

[Section 5.5.2.2 (page 162)]	The ERG on 14th December 2016 suggested using the £359.0 (2012-2013) from Blommestein *et al* (2016) (page 108 in Appendix D of NICE committee papers document). This cost was inflated to 2014-2015 using the using the using the PSSRU HCHS index (2015).		The ERG on 14th December 2016 suggested using input from Blommestein *et al* (2016) [24] (page 108 in Appendix D of NICE committee papers document). The original cost of £359 (2012-2013) from Blommestein *et al* (2016) was inflated to 2019-2020 using the using the NHS cost inflation index (NHSCII) (PSSRU 2020).[23]
Fatigue [Section 5.5.2.2 (page 162)]	£389.62 NICE TA376:[158] NHS Reference Costs 2014-15; Non-Elective Short Stay- Headache, Migraine or Cerebrospinal Fluid Leak (weighted average of the 3 categories: CC score 0-6 (AA31E), CC score 7-10 (AA31D), 11+ (AA31C)	£408.61	NICE TA376, from NHS Reference Costs 2019-20; [22] Non-Elective Short Stay- Headache, Migraine or Cerebrospinal Fluid Leak (weighted average of the 3 categories: CC score 0-6 (AA31E), CC score 7-10 (AA31D), 11+ (AA31C)
Febrile Neutropenia [Section 5.5.2.2 (page 162)]	£3,972.61 The ERG on 14th December 2016 suggested using the £3,894.0 (2012-2013) from Blommestein *et al* (2016) (page 108 in Appendix D of NICE committee papers document). This cost was inflated to 2014-2015 using the using the using the PSSRU HCHS index (2015).	£4,306.13	The ERG on 14th December 2016 suggested using input from Blommestein *et al* (2016) [24] (page 108 in Appendix D of NICE committee papers document). The original cost of £3,894.0 (2012-2013) from Blommestein *et al* (2016) was inflated to 2019-2020 using the using the NHS cost inflation index (NHSCII) (PSSRU 2020).[23]
Hyperglycaemia [Section 5.5.2.2 (page 162)]	£1,173.95 NICE TA338:[160] taken from manufacturers submission, table 52, p.181. This takes a weighted average of the costs of inpatient stays (64%), day cases (20%) and outpatient visits (16%).	£1,298.20	NICE TA338 [27] – inflated to 2019-20 using the using the NHS cost inflation index (NHSCII) (PSSRU 2020).[23]
Hypertension [Section 5.5.2.2 (page 162)]	£366.25 The ERG on 14th December 2016 suggested using the £359.0 (2012-2013) from Blommestein *et al* (2016) (page 108 in Appendix D of NICE committee papers	£397.00	The ERG on 14th December 2016 suggested using input from Blommestein *et al* (2016) [24] (page 108 in Appendix D of NICE committee papers document). The original cost of £359.0 (2012-2013) from Blommestein *et al* (2016) was inflated to 2019-2020 using the using the NHS cost inflation index (NHSCII) (PSSRU 2020).[23]

	document). This cost was inflated to 2014-2015 using the using the using the PSSRU HCHS index (2015).		
Hypocalcaemia [Section 5.5.2.2 (page 162)]	£400.55 NHS reference costs 2014-15; Total HRGs: XD26Z (Intravenous Nutrition, Band 1)	£442.94	NHS Reference Costs 2014-15 [22]; Total HRG's, Intravenous Nutrition, Band 1 (XD26Z), inflated to 2019-2020 using the using the NHS cost inflation index (NHSCII) (PSSRU 2020).[23]
Hypokalaemia [Section 5.5.2.2 (page 162)]	£400.55 NHS reference costs 2014-15;Total HRGs: XD26Z (Intravenous Nutrition, Band 1)	£442.94	NICE TA377; NHS reference costs 2014-2015 [22]; Total HRGs: XD26Z (Intravenous Nutrition, Band 1), inflated to 2019-2020 using the using the NHS cost inflation index (NHSCII) (PSSRU 2020).[23]
Hyponatraemia [Section 5.5.2.2 (page 162)]	£400.55 NHS reference costs 2014-15; Total HRGs: XD26Z (Intravenous Nutrition, Band 1)	£442.94	NHS Reference Costs 2014-15 [22]; Total HRG's, Intravenous Nutrition, Band 1 (XD26Z), inflated to 2019-2020 using the using the NHS cost inflation index (NHSCII) (PSSRU 2020).[23]
Hypophosphatemia [Section 5.5.2.2 (page 162)]	£400.55 NHS reference costs 2014-15;Total HRGs: XD26Z (Intravenous Nutrition, Band 1)	£442.94	NHS Reference Costs 2014-15 [22]; Total HRG's, Intravenous Nutrition, Band 1 (XD26Z), inflated to 2019-2020 using the using the NHS cost inflation index (NHSCII) (PSSRU 2020).[23]
Leukopenia [Section 5.5.2.2 (page 162)]	£961.02 The ERG on 14th December 2016 suggested using the £942.0 (2012-2013) from Blommestein *et al* (2016) (page 108 in Appendix D of NICE committee papers document). This cost was inflated to 2014-2015 using the using the using the PSSRU HCHS index (2015).	£1,041.70	The ERG on 14th December 2016 suggested using input from Blommestein *et al* (2016) [24] (page 108 in Appendix D of NICE committee papers document). The original cost of £942.0 (2012-2013) from Blommestein *et al* (2016) was inflated to 2019-2020 using the using the NHS cost inflation index (NHSCII) (PSSRU 2020).[23]
Neutropenia [Section 5.5.2.2 (page 162)]	£3,972.61 The ERG on 14th December 2016 suggested using the £3,894.0 (2012-2013) from Blommestein *et al* (2016) (page 108 in Appendix D of NICE committee papers document). This cost was inflated to 2014-	£4,306.13	The ERG on 14th December 2016 suggested using input from Blommestein *et al* (2016) [24] (page 108 in Appendix D of NICE committee papers document). The original cost of £3,894.0 (2012-2013) from Blommestein *et al* (2016) was inflated to 2019-2020 using the using the NHS cost inflation index (NHSCII) (PSSRU 2020).[23]

	2015 using the using the using the PSSRU HCHS index (2015).		
Pneumonia [Section 5.5.2.2 (page 162)]	£1,380.61 The ERG on 14th December 2016 suggested using the £1,353.0 (2012-2013) from Blommestein *et al* (2016) (page 108 in Appendix D of NICE committee papers document). This cost was inflated to 2014-2015 using the using the using the PSSRU HCHS index (2015).	£1,496.20	The ERG on 14th December 2016 suggested using input from Blommestein *et al* (2016) [24] (page 108 in Appendix D of NICE committee papers document). The original cost of £1.353.0 (2012-2013) from Blommestein *et al* (2016) was inflated to 2019-2020 using the using the NHS cost inflation index (NHSCII) (PSSRU 2020).[23]
Thrombocytopenia [Section 5.5.2.2 (page 162)]	£1,884.29 The ERG on 14th December 2016 suggested using the £1,847.0 (2012-2013) from Blommestein *et al* (2016) (page 108 in Appendix D of NICE committee papers document). This cost was inflated to 2014-2015 using the using the using the PSSRU HCHS index (2015).	£2,042.48	The ERG on 14th December 2016 suggested using input from Blommestein *et al* (2016) [24] (page 108 in Appendix D of NICE committee papers document). The original cost of £1,847.0 (2012-2013) from Blommestein *et al* (2016) was inflated to 2019-2020 using the using the NHS cost inflation index (NHSCII) (PSSRU 2020).[23]
Laboratory TLS [Section 5.5.2.2 (page 162)]	£1,171.11 Assumes rasburicase is given to 1 out of 4 (25%) of patients at 0.2 mg / kg for 5 days (assuming average weight of 78kgs) and includes the cost of infusions for 5 days. This estimate is based on the actual treatment administered to the 4 patients who suffered from TLS in the M13-982 and M14-032 trials.	£1,232.73	Assumes rasburicase is given to 1 out of 4 (25%) of patients at 0.2 mg / kg for 5 days (assuming average weight of 78kgs) and includes the cost of infusions for 5 days. This estimate is based on the actual treatment administered to the 4 patients who suffered from TLS in the M13-982 and M14-032 trials. Cost per mg of rasburicase: £46.31 (BNF 2021; 208.39 (3 vials of 1.5mg) or £347.32 (1 vial of 7.5 mg)) [28] Infusion cost: Assumed the same as simple chemotherapy infusion: IV administration cost from NHS Reference Costs 2019-20; Chem, SB15Z: deliver subsequent elements of a chemotherapy cycle, Outpatient (£253.78) [22]One hour of pharmacist time performing patient related activities (accounting for overheads, qualifications, and salary on costs) costs £50 (PSSRU, 2020).[23] Millar *et al*. (2008) [29]

			found that the dispensing of drugs administered intravenously takes on average 12 minutes each.
Tumour lysis syndrome prophylaxis costs by risk stratification			
All risks [Section 5.5.2.3 (page 162)]	£2.215,08	£2.393,13	The distribution of patients in risk groups and recourse use across the risk groups were assumed to be the same as in the original appraisal. Unit costs were updated and inflated whenever necessary.
Terminal care costs			
Terminal care costs [Section 5.5.2.5 (page 163)]	£6.186,41	£6.653,61	The original cost of £6,186.41 (2013-2014) from Round *et al* (2015)[30] was inflated to 2019-2020 using the using the NHS cost inflation index (NHSCII) (PSSRU 2020).[23]
Administration costs IV/injection			
Rituximab/HDMP [Section 5.5.2.1 (page 159)]	£214.47	£233.0	IV administration cost from NHS Reference Costs 2018-19; [22]Total HRGs, SB15Z: deliver subsequent elements of a chemotherapy cycle, Outpatient One hour of pharmacist time performing patient related activities (accounting for overheads, qualifications, and salary on costs) costs £50 (PSSRU, 2020).[23] Millar *et al*. (2008) [29] found that the dispensing of drugs administered intravenously takes on average 12 minutes each.
Background Mortality			
Office for National Statistics. National Life Tables: United Kingdom (2012-2014). 2015 [Section 5.3.5 (page 146)]		Source: Office for National Statistics. National Life Tables: England and Wales national life tables 2017-2019, Available at: http://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables	

[1]Note that the resource use for the routine care and monitoring costs was not changed. The inputs remained the same as in the original appraisal (Table 69, page 163, Section 5.5.2.4] and sourced from National Institute of Health and Care Excellence. Leukaemia (chronic lymphocytic) – ibrutinib [ID749], STA in progress. 2016; Available from: https://www.nice.org.uk/guidance/indevelopment/gid-tag492.

Abbreviations: BNF: British National Formulary; CDF: cancer drugs fund; ERG: Evidence Review Group; GP: general practioner; HDMP: high-dose methyl-prednisolone; HRG: health resource group; HCHS: Hospital and community health services; IV: intravenous; LDH: lactose dehydrogenase; NHSCII: National Health Service cost inflation index; OS: overall survival; PFS: progression-free survival; PHE: Public Health England; PSSRU: personal social services research unit; SACT: Systemic Anti-Cancer Therapy.

A.10 Cost-effectiveness results (deterministic)

Deterministic cost-effectiveness results at venetoclax PAS price are presented in Table 9; results at venetoclax list price are presented separately in Appendix C.

1. **Replication of the key cost-effectiveness result(s) considered by the committee to demonstrate plausible potential for cost-effectiveness at entry to the CDF**.

In the FAD of the venetoclax monotherapy treatment, the final base case analysis for adults with a del(17p)/*TP53* mutation, whose disease has progressed after a B-cell receptor pathway inhibitor or for whom a B-cell receptor pathway inhibitor is unsuitable, the deterministic ICER for venetoclax at PAS price compared with BSC was £39,940 per QALY gained and at list price was [redacted] per QALY gained. For adults without a del(17p)/*TP53* mutation, and whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor, the deterministic ICER for venetoclax at PAS price compared with BSC was £47,370 per QALY gained and at list price was [redacted] per QALY gained.

2. **Cost-effectiveness results that incorporate the data collected during the CDF data collection period, with all model inputs and parameters unchanged from the cost-effectiveness analysis in point one above.**

The cost-effectiveness results that incorporate only updates on OS and ToT survival data, as these were produced by fitted the survival data of the SACT report for the CDF cohort, at venetoclax PAS price were £42,259 and £48,225 per QALY gained for the patient populations with and without a del17p/*TP53* mutation, respectively. At venetoclax list price, the ICERs were [redacted] and [redacted] per QALY gained for the patient populations with and without a del17p/*TP53* mutation, respectively.

3. **Cost-effectiveness results that incorporate data collected during the CDF data collection period plus any associated changes to the company's preferred assumptions.**

The cost-effectiveness results based on updated survival data from the CDF cohort, cost parameters and life tables as indicated in previous section (Table 8), at venetoclax PAS price were estimated at £43,201 and £49,104 per QALY gained for the patient populations with and without a del17p/*TP53* mutation, respectively. This forms the new base case analysis of the company for the resubmission. The results using venetoclax list price were estimated at [redacted] and [redacted] per QALY gained for the patient populations with and without a del17p/*TP53* mutation, respectively.

Table 9: Cost effectiveness results at venetoclax PAS price (deterministic)

Technologies	Total costs (£)	Total LYG (undiscounted)	Total QALYs	Incremental. Costs (£)	Incremental LYG (Discounted)	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Cost-effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry								
Patient population with a del(17p)/*TP53* mutation								
Venetoclax	[redacted]	4.620	[redacted]	[redacted]	3.192	[redacted]		£39,940
BSC	[redacted]	0.950	0.627	-	-	-	-	-
Patient population without a del(17p)/*TP53* mutation								
Venetoclax	[redacted]	6.848	[redacted]	[redacted]	4.090	[redacted]		£47,370
BSC	[redacted]	1.797	1.160	-	-	-	-	-
Cost-effectiveness analysis 2: Analysis that demonstrated plausible potential for cost-effectiveness at CDF entry – incorporating updated clinical evidence								
Del(17p)/*TP53* positive patient population	[redacted]	4.456	[redacted]	[redacted]	2.901	[redacted]		£42,259
Non- Del(17p)/*TP53* positive patient population	[redacted]	5.538	[redacted]	[redacted]	2.958	[redacted]		£48,225
Cost-effectiveness analysis 3: New company base case								
Patient population with a del(17p)/*TP53* mutation								
Venetoclax	[redacted]	4.466	[redacted]	[redacted]	2.908	[redacted]		£43,201
BSC	[redacted]	0.950	0.627	-	-	-		-
Patient population without a del(17p)/*TP53* mutation								
Venetoclax	[redacted]	5.558	[redacted]	[redacted]	2.972	[redacted]		£49,104
BSC	[redacted]	1.797	1.160	-	-	-		-

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

A.11 Probabilistic sensitivity analysis

Figure 21 and Figure 22 below present the cost-effectiveness plane plotting incremental costs at PAS price and QALYs for 1,000 probabilistic simulations for the patient populations with and without del17p/*TP53* mutations, respectively. The average total costs and QALYs (including confidence intervals) for the probabilistic simulations at venetoclax PAS price are presented in Table 10. The average ICER at venetoclax PAS price following the probabilistic simulations is £44,652/QALY gained vs BSC for the patient population with a del(17p)/*TP53* mutation and £50,996/QALY gained for the patient population without a del(17p)/*TP53* mutation. The average ICER at venetoclax list price following the probabilistic simulations is [redacted]/QALY gained vs BSC for the patient population with a del(17p)/*TP53* mutation and [redacted]/QALY gained for the patient population without a del(17p)/*TP53* mutation; list price results are presented in full in Appendix C.

Table 10: Updated base case results at venetoclax PAS price (probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
Patient population with del(17p)/*TP53* mutation					
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	£44,652 (£31,207, £62,909)
BSC	[redacted]	0.638 (0.517, 0.809)	-	-	-
Patient population without del(17p)/*TP53* mutation					
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	£50,966 (£36,894, £72,846)
BSC	[redacted]	1.178 (0.974, 1.482)	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure 21: Scatterplot of probabilistic results for the patient population with a del(17p)/*TP53* mutation at venetoclax PAS price

Abbreviations: BSC: best supportive care; PAS: patient access scheme.

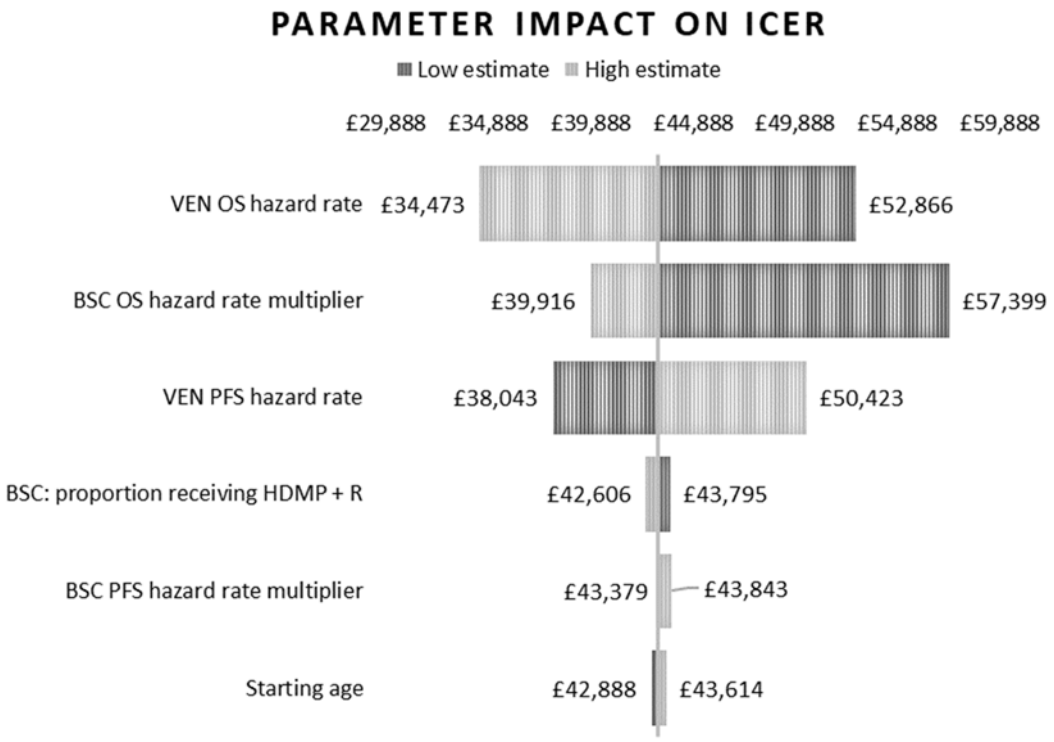
Figure 22: Scatterplot of probabilistic results for the patient population without a del(17p)/*TP53* mutation at venetoclax PAS price

Abbreviations: BSC: best supportive care; PAS: patient access scheme.

A.12 Key sensitivity and scenario analyses

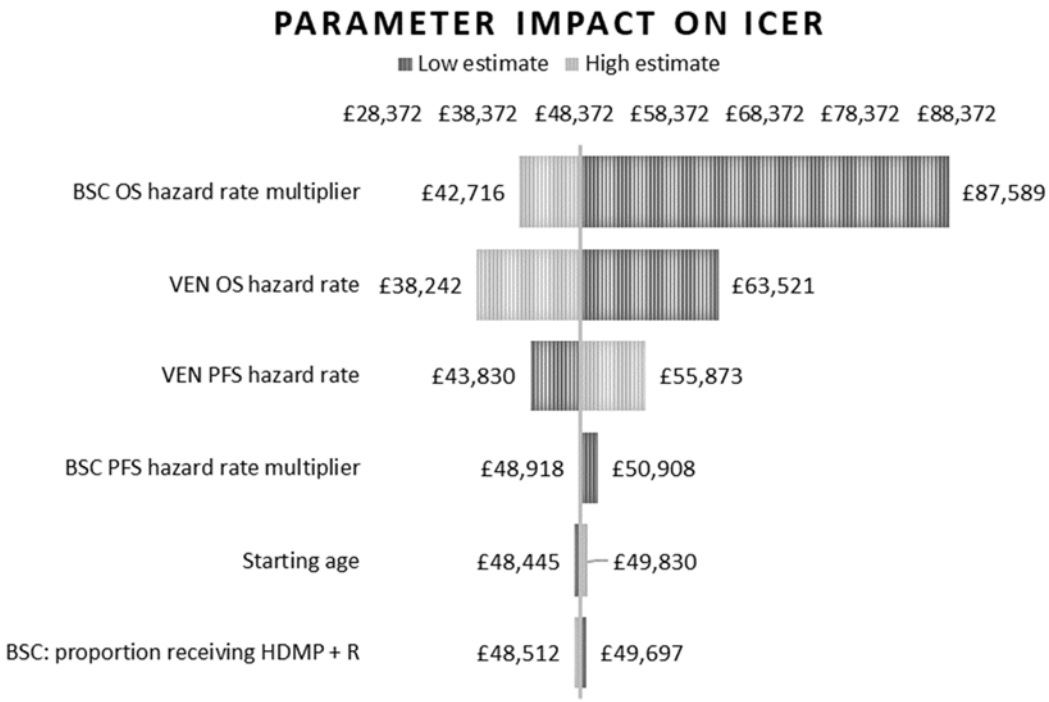
Figure 23 and Figure 24 present the ICER tornado plots for venetoclax compared with BSC for the patient populations with and without a del(17p)/*TP53* mutation, respectively. The main drivers are a combination of the key drivers behind incremental costs and incremental QALYs: venetoclax OS and PFS hazard rates (approached by ToT survival curves of the CDF cohort; see section A.8 and A.9), and the BSC OS hazard rate multiplier. Since the PFS of venetoclax plays such a large role in determining its active treatment costs, it is unsurprising that the venetoclax PFS HR is one of the most important parameters determining incremental costs. The largest driver of incremental QALYs for the patient population with a del(17p)/*TP53* mutation is the venetoclax OS hazard rate as this parameter determines the life years gained by venetoclax patients in the model which subsequently affects QALYs. The largest driver of incremental QALYs for the patient population without a del(17p)/*TP53* mutation is the BSC OS hazard rate multiplier as this parameter determines the life years gained by BSC patients in the model which subsequently affects QALYs. Beyond the top three drivers, the ICER remains reasonably stable in response to changes in other model parameters.

Figure 23: Tornado diagram – patient population with a del(17p)/*TP53* mutation



Abbreviations: BSC: best supportive care; HDMP: high-dose methylprednisolone; ICER: incremental cost-effectiveness ratio; OS: overall survival; PFS: progression-free survival: R: rituximab; VEN: venetoclax.

Figure 24: Tornado diagram – patient population without a del(17p)/*TP53* mutation



Abbreviations: BSC: best supportive care; HDMP: high-dose methylprednisolone; ICER: incremental cost-effectiveness ratio; OS: overall survival; PFS: progression-free survival: R: rituximab; VEN: venetoclax.

A set of exploratory scenario analyses providing insight into model parameters and their relationship with key model outcomes is presented in Table 11 below separate for both populations.

Table 11: Key scenario analyses using venetoclax PAS price

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base case ICER
Base case: patients with a del(17p)/*TP53* mutation			£43,201
Uncertainty in OS Extrapolations			
OS log-normal	Uncertainty in OS extrapolations	Alternative parametric fits for OS curves considering the uncertainty over time due to censoring.	£36,134
OS log-logistic			£37,379
OS Gompertz			£29,314
OS Exponential			£54,708
Uncertainty in ToT Extrapolations			
ToT log-normal	Uncertainty in ToT survival extrapolations	Alternative parametric fits for ToT curves considering the uncertainty over time due to censoring.	£54,791
ToT log-logistic			£54,038
ToT Gompertz			£53,743
ToT Exponential			£34,225
Base case: patients without a del(17p)/*TP53* mutation			£49,104
Uncertainty in OS Extrapolations			

OS log-normal	Uncertainty in OS extrapolations	Alternative parametric fits for OS curves considering the uncertainty over time due to censoring.	£39,755
OS log-logistic			£42,307
OS Gompertz			£36,049
OS Exponential			£61,239
Uncertainty in ToT Extrapolations			
ToT log-normal	Uncertainty in ToT survival extrapolations	Alternative parametric fits for ToT curves considering the uncertainty over time due to censoring.	£63,100
ToT log-logistic			£61,553
ToT Gompertz			£51,960
ToT Exponential			£41,203

Abbreviations: ICER: incremental cost-effectiveness ratio; OS: overall survival; PAS: patient access scheme; ToT: time on treatment.

A.13 End-of-life criteria

The committee concluded during the appraisal of TA487 that venetoclax met both end-of-life criteria.

A.14 Key issues and conclusions based on the data collected during the CDF review period

The SACT CDF cohort represents the key data collected during the CDF review period and informs the update to the economic model. At final follow up, venetoclax was associated with a median OS of 33 months in patients with a del(17p)/*TP53* mutation and had not been reached in patients without a del(17p)/*TP53* mutation. Median treatment duration for venetoclax was 17.9 months in patients with a del(17p)/*TP53* mutation and 22.3 months in patients without a del(17p)/*TP53* mutation.

The baseline characteristics of patients included in the SACT CDF dataset represent patients with a higher mean age compared with those in the venetoclax trials – more closely aligned to the average age of patients with CLL at diagnosis in UK clinical practice (71 years) – as well as patients with a trend towards more advanced disease, as based on ECOG status scores. The data from SACT therefore address the committee's original uncertainty surrounding the generalisability of the data from venetoclax clinical trials, by providing an alternative source of efficacy in a population of direct relevance to those who would receive venetoclax in the NHS.

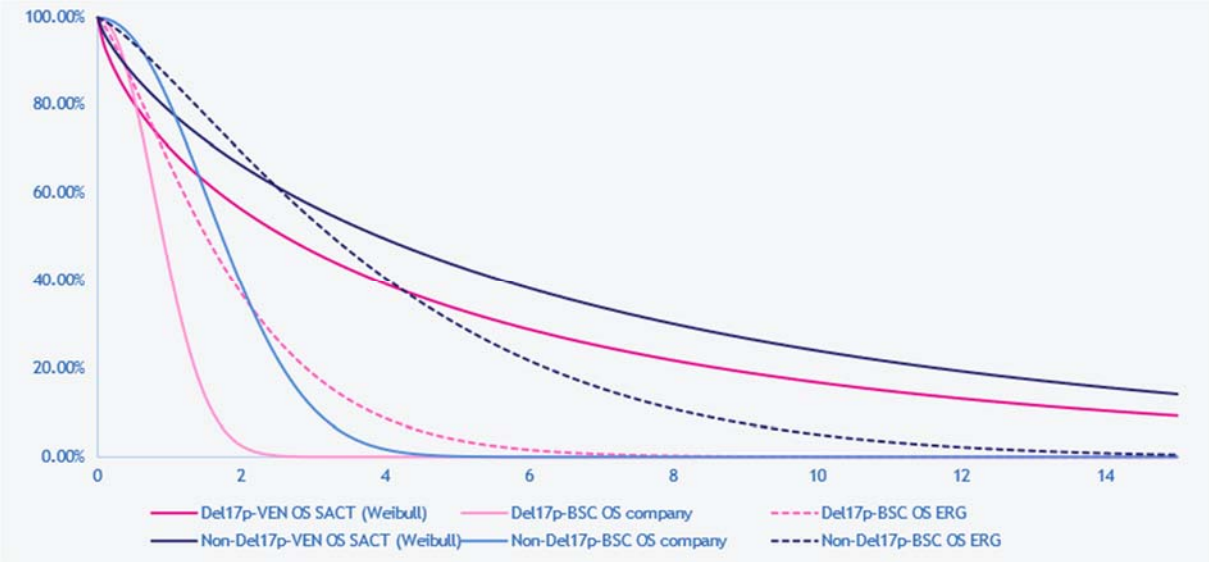
Updated data on BSC were not provided in the SACT report, due to the under reporting of haematological malignancies in the SACT CDF dataset at the time the BSC treatment option was available (i.e. prior to the availability of venetoclax monotherapy). Furthermore, PHE conducted a feasibility assessment of the SACT CDF dataset that determined that a matched cohort analysis would not provide meaningful analyses. These analyses were therefore not produced and, as such, there remains a lack of comparative data in a population matched to that of the venetoclax trials or the SACT CDF cohort.

In the original appraisal, there was uncertainty associated with both the Company's and ERG's preferred source of data for modelling BSC. Both estimates considered the 116 trial, a phase 3 study comparing rituximab plus idelalisib with rituximab plus placebo, with the Company utilising the rituximab arm data and the ERG utilising the idelalisib arm data. Overall, the committee concluded that they preferred the ERG's approach of comparing venetoclax data with that of the idelalisib arm due to closer similarities between those patients and the patients included in the venetoclax trials.[1] However, modelling based on data from the idelalisib arm estimated that post-

progression survival was significantly longer than progression-free survival (4.02 years versus 1.62 years). The committee heard from UK clinical experts that post-progression survival of four years did not reflect clinical practice in the UK, with broad agreement from stakeholders that survival would be considerably shorter than this;[1] the committee also agreed that patients in this indication met the end-of-life criterion of having a life expectancy of <24 months, further contradicting the ERG's BSC estimate. Real-world evidence data published by the UK CLL forum additionally suggests that median survival after stopping ibrutinib treatment within the first year is 95 days;[31] a post-progression survival of four years following treatment with idelalisib or ibrutinib is therefore greatly overestimated compared with observed clinical practice.

Considering the updated data source of venetoclax for this appraisal, the modelled venetoclax patients now more closely align with clinical opinion around the population who would receive venetoclax in UK clinical practice (i.e. older and with more advanced disease), and more closely align with the rituximab arm than previously (where the committee previously considered the patients in the rituximab arm to have more advanced disease than those in the venetoclax trials). Estimates for BSC should also be aligned to clinical opinion. Post-progression survival in the rituximab arm of the 116 trial (0.51 years) is more similar to both clinical opinion and real-world evidence data with estimates from the idelalisib arm lacking face validity.[1, 5] Additionally, a comparison of the two sources of BSC data with the latest data for venetoclax from SACT further highlights the lack of appropriateness of the idelalisib arm, with the ERG's previously preferred curves demonstrating unrealistically higher survival rates for patients across years 1–3 in patients without a del(17p)/*TP53* mutation (Figure 25). Based on both the face validity of the data, and the closer alignment of population with the SACT cohort, the rituximab arm has therefore been used to inform BSC data for this submission. In the original appraisal, the committee stated that based on comparison to the rituximab arm of the 116 trial, venetoclax had "plausible potential" to be cost-effective.

Figure 25: Comparison of OS from updated venetoclax SACT data (base case extrapolation) and the different sources of BSC data from the 116 trial



Abbreviations: BSC: best supportive care; ERG: Evidence Review Group; OS: overall survival; SACT: systemic anti-cancer therapy; VEN: venetoclax.

The results of the updated economic analysis found that greater LY and QALY gains were observed for venetoclax (with del(17p)/*TP53* mutation: 4.466 and [redacted]; without del(17p)/*TP53* mutation: 5.558 and [redacted]) compared with BSC (with del(17p)/*TP53* mutation: 0.950 and 0.627;

without del(17p)/*TP53* mutation: 1.797 and 1.160). These results indicate that venetoclax provides greater clinical benefit for patients both with and without a del(17p)/*TP53* mutation.

Based on the agreed PAS price of venetoclax, the base case analysis produced an ICER for venetoclax of £43,201 per QALY gained compared with BSC in patients with del(17p)/*TP53* mutation and £49,104 in patients without a del(17p)/*TP53* mutation. These results indicate that venetoclax represents a cost-effective treatment option at a threshold of £50,000 per QALY gained. Given that this analysis uses RWE for venetoclax, but clinical trial data – which have been shown to commonly report improved outcomes compared with RWE – for BSC, this comparison likely overestimates the survival rates in the BSC arm; even using the more clinically plausible rituximab arm of the 116 trial, the extrapolated OS curves for BSC still fall higher than venetoclax for the first two years of treatment (Figure 25).[32] Considering this overestimation of survival in the BSC arm, the cost-effectiveness results in this submission represent a conservative estimate of the true cost-effectiveness of venetoclax.

Venetoclax monotherapy should be maintained as a treatment option for CLL patients both with and without a del(17p)/*TP53* mutation. Clinical experts have indicated to AbbVie that, particularly as cycling through available therapies is the best option for CLL patients, removal of venetoclax monotherapy from the treatment landscape would remove a vital component of the CLL treatment armamentarium. Based on the substantial survival improvements venetoclax offers patients with CLL and the conservative cost-effective ICERs presented within this submission, venetoclax monotherapy should be considered for recommendation.

A.15 References

1. National Institute for Health and Care Excellence. Venetoclax for treating chronic lymphocytic leukaemia; Final appraisal determination. 2017 Available at https://www.nice.org.uk/guidance/ta487/documents/final-appraisal-determination-document. Accessed on: 22-Oct-2021.
2. Davids MS, Roberts AW, Seymour JF, et al. Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma. J Clin Oncol 2017;35:826-833.
3. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax for Patients With Chronic Lymphocytic Leukemia With 17p Deletion: Results From the Full Population of a Phase II Pivotal Trial. J Clin Oncol 2018;36:1973-1980.
4. Jones JA, Mato AR, Wierda WG, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. The Lancet Oncology 2018;19:65-75.
5. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia. N Engl J Med 2014;370:997-1007.
6. Hanada M, Delia D, Aiello A, et al. Bcl-2 gene hypomethylation and high-level expression in B-cell chronic lymphocytic leukemia. Blood 1993;82:1820-8.
7. Souers AJ, Leverson JD, Boghaert ER, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. Nat Med 2013;19:202-8.
8. Yip KW, Reed JC. Bcl-2 family proteins and cancer. Oncogene 2008;27:6398-406.
9. Anderson MA, Tam CCS, Seymour JF, et al. Selective Bcl-2 Inhibition With ABT-199 Is Highly Active Against Chronic Lymphocytic Leukemia (CLL) Irrespective Of TP53 Mutation Or Dysfunction. Blood 2013;122:1304.
10. European Medicines Agency. Summary of Product Characteristics: Venclyxto. Available at: https://www.ema.europa.eu/en/documents/product-information/venclyxto-epar-product-information_en.pdf. Accessed on: 06-Sept-2021.
11. European Medicines Agency. Venclyxto. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/venclyxto. Accessed on: 13-Oct-2021
12. National Institute for Health and Care Excellence. Technology appraisal guidance: Venetoclax for treating chronic lymphocytic leukaemia [TA487]. 2017. Available at https://www.nice.org.uk/guidance/ta487. Accessed on: 12-Oct-2021
13. Public Health England (PHE). Venetoclax for treating chronic lymphocytic leukaemia – data review, 2021.
14. National Institute for Health and Care Excellence. Venetoclax for treating chronic lymphocytic leukaemia: Committee papers. 2017. Available at: https://www.nice.org.uk/guidance/ta487/documents/committee-papers. Accessed on: 23-Nov-2021.
15. Ankit R. WebPlotDigitizer v4.4. 2020. Volume 2021, 2020.
16. Guyot P, Ades A, Ouwens MJ, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med. Res. Methodol. 2012;12:1-13.
17. National Institute of Health and Care Excellence Decision Support Unit (NICE). TSD 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data (last updated March 2013). Volume 2016, 2013.
18. Hess K, Gentleman R. Muhaz: hazard function estimation in survival analysis. R package version 1.2. 6, 2014.
19. AbbVie Data on File. Clinical expert opinion: October 2021.
20. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax–Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. New England Journal of Medicine 2018;378:1107-1120.
21. Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2020;21:1188-1200.
22. Department of Health. NHS Reference Costs 2014-2015: Direct Access Pathology Services. Available at: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015. Accessed on: 13-Jul-2021. Volume 2021, 2016.

23. A. CLB. Unit Costs of Health and Social Care 2020, Personal Social Services Research Unit (PSSRU), University of Kent, Canterbury. Available at: https://kar.kent.ac.uk/id/eprint/84818. Accessed on: 13-Jul-2021. Volume 2021, 2020.
24. Blommestein HM, de Groot S, Aarts MJ, et al. Cost-effectiveness of obinutuzumab for chronic lymphocytic leukaemia in The Netherlands. Leukemia research 2016;50:37-45.
25. Jäger U, Barcellini W, Broome CM, et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the First International Consensus Meeting. Blood Rev. 2020;41:100648.
26. Zanella AB, W. Treatment of autoimmune hemolytic anemias Haematologica. Volume 99: Haematologica, 2014.
27. National Institute for Health and Care Excellence. Technology appraisal guidance: Pomalidomide for treating relapsed and refractory multiple myeloma previously treated with both lenalidomide and bortezomib [TA338]. March 2015. Available at https://www.nice.org.uk/guidance/ta427/resources/pomalidomide-for-multiple-myeloma-previously-treated-with-lenalidomide-and-bortezomib-pdf-82604668730821. Accessed on: 12-Oct-2021.
28. British National Formulary (BNF). Available at: https://bnf.nice.org.uk/. Accessed on: 15-Oct-2021.
29. Millar D, Corrie P, Hill M, et al. PCN74 A service evaluation to compare secondary care resource use between Xelox and Folfox-6 regimens in the treatment of metastatic colorectal cancer (MCRC) from a UK National Health Service (NHS) perspective. Value in Health 2008;6:A483.
30. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: a modelling study. Palliative medicine 2015;29:899-907.
31. UK CLL Forum. Ibrutinib for relapsed/refractory chronic lymphocytic leukemia: a UK and Ireland analysis of outcomes in 315 patients. Haematologica 2016;101:1563-1572.
32. Boyle JM, Hegarty G, Frampton C, et al. Real-world outcomes associated with new cancer medicines approved by the Food and Drug Administration and European Medicines Agency: A retrospective cohort study. European Journal of Cancer 2021;155:136-144.

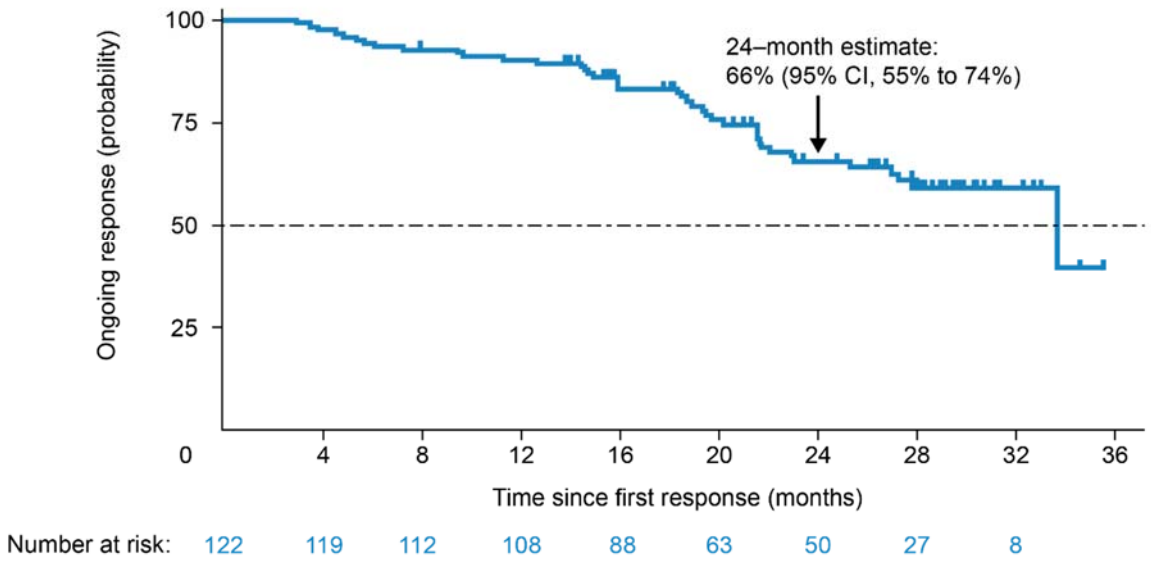
Appendix A Updated venetoclax trial data

A.1 M13-982

As of 4th April 2017, the median time on venetoclax in the M13-982 study was 23.1 months (range: 0–44.2 months) and median time on study was 26.6 months (0–44.2 months). 122 of 158 patients (77%) had an investigator-assessed overall response with median time to first response at 1 month (range: 0.5–4.4 months).[4]

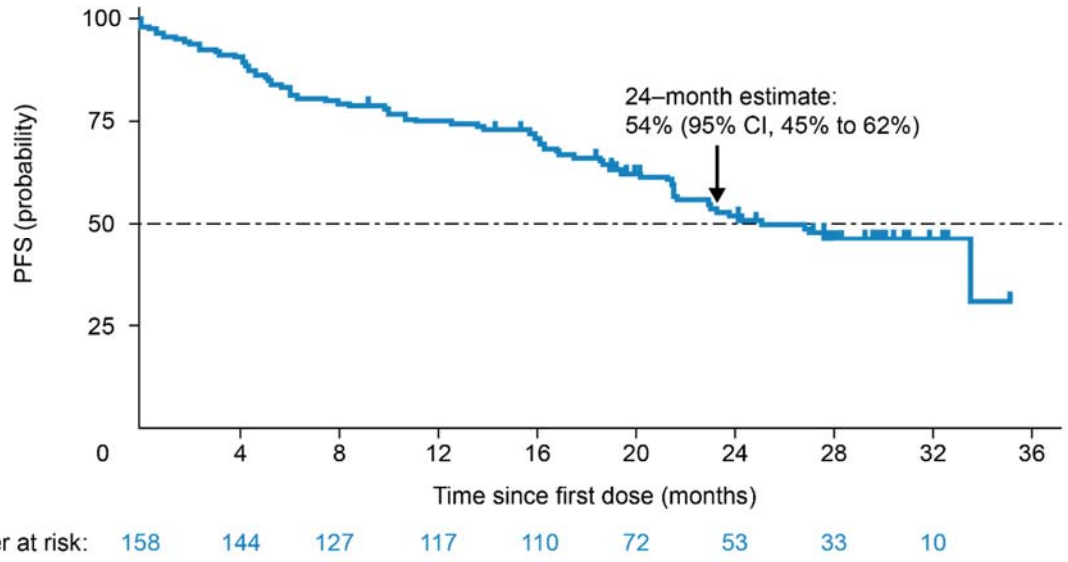
For patients who achieved a response, the Kaplan–Meier duration-of-response estimate at 24 months was 66% (95% CI: 55% – 74%), with an estimated median DOR of 33.2 months (95% CI: 26.7 months – not reached; Figure 26). For all patients, 24-month estimates of PFS and OS were 54% (95% CI: 45% – 62%) and 73% (95% C:, 65% – 79%), respectively (Figure 27 and Figure 28) Estimated median PFS was 27.2 months (95% CI, 21.9 months – not reached; Figure 27), median OS was not yet available. [4]

Figure 26: Kaplan–Meier duration-of-response estimates for patients receiving venetoclax in the M13-982 trial



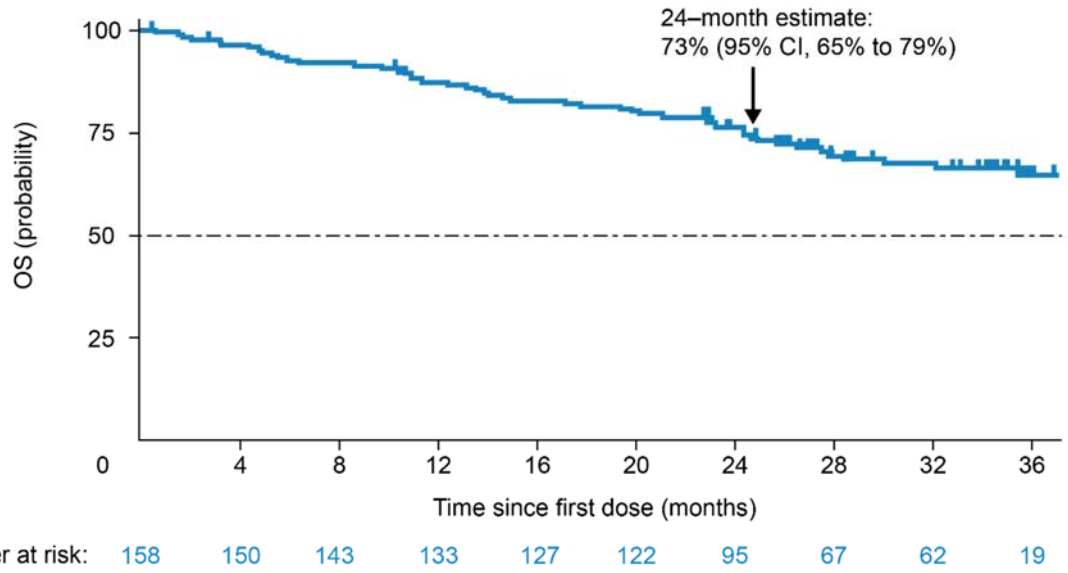
Source: Jones *et al* (2018). [4]

Figure 27: Kaplan–Meier PFS estimates for patients receiving venetoclax in the M13-982 trial



Abbreviations: PFS: progression-free survival.
Source: Jones *et al* (2018). [4]

Figure 28: Kaplan–Meier OS estimates for patients receiving venetoclax in the M13-982 trial



Abbreviations: OS: overall survival.
Source: Jones *et al* (2018). [4]

A.2 M14-032

As of 30th June 2017, the median follow-up in the M14-032 trial was 14 months (IQR: 8–18) for all 91 patients, 19 months (IQR: 9–27) for the main cohort, and 12 months (IQR: 8–15) for the expansion cohort. 59 of 91 patients (65%, 95% CI: 53, 74) had an investigator-assessed overall

response; 30 (70%, 95% CI: 54, 83) of 43 patients in the main cohort and 29 (60%,95% CI: 43, 72) of 48 patients in the expansion cohort. Details of the responses achieved by patients in the main cohort and expansion cohort are shown in Table 12. Median follow-up to first response was 2.5 months (IQR: 1.6 – 2.6) and median follow-up to best response was 7.9 months (IQR: 5.3 – 8.1).[3]

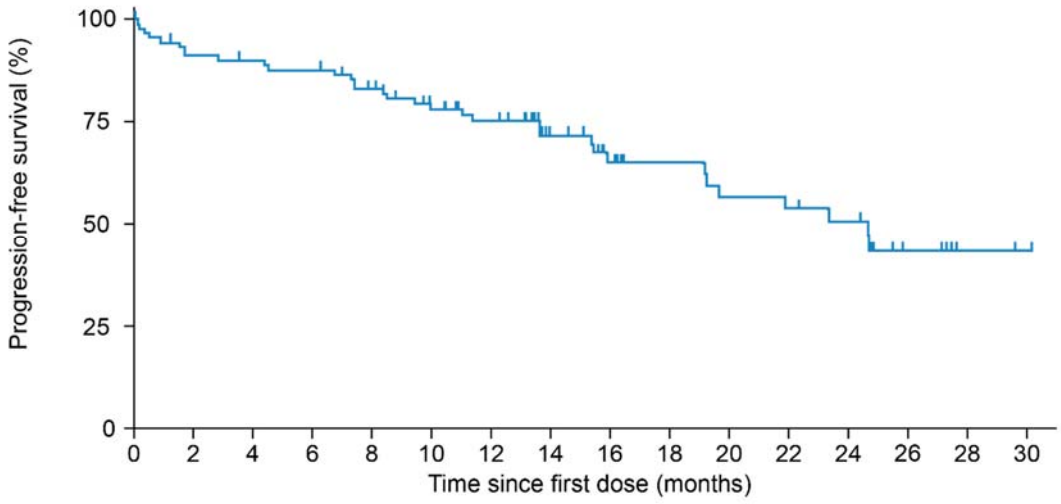
Table 12: Response with venetoclax monotherapy as assessed by the investigator

	Main cohort (n=43)	Expansion cohort (n=48)	All patients (n=91)
Overall response n (%; 95% CI)	30 (70; 54, 83)	29 (60; 43, 72)	59 (65; 53, 74)
Complete response complete response with incomplete bone marrow recovery; n (%)	4 (9)	4 (8)	8 (9)
Nodular partial response; n (%)	2 (5)	1 (2)	3 (3)
Partial response; n (%)	24 (56)	24 (48)	48 (52)
Stable disease; n (%)	8 (19)	14 (29)	22 (24)
Disease progression; n (%)	1[a] (2)	4[a] (8)	5 (5)
Discontinued before response assessment; n (%)	4 (9)	2 (4)	6 (7)

[a] Patients who discontinued because of progression.
Source: Stilgenbauer *et al* (2018). [3]

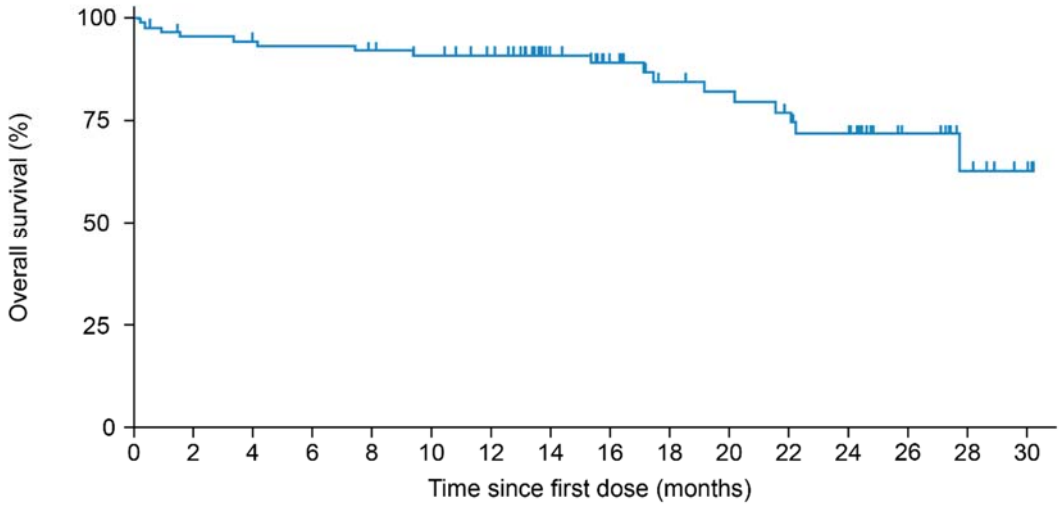
At DCO, 26 patients had experienced a disease progression event. Investigator-assessed median time to progression for all patients was 24. 7 months (95% CI: 19. 6, not reached); an estimated 80% (95% CI: 69, 87) of patients had not progressed at 12 months. 33 patients had a progression-free survival event (disease progression or death) at DCO. Median PFS was 24.7 months (95% CI 19. 2, not reached) and estimated 12-month PFS was 75% (64–83; Figure 29). Median OS was not reached (27. 8 – not reached) and estimated 12-month OS was 91% (95% CI: 83, 95; Figure 30). 15 patients had a duration-of-response event (recurrence or disease progression). In the 59 responding patients, median duration of response was not reached (95% CI: 17. 6, not reached), and an estimated 88% (95% CI: 76, 95) of patients were still responding at 12 months (Figure 31). [3]

Figure 29: Kaplan–Meier PFS estimates for patients receiving venetoclax in the M14-032 trial



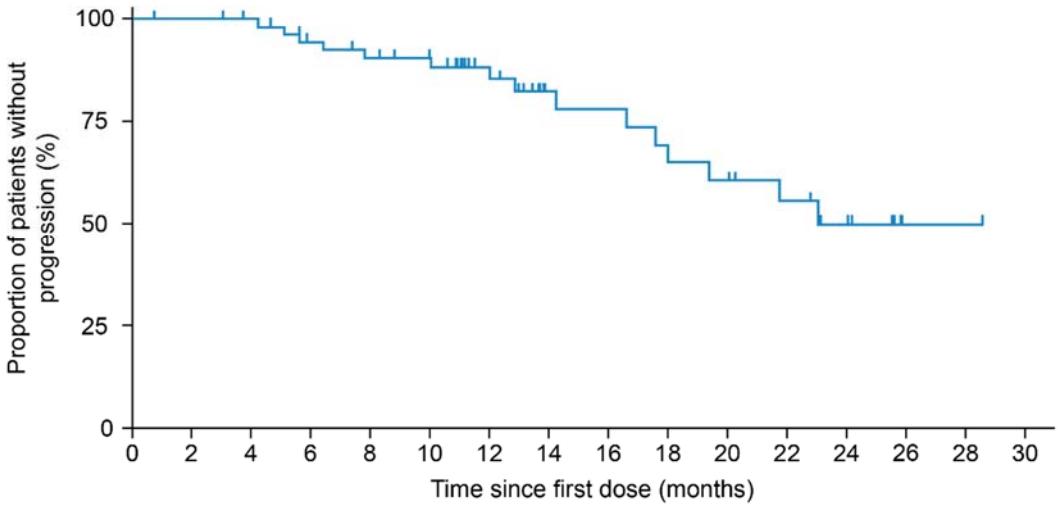
Abbreviations: PFS: progression-free survival.
Source: Stilgenbauer *et al* (2018).[3]

Figure 30: Kaplan–Meier OS estimates for patients receiving venetoclax in the M14-032 trial



Abbreviations: OS: overall survival.
Source: Stilgenbauer *et al* (2018).[3]

Figure 31: Kaplan–Meier duration-of-response estimates for patients receiving venetoclax in the M14-032 trial



Number at risk:	59	57	55	49	45	42	30	19	18	16	14	11	8	2	2	2
(number censored)	(0)	(1)	(3)	(6)	(8)	(11)	(22)	(31)	(31)	(31)	(31)	(33)	(36)	(42)	(0)	(0)

Source: Stilgenbauer *et al* (2018).[3]

Appendix B Additional data collection results (SACT CDF dataset)

B.1 Treatment Duration

Treatment status and treatment outcomes for patients, in both mutation groups, that received venetoclax in the full SACT CDF cohort are presented in Table 13. Table 14 and Table 15 show the number of patients at risk, the number of patients that were censored and the number of patients that had ended treatment (events) from the time patients started treatment to the end of the follow-up period

Table 13: Treatment outcomes and treatment status for patients that have ended treatment (n=220)

Outcome	Patient died not on treatment	Treatment stopped	Patient died on treatment
Stopped treatment – progression of disease	36	17	-
Stopped treatment – acute toxicity	11	9	-
Stopped treatment – patient choice	8	8	-
Stopped treatment – died not on treatment	74	-	-
Stopped treatment – died on treatment	-	-	24
Stopped treatment – completed as prescribed	4	2	-
Stopped treatment – no treatment in at least 3 months	-	27	-
Total	**133**	**63**	**24**

Source: Public Health England SACT Data Review. [13]

Table 14: Number of SACT patients at risk, by mutation status and quarterly breakpoints

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Number at risk Absence of del(17p)/*TP53* mutation	245	204	177	158	134	120	108	85	71	53	33	22	12	3	1
Number at risk Presence of del(17p)/*TP53* mutation	161	127	105	90	73	61	56	49	43	27	14	8	6	2	0

Source: Public Health England SACT Data Review. [13]

Table 15: Number of patients at risk, by quarterly breakpoints and mutation status, split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Patients without a del(17p)/*TP53* mutation															
Censored	117	116	107	96	83	76	72	61	53	42	25	19	12	3	1
Events	128	88	70	62	51	44	36	24	18	11	8	3	0	0	0
Patients with a del(17p)/*TP53* mutation															
Censored	69	69	64	55	47	42	39	35	32	21	11	7	5	1	0
Events	92	58	41	35	26	19	17	14	11	6	3	1	1	1	0

Source: Public Health England SACT Data Review. [13]

B.2 Overall Survival

Table 16, Table 17 and Table 18 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 44.9 months (1366 days). All patients were traced on 2nd July 2021.

Table 16: Number of SACT patients at risk, by mutation status and quarterly breakpoints

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Number at risk Absence of del(17p)/*TP53* mutation	245	223	211	191	170	154	141	120	103	81	67	46	34	18	13
Number at risk Presence of del(17p)/*TP53* mutation	161	140	125	116	96	83	72	65	58	54	36	24	16	9	6

Source: Public Health England SACT Data Review. [13]

Table 17: Number of patients at risk, amongst patients who do not have a del(17p)/*TP53* mutation, by quarterly breakpoints split between patients that have died (events) and patients that are still alive (censored)

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Censored	159	159	159	146	135	123	118	104	92	74	65	44	32	17	13
Events	86	64	52	45	35	31	23	16	11	7	2	2	2	1	0

Source: Public Health England SACT Data Review. [13]

Table 18: Number of patients at risk, amongst patients who have a del(17p)/*TP53* mutation, by quarterly breakpoints split between patients that have died (events) and patients that are still alive (censored)

Time intervals (months)	0-42	3-42	6-42	9-42	12-42	15-42	18-42	21-42	24-42	27-42	30-42	33-42	36-42	39-42	42
Censored	90	90	90	88	74	68	60	55	50	48	33	22	15	8	5
Events	71	50	35	28	22	15	12	10	8	6	3	2	1	1	1

Source: Public Health England SACT Data Review. [13]

Appendix C Cost-effectiveness results at list price

Table 19: Cost effectiveness results at venetoclax list price (deterministic)

Technologies	Total costs (£)	Total LYG (undiscounted)	Total QALYs	Incremental. Costs (£)	Incremental LYG (Discounted)	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Cost-effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry								
Patient population with a del(17p)/*TP53* mutation								
Venetoclax	[redacted]	4.620	[redacted]	[redacted]	3.192	[redacted]		[redacted]
BSC	[redacted]	0.950	0.627	-	-	-	-	-
Patient population without a del(17p)/*TP53* mutation								
Venetoclax	[redacted]	6.848	[redacted]	[redacted]	4.090	[redacted]		[redacted]
BSC	[redacted]	1.797	1.160	-	-	-	-	-
Cost-effectiveness analysis 2: Analysis that demonstrated plausible potential for cost-effectiveness at CDF entry – incorporating updated clinical evidence								
Del(17p)/*TP53* positive patient population	[redacted]	4.456	[redacted]	[redacted]	2.901	[redacted]		[redacted]
Non- Del(17p)/*TP53* positive patient population	[redacted]	5.538	3.168	[redacted]	2.958	[redacted]		[redacted]
Cost-effectiveness analysis 3: New company base case								
Patient population with a del(17p)/*TP53* mutation								
Venetoclax	[redacted]	4.466	[redacted]	[redacted]	2.908	[redacted]		[redacted]
BSC	[redacted]	0.950	0.627	-	-	-		-
Patient population without a del(17p)/*TP53* mutation								
Venetoclax	[redacted]	5.558	[redacted]	[redacted]	2.972	[redacted]		[redacted]
BSC	[redacted]	1.797	1.160	-	-	-		-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 20: Updated base case results at venetoclax list price (probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
Patient population with del(17p)/*TP53* mutation					
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.639 (0.519, 0.809)	-	-	-
Patient population without del(17p)/*TP53* mutation					
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	1.176 (0.955, 1.477)	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure 32: Scatterplot of probabilistic results for the patient population with a del(17p)/*TP53* mutation at venetoclax list price

Abbreviations: BSC: best supportive care.

Figure 33: Scatterplot of probabilistic results for the patient population without a del(17p)/*TP53* mutation at venetoclax list price

Abbreviations: BSC: best supportive care.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund review

Venetoclax for treating chronic lymphocytic leukaemia (CDF review of TA487) [ID3886]

Clarification questions

16th December 2021

File name	Version	Contains confidential information	Date
ID3866 venetoclax clarification questions response_AbbVie [noACIC]_16Dec21	1.0	No	16/12/2021

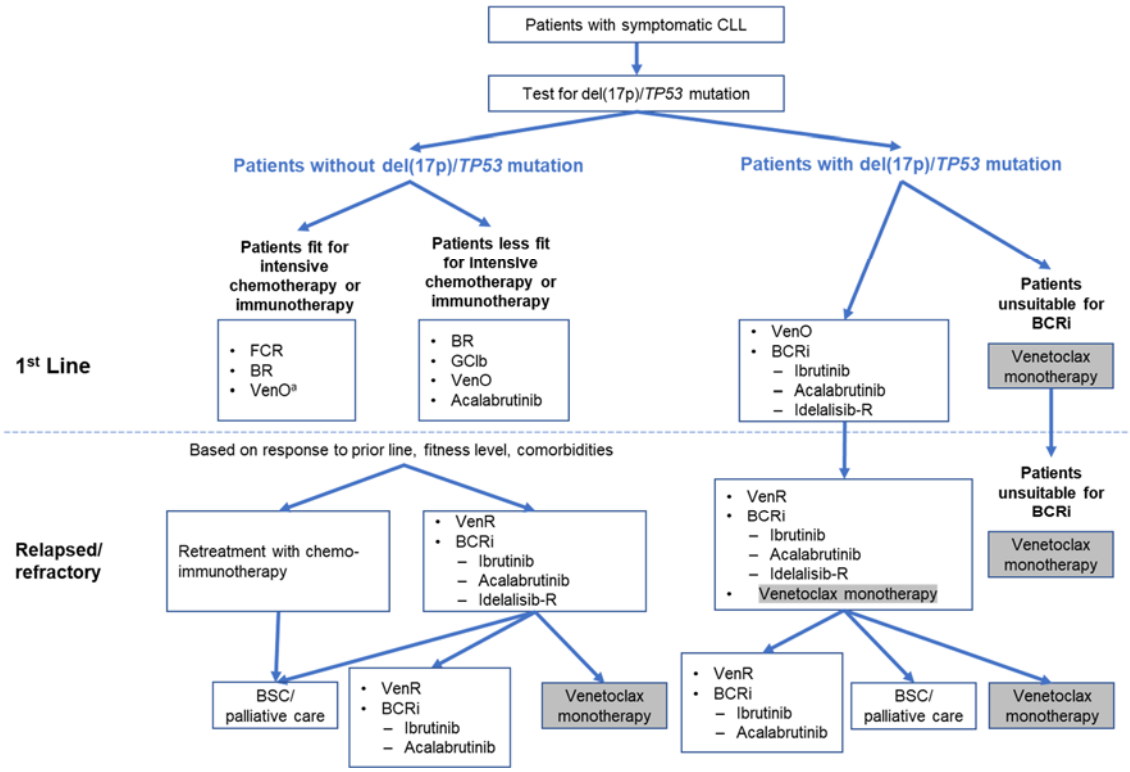
Section A: Clarification on effectiveness data

Clinical Information Issues

A1. Priority question: Please reproduce Figure 2 from the company submission in the original appraisal, updated for the current clinical pathway.

Please find an updated treatment pathway below which reflects the treatment landscape of today (Figure 1). It is important to note that the relevant comparator for venetoclax is, as per the Terms of Engagement, BSC. We have not altered the committee's preferred assumptions or the decision problem from the original appraisal, therefore the treatment pathway below is not entirely relevant to this CDF review. The updated pathway is based on NICE guidance, NICE Pathway Lymphoid Leukaemia as well as UK BSH and European ESMO guidelines.[1]

Figure 1. Updated treatment pathway, December 2021



[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.*

[1]Guideline for the treatment of chronic lymphocytic leukaemia, British Journal of Haematology, 2018, 182, 344–359; NICE Pathway Blood and bone marrow cancers accessed at https://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers; Munir T. et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma, Am J Hematology 2019 Dec; 94(12): 1353–1363; B. Eichhorst et al., Chronic Lymphocytic Leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann Oncol (2020).

A2. Priority question: Please perform a naïve comparison of the Systemic Anti-Cancer Therapy (SACT) Cancer Drugs Fund (CDF) overall survival (OS) and time-on-treatment to the company's preferred choice of best supportive care (BSC) data (e.g. using a Cox proportional hazards (PH) model) and provide full results. Also perform an analysis adjusting for differences between the populations if possible.

A naïve comparison (e.g., using a Cox proportional hazards model) between our choice of BSC and the SACT data is not possible, as we do not have access to suitable data to generate this analysis. This is because we do not use the observed data from Study 116 for BSC (nor is it available stratified by del(17p)/TP53 mutation status or adjusted for crossover). We instead use the coefficients from models fitted to this data, as presented in the idelalisib submission (TA359), to generate our BSC survival outcomes. This is described in more detail in Section 5.3.4.4 of the TA487 submission.

A3. Priority question: Please amend the censoring in the digitised data as it clearly differs from the original dataset in the tail of the curves, and refit and update the parametric survival models accordingly.

We have investigated this issue and acknowledge a minor difference in censoring between the digitised and original dataset. This difference in censoring in the tail of the curves is attributed to the fact that censoring in the tail is allocated to the end of the interval, while this is only expected to marginally impact the parametric model fit. Nonetheless as requested, the censoring in the end of the curve has been amended manually to align with the censoring in the original curves. In doing so, the observations which were clustered at the end of the interval have been spread over the interval, to mimic the censoring observed in the original survival figures. Therefore, the survival figures based on the digitised data are updated accordingly and presented in Figure 2 and Figure 3. The parametric models were also re-run; aligned with initial expectations these changes have a marginal impact on the fit of the parametric survival models and therefore also in the results of the resubmission document: the ICER (with PAS price) for the patient population with a del(17p)/TP53 mutation changed from £43,201 per QALY gained to £43,239 per QALY gained and for the patient population without a del(17p)/TP53 mutation changed from £49,104 per QALY gained to £49,213 per QALY gained. Updated models incorporating these

new analyses are included alongside this letter, and the updated parametric extrapolations are included in the appendix to this letter.

Figure 2. K-M plot of overall survival from SACT dataset, updated censoring

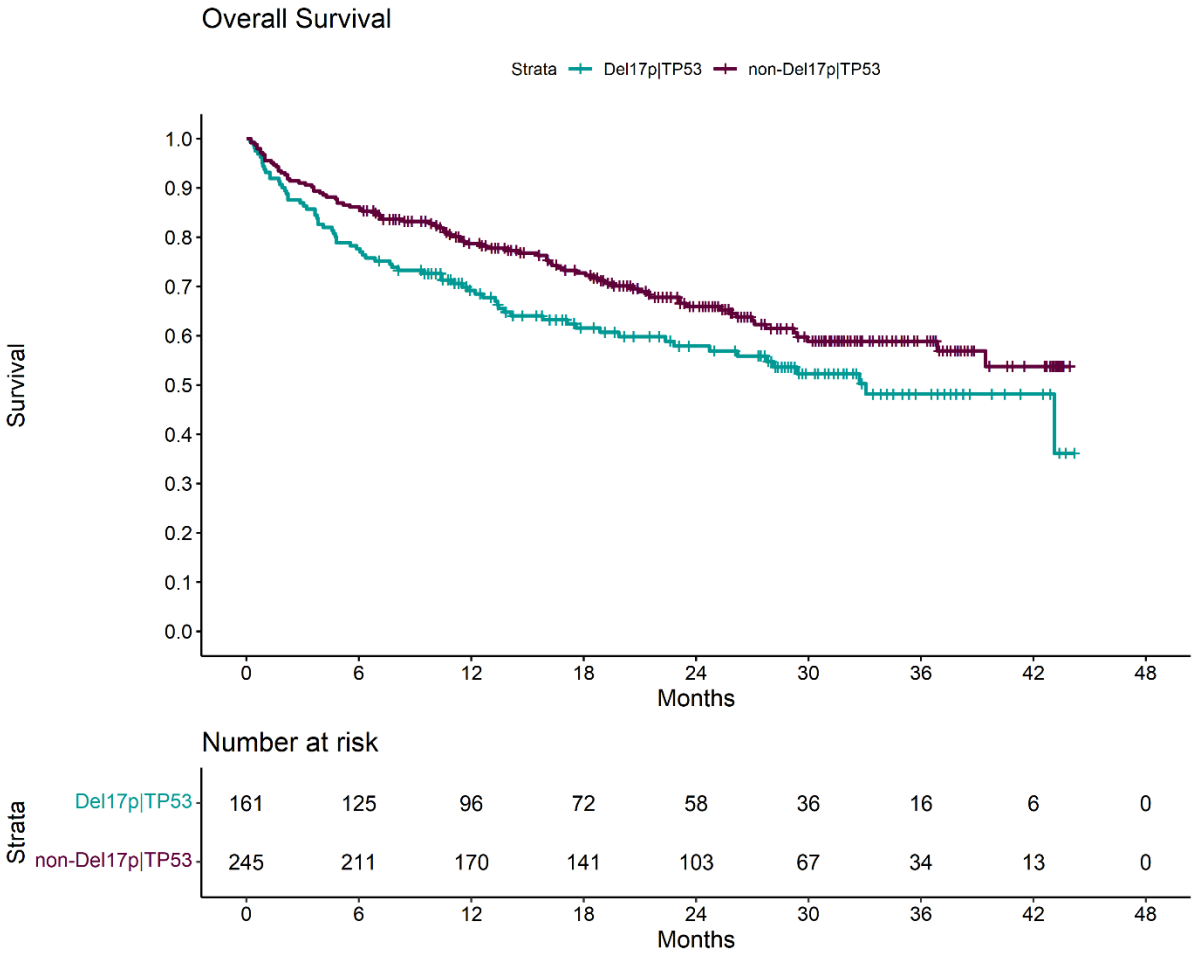
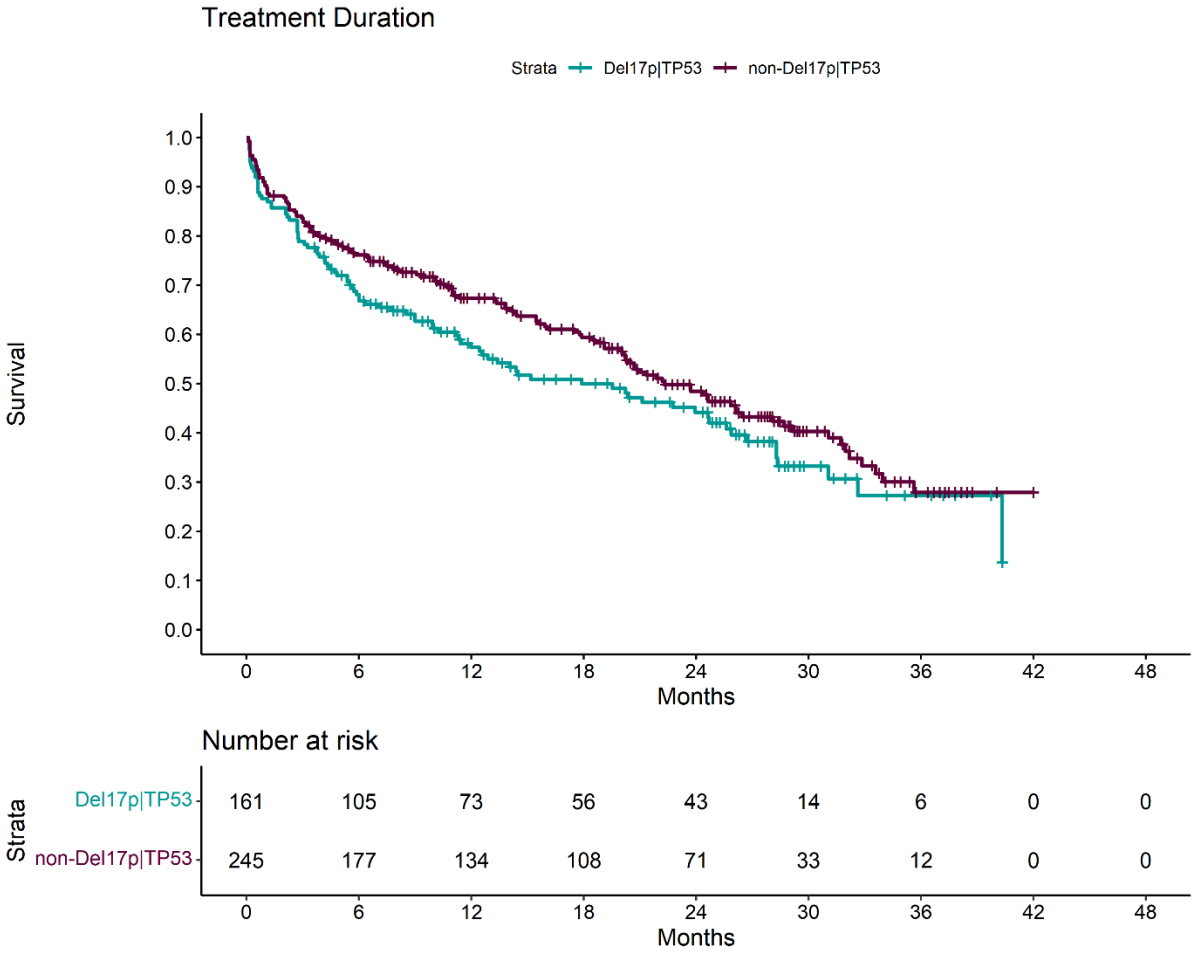


Figure 3. K-M plot of time on treatment from SACT dataset, updated censoring



A4. Please provide together on the same Kaplan-Meier (KM) plot the original pooled trial time-on-treatment (TOT) data for venetoclax, the updated pooled trial TOT data, and the SACT CDF TOT data.

Please see our response to question A5 which also covers this question.

A5. Priority question: Please estimate a hazard ratio and 95% confidence interval comparing progression-free survival (PFS) to TOT data from the pooled venetoclax trials, to establish the similarity of the two outcomes.

It was agreed during calls with NICE on 9th March 2021 and 28th October 2021 that AbbVie should use the SACT data for the CDF review, given that the small amount of additional follow-up from the venetoclax trials was unlikely to resolve the existing uncertainties. Indeed, the committee in TA487 criticised the venetoclax trial data presented in the original submission and noted a lack of generalisability to UK NHS patients. As such, further analyses on the venetoclax trial data have not been

undertaken. The SACT dataset represents fully generalisable real-world evidence on the use of venetoclax in the NHS that informs the updated model results, as requested. While the lack of PFS in the SACT dataset means that we must rely on ToT as a proxy for PFS, evidence from two studies of relapsed/refractory CLL (one study of ibrutinib[2] and one of the venetoclax trials – M13-982[3]), illustrates that ToT was 3-4 months shorter than PFS.

Both of these studies evaluated regimes that were administered until disease progression or unacceptable toxicity. Within the ibrutinib study,[2] median ibrutinib ToT was 41 months (range 0.2-71.1) and median PFS was 44.1 months. Within the venetoclax study (M13-982),[3] median ToT was 23.1 months (range 0-44.2) and median PFS was 27.2 months. These results suggest that ToT may be utilised as a suitable proxy for PFS for treat-to-progression therapies in CLL.

A6. Updated follow-up from Trial 116 is now available, however it was not publicly reported to the detail necessary for inclusion in this appraisal. Please confirm the extent of effort made to obtain updated relevant information from Trial 116.

As Trial 116 is not an AbbVie trial, we were reliant on publicly available data to support our submission; efforts were made to identify any useful updates to Trial 116 to inform this submission, but none were appropriate. As noted, the final publication of the 116 trial was published in 2019[4] and provides additional follow-up beyond that provided in the original NICE submission. In our original venetoclax submission, PFS and OS curves for BSC from 116 were extracted directly from the idelalisib NICE submission (TA359), where the manufacturer was able to adjust for patient crossover during the trial (see page 124 of the original TA487 submission). Sharman et al. (2019) does not adjust for crossover and is not reported to sufficient detail to be

[2]Munir T. et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma, Am J Hematology 2019 Dec; 94(12): 1353–1363
[3] Stilgenbauer S., et al. Venetoclax for Patients With Chronic Lymphocytic Leukemia With 17p Deletion: Results From the Full Population of a Phase II Pivotal Trial. J Clin Oncol. 2018 Jul 1;36(19):1973-1980. doi: 10.1200/JCO.2017.76.6840. Epub 2018 May 1. Erratum in: J Clin Oncol. 2019 Sep 1;37(25):2299. PMID: 29715056.
[4]Sharman, J. P. et al. (2019) Final Results of a Randomized, Phase III Study of Rituximab With or Without Idelalisib Followed by Open-Label Idelalisib in Patients With Relapsed Chronic Lymphocytic Leukemia. Journal of clinical oncology. 37 (16), 1391–1402.

included in this appraisal. As such we were satisfied that, given the lack of publicly available data, nothing further could be done to inform estimates from the 116 trial.

A7. Please confirm if any updated follow-up from trial M12-175 is available since the original appraisal. If so, please provide detailed results.

We can confirm that no further follow-up for trial M12-175 is available since the original appraisal.

Literature Searching

A8. The company has not presented any details of updated searches to identify alternative sources of evidence for this appraisal. Please provide these details and a summary of results.

No formal updated searches were performed as part of this appraisal, but attempts were made to explore alternative sources of BSC data through clinical expert opinion; however, none were able to identify any further sources of evidence.

Section B: Clarification on cost-effectiveness data

Survival Related Questions

B1. Priority question: Please fit a generalised gamma and restricted cubic spline curves to the SACT CDF and BSC time-to-event data, updating the survival information included in the submission and allow its selection within the economic model.

At this time, we have not been able to provide this analysis; the economic model is not currently designed to generate generalised gamma and cubic spline survival models. The structural adjustments required to implement these models are not feasible within the 5-day time frame we have to respond.

We would like to note that the choice of model fits in the original and updated submissions was informed by expert clinical opinion, and in the original appraisal the committee agreed that the company's use of Weibull extrapolations was appropriate. Furthermore, as the survival models for the BSC data source were informed by

coefficients from the idelalisib NICE submission (in the absence of patient-level data), it would not be possible to explore these alternative fits for the comparator.

Economic Modelling Issues

B2. Please clarify which NHS Cost Inflation Index (NHSCII) was used to make all inflation adjustments (pay, prices or pay and prices)?

The NHS cost Inflation Index (NHSCII) as constructed by the Department of Health and Social Care (DHSC) reported in section 15.3 of the Personal Social Services Research Unit (PSSRU) (2020) report was used.[5] Until 2016/2017, a hospital & community health services (HCHS) index was calculated by the DHSC. The hospital and community health services (HCHS) pay and price inflation was a weighted average of two separate inflation indices: the pay index was calculated using the annual increase in NHS salaries and the Health Service Cost Index (HSCI) measured the price change for each of 40 sub-indices of goods and services purchased by the HCHS. These were weighted according to the proportion of expenditure on pay and prices to give the HCHS pay and prices index. In 2016, this index was discontinued, and has now been replaced by the NHS cost Inflation Index (NHSCII) constructed by the DHSC, in conjunction with the ONS (section 15.3 in page 163 of the Personal Social Services Research Unit (PSSRU) (2020) report[5]). The annual percentage increase of HCHS pay and prices was used to inflate cost items in the updated economic models.

B3. Please add the previous ERG preferred modelling of BSC using the idelalisib arm data, into the economic model

To add the ERG preferred modelling options of BSC using the idelalisib arm data would require substantial reconstruction of the model and further quality control, which was not feasible considering the 5-day response timelines of the clarification questions. Nonetheless, to address this comment, we have prepared separate economic model versions for both the positive and negative del17p/TP53 patient populations, which are adapted to replace the company-preferred model options for

[5] Source: Curtis, L.B., A. . *Unit Costs of Health and Social Care 2020, Personal Social Services Research Unit (PSSRU), University of Kent, Canterbury*. 2020 [cited 2021 July 13]; Available from: https://kar.kent.ac.uk/id/eprint/84818

BSC with the previous ERG-preferred model options for BSC. These two models are provided as separate attachments to this response.

Section C: Textual clarification and additional points

Data query

C1. Please clarify how Figure 1 and 2 of the present submission were obtained as they do not match the formatting of the plots provided to the ERG in the SACT submission, yet the information looks identical. It appears the digitisation shown in later figures may not have been necessary.

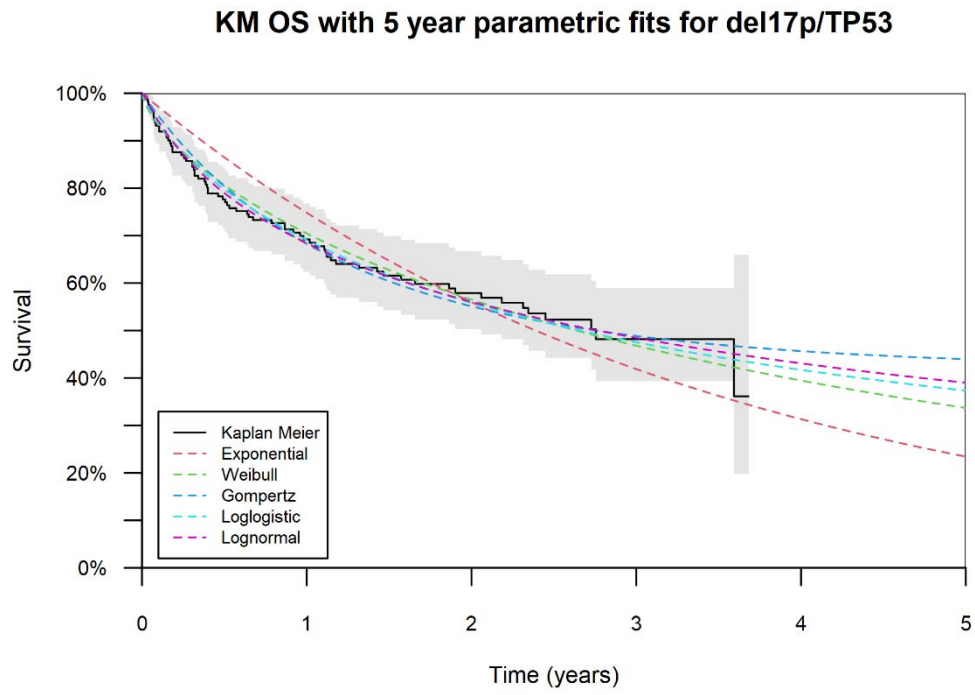
We can confirm that Figures 1 and 2 were digitised for copyright reasons, and these are identical to the figures provided in the SACT report. Figures 3 and 4 were also digitised from the SACT report and were redrawn in the submission for consistency.

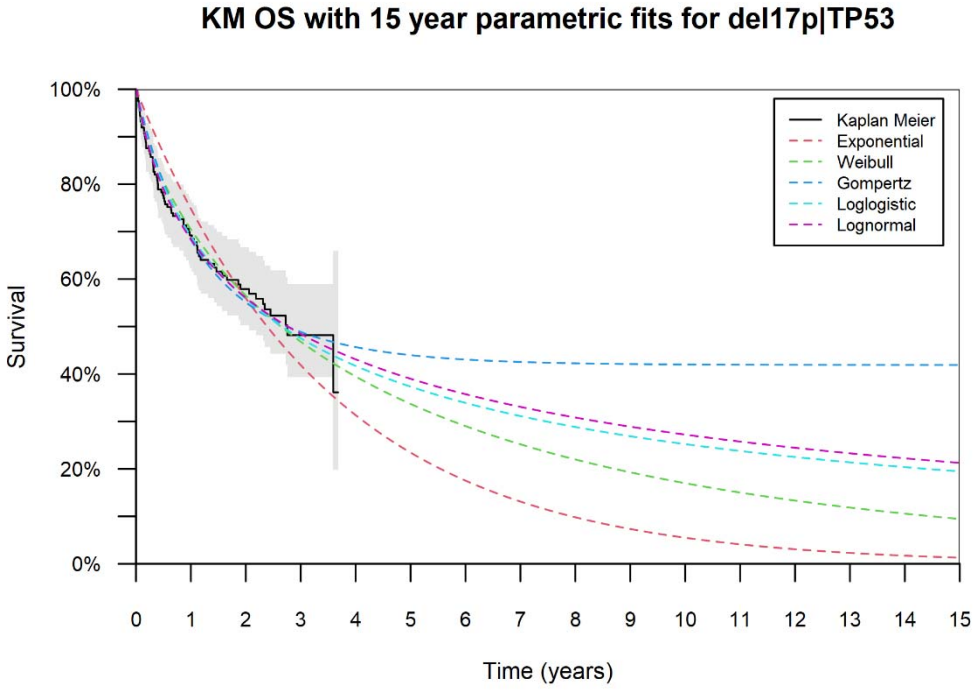
C2. Please provide reference 19: AbbVie Data on File. Clinical expert opinion: October 2021, as it is currently omitted from the reference pack.

Apologies for this oversight, a copy of this reference has been included alongside this response.

Appendix – updated parametric extrapolations (A3)

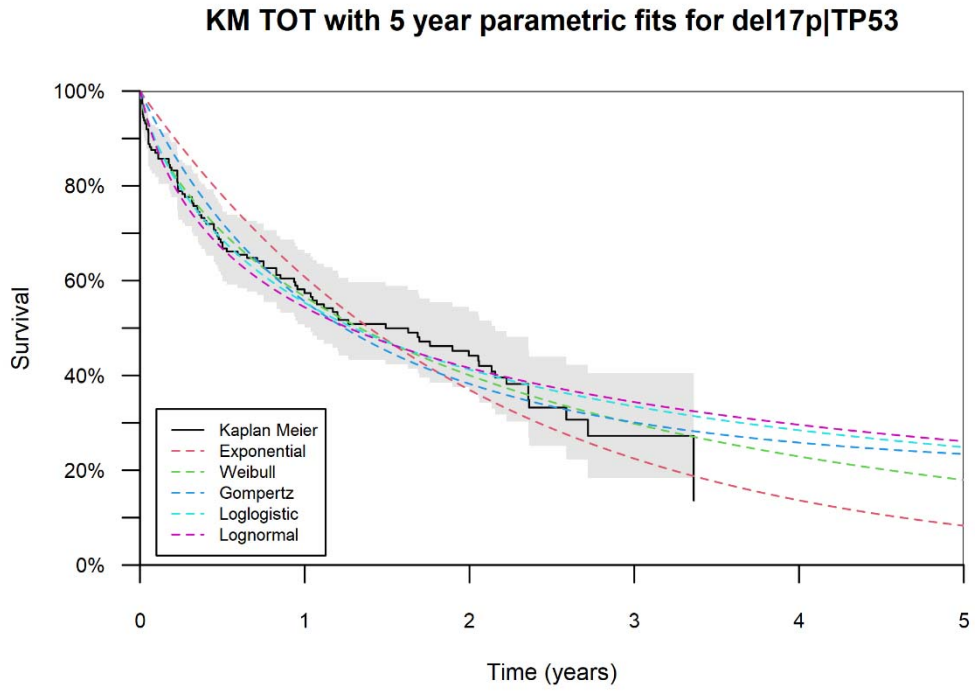
Figure 4: OS parametric fits – patient population with a del(17p)/TP53 mutation using 5 years (top) and 15 years (bottom) time horizon

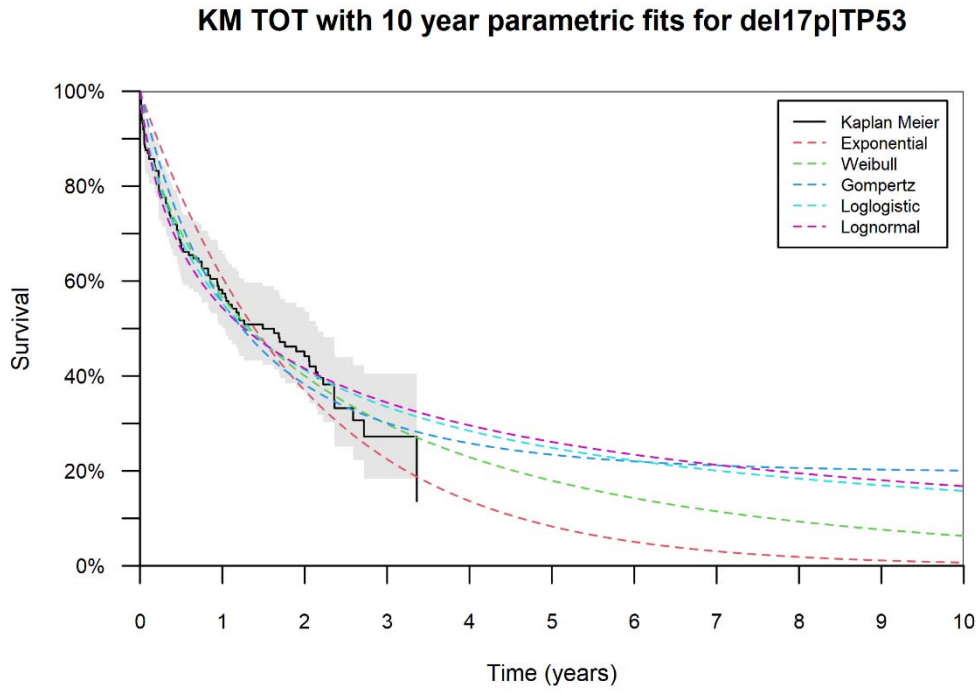




Abbreviations: OS: overall survival.

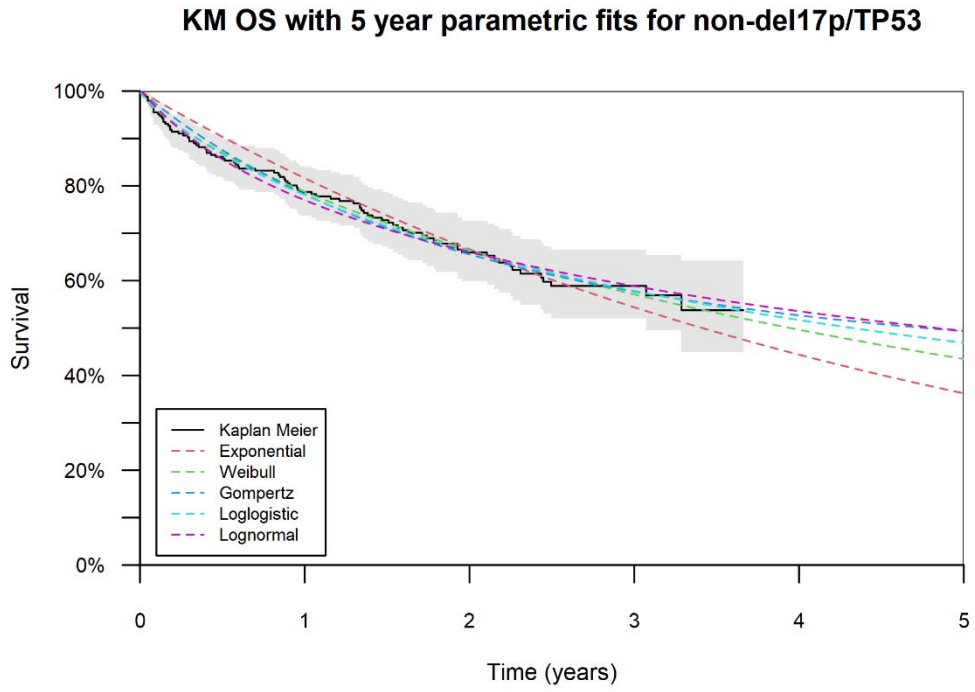
Figure 5: ToT parametric fits – patient population with a del(17p)/TP53 mutation using 5 years (top) and 10 years (bottom) time horizon.

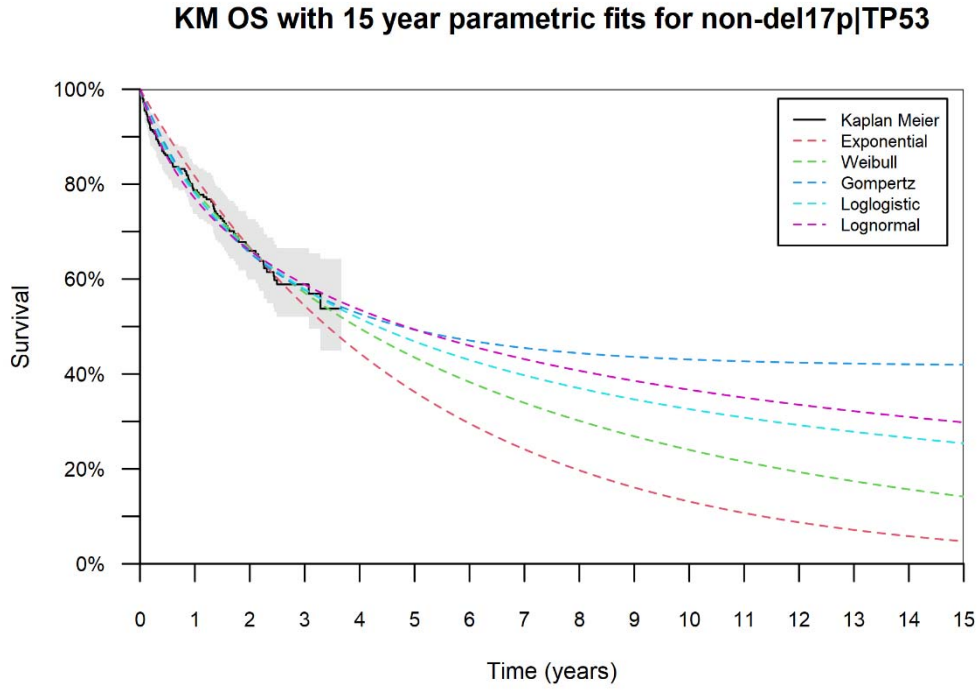




Abbreviations: ToT: time on treatment.

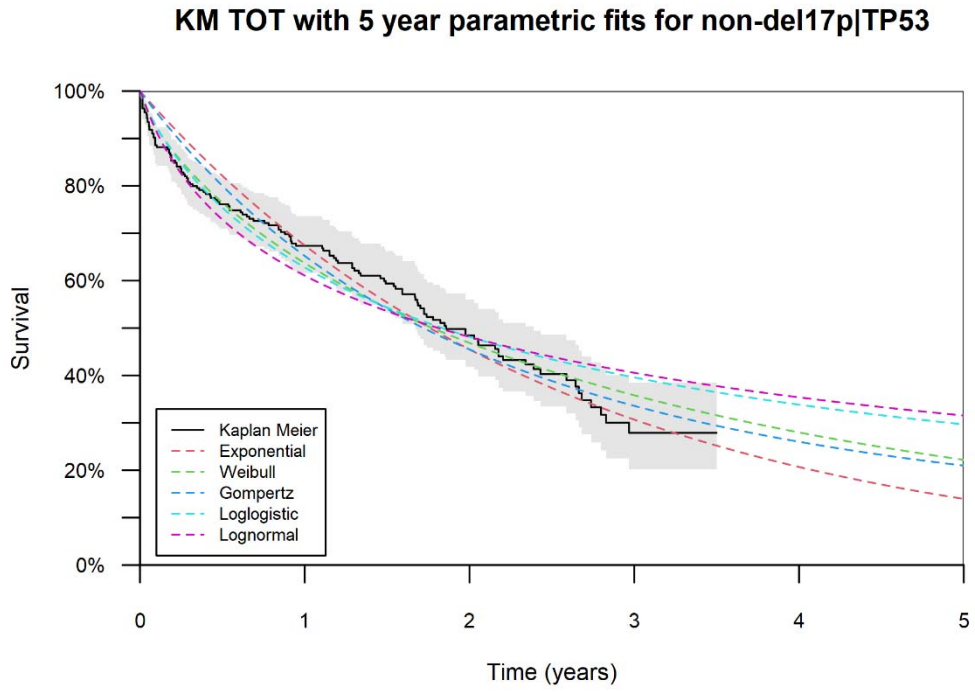
Figure 6: OS parametric fits – patient population without a del(17p)/TP53 mutation using 5 years (top) and 10 years (bottom) time horizon

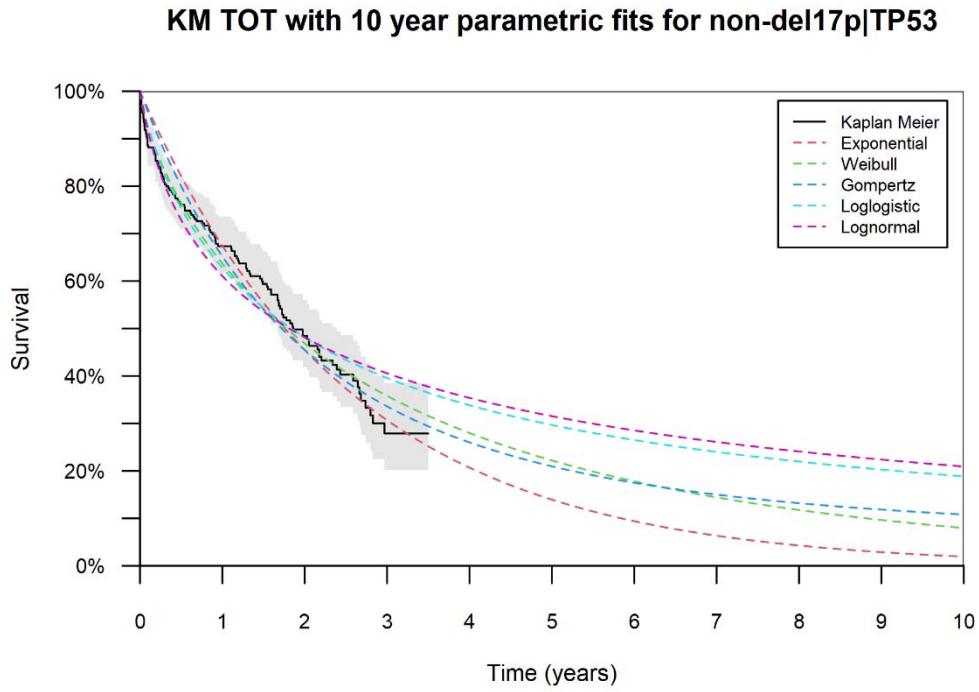




Abbreviations: OS: overall survival.

Figure 7: ToT parametric fits – patient population without a del(17p)/TP53 mutation 5 years (top) and 10 years (bottom) time horizon.





Abbreviations: ToT: time on treatment.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund review

Venetoclax for treating chronic lymphocytic leukaemia (CDF review of TA487) [ID3886]

Clarification questions

[December 2021]

File name	Version	Contains confidential information	Date
		Yes/no	

Section A: Clarification on effectiveness data

CDF data-related issues (the ERG understands the company may be unable to assist with these queries)

A9. Please clarify if Eastern Cooperative Oncology Group (ECOG) performance status at the start of treatment or first diagnosis was used for the CDF cohort of the SACT data.

Performance status is at the start of treatment

A10. Please clarify if age at the start of treatment or first diagnosis was used for the CDF cohort of the SACT data.

Age is the patients age at the start of treatment

A11. Please provide confidence intervals/interquartile range (IQR) for the mean and median age for the overall CDF cohort of the SACT data.

Table 1. confidence intervals, interquartile range (IQR) mean and median age for the overall CDF cohort of the SACT data.

Cohort	N	Mean	Median	IQR
Full CDF cohort	406	71.3 [95% CI: 70.3, 72.2]	72 [95% CI: 71, 73]	13

A12. Please provide age by mutation status (mean and median age [with confidence intervals/IQR]) for the CDF cohort of the SACT data.

Table 2. confidence intervals, interquartile range (IQR) mean and median age for the CDF cohort of the SACT data, split by mutation status.

Cohort	N	Mean	Median	IQR
ABSENCE of 17p deletion	245	71.2 [95% CI: 70.0, 72.3]	72 [95% CI: 70, 74]	13
PRESENCE of 17p deletion or TP53 mutation	161	71.4 [95% CI: 69.9, 73.0]	72 [95% CI: 70, 74]	12

A13. Please provide further information on the 7 patients that did not receive treatment CDF cohort of the SACT data, and the reasons for not receiving treatment.

- The SACT dataset does not collect why patients did not receive treatment

A14. Please provide the patient characteristics, treatment duration, and OS by mutation status for the venetoclax treatment (excluding the venetoclax treatment switchers) for the overall CDF cohort of the SACT data.

- Included as Appendix A – Patient characteristics_trt_duration_OS_A14A15.

A15. CDF cohort of the SACT data – For patients with a 17p deletion or TP53 mutation included in the SACT CDF data, was there any condition for previous venetoclax therapy, like that for those without the mutation/deletion?

- Blueteq eligibility for these patients included: must never received venetoclax before or has been previously treated with the combination of venetoclax with an anti-CD20 antibody (obinutuzumab or rituximab), in which case the patient must not have progressed during such treatment with venetoclax.

A16. CDF cohort of the SACT data – Population with a del(17p)/TP53 mutation, please provide:
- the number of patients who have never received venetoclax before

- Patients could have received prior ventoclax within the CDF cohort of the SACT data after TA561 and TA561 were recommended. Patients who were previously treated with a venetoclax combination were captured by the NHS England and NHS Improvement Blueteq eligibility form but NHS Digital did not receive this information. We have requested this from Blueteq.

- the number of patients that have been previously treated with the combination of venetoclax and rituximab (where the patient must not have progressed during treatment).

- See above.

A17. CDF cohort of the SACT data – Population without a del(17p)/TP53 mutation, please provide:

- the number of patients who have never received venetoclax before

- See A16.

- the number of patients that have been previously treated with the combination of venetoclax and rituximab (where the patient must not have progressed during treatment).

- See A16.

A18. Please provide further details of the feasibility assessment of the SACT CDF dataset conducted by Public Health England (PHE) that determined that a matched cohort analysis of the BSC data would not provide meaningful analyses.

Included as Appendix B – venetoclax feasibility assessment_confidential

A19. CDF cohort of the SACT data – Please provide data on adverse events?

- The SACT dataset does not collect information on adverse events

A20. Please could you clarify what is meant by 'baseline' in table 4 of the company submission? Is this the time of entry into the SACT cohort, treatment start date or date of diagnosis?

Patient characteristics are those at start of treatment

A21. Please provide the baseline characteristics for patients in the SACT CDF cohort in the same format as table 4 of the company submission (section A.6.2.1) but further stratified by del(17p)/TP53 mutation status.

- Included as Appendix C – Patient characteristics_A21

Table 1. Patient characteristics, full CDF cohort excluding treatment switchers, overall (N=326)

Patient characteristics[1]			
		N	**%**
Sex	Male	219	67%
	Female	107	33%
Age	<40	0	0%
	40 to 49	3	1%
	50 to 59	25	8%
	60 to 69	83	25%
	70 to 79	142	44%
	80+	73	22%
Performance status	0	61	19%
	1	115	35%
	2	34	10%
	3	6	2%
	4	0	0%
	Missing	110	34%

[1] Figures may not sum to 100% due to rounding.

Table 2. Patient characteristics CDF cohort by mutation status excluding treatment switchers, ABSENCE of 17p deletion (N=188)

Patient characteristics[2]			
		N	**%**
Sex	Male	133	71%
	Female	55	29%
Age	<40	0	0%
	40 to 49	2	1%
	50 to 59	14	7%
	60 to 69	48	26%
	70 to 79	83	44%
	80+	41	22%
Performance status	0	43	23%
	1	64	34%
	2	17	9%
	3	1	1%
	4	0	0%
	Missing	63	34%

[2] Figures may not sum to 100% due to rounding.

Table 3. Patient characteristics CDF cohort by mutation status excluding treatment switchers, PRESENCE of 17p deletion or TP53 mutation (N=138)

Patient characteristics[3]			
		N	**%**
Sex	Male	86	62%
	Female	52	38%
Age	<40	0	0%
	40 to 49	1	1%
	50 to 59	11	8%
	60 to 69	35	25%
	70 to 79	59	43%
	80+	32	23%
Performance status	0	18	13%
	1	51	37%
	2	17	12%
	3	5	4%
	4	0	0%
	Missing	47	34%

[3] Figures may not sum to 100% due to rounding.

Treatment duration

The median treatment duration for all patients, for the full CDF cohort, excluding treatment switchers was 24.7 months [95% CI: 20.3, 31.1] (751 days) (N=326).

The median treatment duration for all patients without a 17p deletion or TP53 mutation, excluding treatment switchers was 26.4 months [95% CI: 20.9, 35.6] (803 days) (N=188).

The median treatment duration for all patients with a 17p deletion or TP53 mutation, excluding treatment switchers was 20.4 months [95% CI: 11.3, 28.3] (620 days) (N=138).

Table 4. Treatment duration, CDF cohort, overall and by mutation status excluding treatment switchers (N=326)

Time period	Overall (N=326)	ABSENCE of 17p deletion or TP53 mutation (N=188) (%)	PRESENCE of 17p deletion or TP53 mutation (N=138) (%)
6 months	73% [95% CI: 68%, 77%]	76% [95% CI: 70%, 82%]	68% [95% CI: 59%, 75%]
12 months	65% [95% CI: 59%, 70%]	70% [95% CI: 62%, 76%]	58% [95% CI: 49%, 66%]
18 months	59% [95% CI: 53%, 64%]	64% [95% CI: 56%, 71%]	52% [95% CI: 42%, 60%]
24 months	52% [95% CI: 46%, 58%]	55% [95% CI: 47%, 62%]	48% [95% CI: 39%, 57%]
36 months	36% [95% CI: 28%, 44%]	38% [95% CI: 27%, 48%]	35% [95% CI: 23%, 47%]

Overall survival (OS)

The median OS for all patients, for the full CDF cohort, excluding treatment switchers was 43.1 months[4] (1,311 days) (N=326).

The median OS for all patients without a 17p deletion or TP53 mutation, excluding treatment switchers (N=188) was not reached.

The median OS for all patients with a 17p deletion or TP53 mutation, excluding treatment switchers was 43.1 months (1,311 days) (N=138).

Table 5. OS, CDF cohort, overall and by mutation status excluding treatment switchers (N=326)

Time period	Overall (N=326) (%)	ABSENCE of 17p deletion or TP53 mutation (N=188) (%)	PRESENCE of 17p deletion or TP53 mutation (N=138) (%)
6 months	79% [95% CI: 75%, 83%]	82% [95% CI: 76%, 87%]	75% [95% CI: 67%, 82%]
12 months	73% [95% CI: 67%, 77%]	76% [95% CI: 69%, 82%]	68% [95% CI: 59%, 75%]
18 months	67% [95% CI: 62%, 72%]	72% [95% CI: 65%, 78%]	61% [95% CI: 52%, 68%]
24 months	64% [95% CI: 58%, 69%]	67% [95% CI: 59%, 73%]	59% [95% CI: 50%, 67%]
36 months	59% [95% CI: 52%, 65%]	65% [95% CI: 56%, 72%]	50% [95% CI: 39%, 60%]

[4] Confidence intervals are not shown if there was an insufficient number of events at the time this report was produced.

Public Health England

Protecting and improving the nation's health

Venetoclax for use in chronic lymphocytic leukaemia in the Cancer Drugs Fund

Analytical feasibility assessment

Working document on analytical challenges and concerns for the evaluation of venetoclax in the Cancer Drugs Fund (CDF) [TA487]

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Contents

NICE committee uncertainty regarding the use of venetoclax in chronic lymphocytic leukamia

The venetoclax Data Collection Agreement (DCA) forms the basis of the agreement between National Institute for Health and Care Excellence (NICE), Public Health England (PHE) and the pharmaceutical company (AbbVie) regarding the data which need to be collected, and the analyses which need to be performed in order to address the NICE committee uncertainty regarding whether the drug should enter routine commissioning in the NHS.

The DCA states that the systemic anti cancer therapy (SACT) database at PHE will be the primary source of data for the evaluation of venetoclax in the Cancer Drugs Fund (CDF). No additional data will be provided by a concurrent randomised controlled trial (RCT).

The following areas of uncertainty were identified for venetoclax in the DCA.

1. **Venetoclax overall survival** - Patients for whom venetoclax would be an option in routine clinical practice in England have more advanced disease than patients in venetoclax clinical trials. As such, revised estimates of overall survival are required in a more appropriate real world population.

2. **Comparator cohort** - Venetoclax trials are all single-arm, and there is no comparative data in a matched population. A valid comparator cohort is required to evaluate differential treatment effectiveness and outcomes. Venetoclax is approved for use after progression on a B cell receptor inhibitor (BCRi) in place of best supportive care (BSC). Ibrutinib or idelalisib are NICE approved BCRi's for use in CLL, and therefore the SACT dataset could be used to generate post-progression survival data for this cohort. This would provide an approximation of the outcomes of best supportive care (BSC) in a population which is more relevant to clinical practice in England than either the population used by the company or Evidence Review Group (ERG) in the appraisal.

The recommendations section (below) provides the full requirements, as set out in the DCA, for the data to be collected and outcomes to be analysed for both venetoclax and BSC. There are significant limitations in the ability of the SACT database to provide the data required to support these analyses. This report details the limitations and concerns.

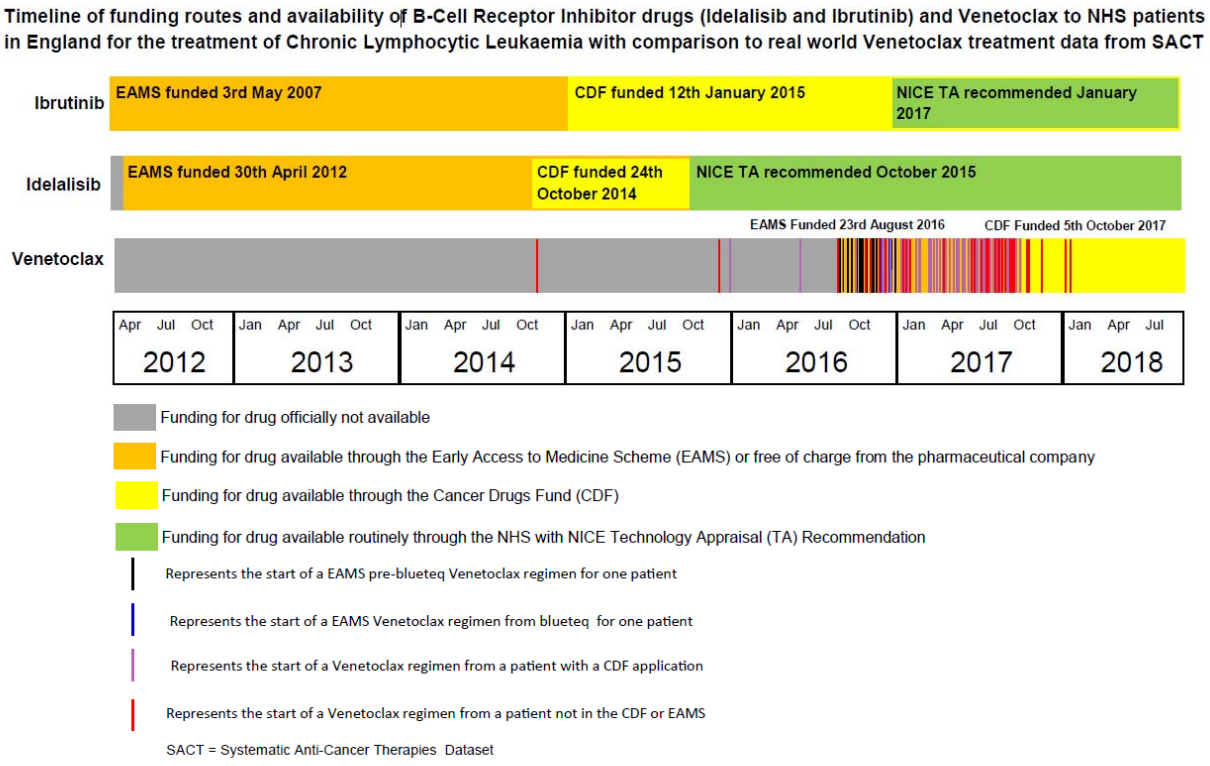
Overview of study design proposed to answer NICE committee uncertainty

Venetoclax is a treatment option available through the CDF to patients with chronic lymphocytic leukaemia (CLL)(TA487).

Analysis in the CDF will compare a retrospective cohort of patients who received BSC (pre-venetoclax), to a prospective cohort of patients who received venetoclax when the drug became available. This retrospective/prospective design is required because pre-venetoclax, all patients would have received BSC. This group of patients now have the option of venetoclax or BSC. Some patients who continue to receive BSC, even though venetoclax is now available may be very ill, and therefore are not a fair comparator. Therefore, ideally there would be no temporal overlap between these two cohorts of patients.

Definition of venetoclax and best supportive care cohorts

Figure 1: Timelines for availability and funding source of ibrutinib, idelalisib and venetoclax. The Best Supportive Care (BSC) cohort comprises patients who have progressed post B cell receptor inhibitor (ibrutinib or idelalisib) therefore these drugs must be available to generate the cohort



Venetoclax

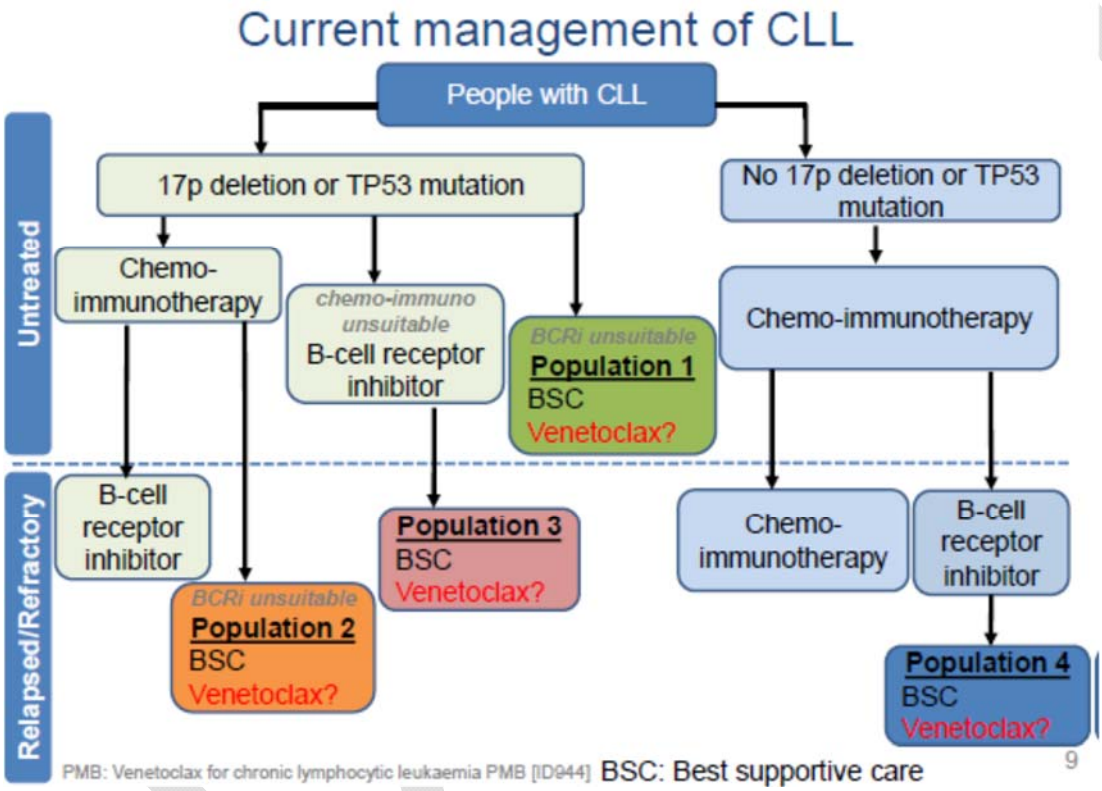
1. Time period

The prospective venetoclax cohort will start 23rd August 2016 (when funding for the drug was made available through the Early Access to Medicines Scheme (EAMS)) and end 5th December 2020 (estimated end date for CDF data collection).

Figure 1 demonstrates that patients received venetoclax before it entered the CDF. Venetoclax was available pre-CDF through EAMS and compassionate access schemes run by the pharmaceutical company (AbbVie). Patients who received venetoclax through EAMS will be included in the venetoclax cohort but any patients who received venetoclax pre-EAMS (before 23rd August 2016) will be excluded from the analysis. Ideally there would be no temporal overlap between the venetoclax and BSC cohort. However, only 3 patients received venetoclax prior to this being made available via EAMS, and therefore this represents exceptional circumstances. The alternative option of including these 3 patients and not allowing any temporal overlap between the 2 cohorts would result in too much truncation of the BSC cohort.

2. Eligibility criteria

Figure 2: Patient populations eligible for best supportive care (BSC) or venetoclax



The current eligibility criteria for patients to receive venetoclax through the CDF are as follows;

Venetoclax in treatment of chronic lymphocytic leukaemia in the absence of 17p deletion or TP53 mutation

1. Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
2. Confirmed diagnosis of chronic lymphocytic leukaemia or small lymphocytic lymphoma that requires treatment
3. Patient has been tested for 17p deletion and TP53 mutation and both results are negative

4. Patient must have progressive disease on or after chemoimmunotherapy
5. Patient must also have progressive disease on or after treatment with a BCRi (e.g. ibrutinib, idelalisib)
6. Patient has a performance status of 0-2
7. Patients has been prospectively assessed for the risk of the development of tumour lysis syndrome following the start of venetoclax
8. Patient has been assessed specifically for potential drug interactions with venetoclax
9. Venetoclax is to be used as a single agent
10. Venetoclax is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment
11. No treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve)
12. Venetoclax to be otherwise used as set out in its Summary of Product Characteristics

Venetoclax in treatment of chronic lymphocytic leukaemia in the presence of 17p deletion or TP53 mutation

1. Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
2. Confirmed diagnosis of chronic lymphocytic leukaemia or small lymphocytic lymphoma that requires treatment
3. Patient is positive for testing for 17p deletion or TP53 mutation
4. Patient must either have relapsed on or after a BCRi (eg ibrutinib, idelalisib) or there must be a contraindication to the patient receiving a BCRi
5. Patient has a performance status of 0-2
6. Patients has been prospectively assessed for the risk of the development of tumour lysis syndrome following the start of venetoclax
7. Patient has been assessed specifically for potential drug interactions with venetoclax
8. Venetoclax is to be used as a single agent
9. Venetoclax is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment
10. No treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve)
11. Venetoclax to be otherwise used as set out in its Summary of Product Characteristics

Best Supportive Care

1. Time period

The retrospective BSC cohort will start 1st April 2012 (start of SACT data collection) and end 22nd August 2016 (prior to venetoclax being made available via EAMS). We are aware that some patients received venetoclax during the retrospective BSC period (see figure 1). Truncating the cohort earlier, for example in October 2014, before any patients received venetoclax will vastly reduce the number of patients available for the BSC cohort. Very few patients received venetoclax between October 2014 and 22nd August 2016 (N=3), and therefore we expect any impact on results to be minimal.

2. Diagnosis

The BSC will include patients diagnosed with CLL (C91.10) who finished treatment with ibrutinib or idelalisib in the BSC time period (1st April 2012 - 22nd August 2016).

ICD10 codes in the SACT database can be poor quality. However, we will use the Cancer Outcomes and Services Dataset (COSD) data to identify all patients diagnosed with C91.1 from 1990 onwards (prior to 1994, ICD-09 204.1 was used). Using NHS numbers, we will link this data to the SACT database to identify which CLL patients were prescribed and completed either ibrutinib or idelalisib in the BSC time period.

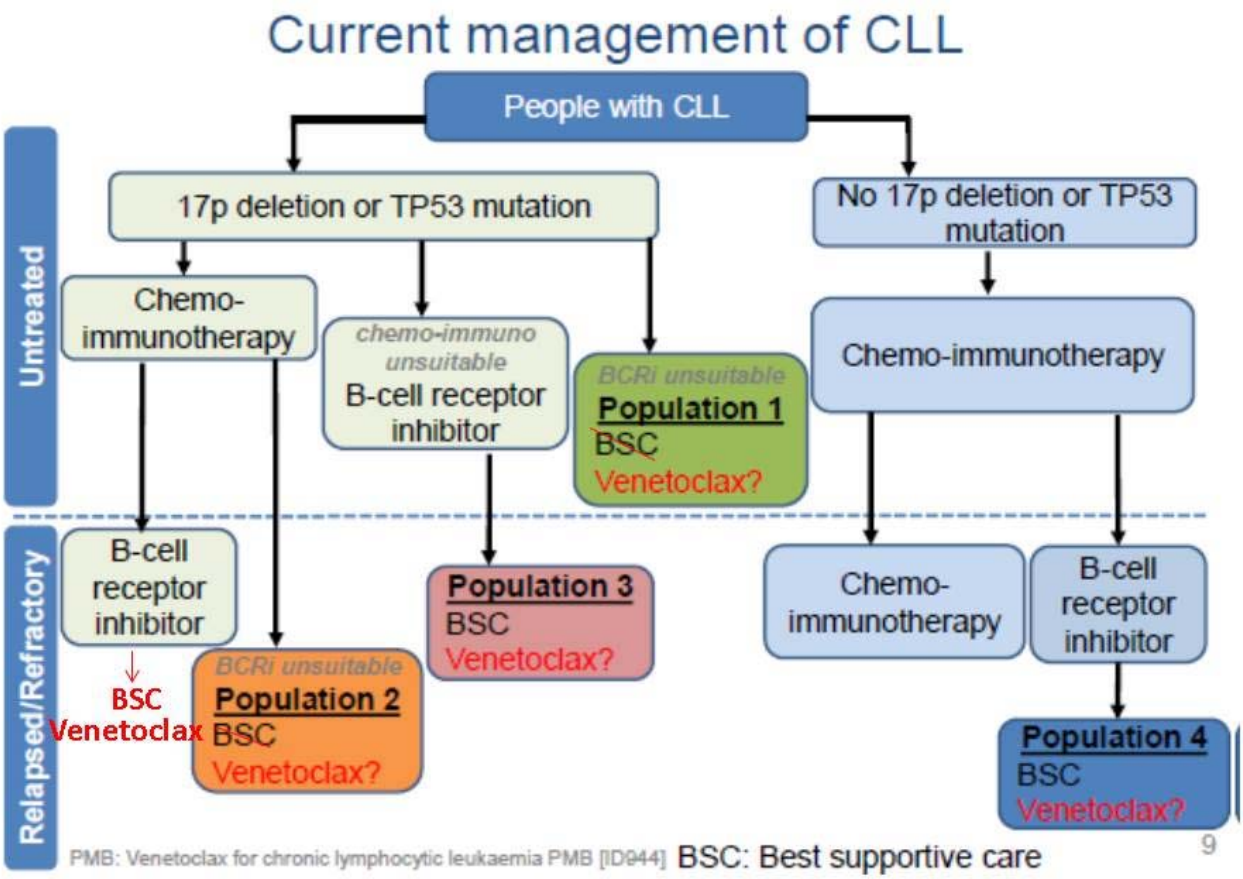
3. BSC treatments

BSC can be interpreted as supportive care packages such as infection control, blood transfusions and psychological care, or active SACT treatments such as rituximab (sometimes with high dose steroids). For the purposes of this analysis, the BSC cohort will include all patients who have ended treatment with ibrutinib or idelalisib, irrespective of their subsequent care.

Differences between venetoclax and BSC comparator cohort

It is critical to note that the analytical design means there are differences between the venetoclax cohort and the BSC cohort in terms of their diagnosis, previous lines of therapy and their suitability for BCRi's, which may be linked to their prognosis.

Figure 3: Discrepancies between the populations of patients eligible for best supportive care (BSC) and venetoclax.



- The analytical design means that the BSC cohort will only contain patients from populations 3 and 4 (see Figure 3 above).
- Although we assume patients in population 4 received chemo-immunotherapy prior to their BCRi, we will not confirm this treatment.
    - Information regarding prior chemo-immunotherapy use should have been submitted to the SACT database. However, it is possible that ascertainment issues with haematological malignancies in the SACT database (see below) mean that there are issues here with missing data, which will would prevent the accurate identification of this cohort.
- The far-left patient pathway corresponds to patients who could hypothetically enter either the BSC or venetoclax cohort. This population were not considered in the DCA and will form part of the BSC cohort.
- We do not have information on 17p deletion or TP53 mutation status available for the BSC cohort and will not be able to distinguish between populations 3 and 4.
- The analytical design does not differentiate between patients in the BSC cohort who are treated with supportive care packages (as described above), and those who receive additional lines of active SACT. From the SACT database, we can

identify patients who receive additional lines of SACT (although see caveats regarding ascertainment). Patients may end their treatment with a BCRi due to toxicity or progression. However, stable patients may also take an extended treatment break between cycles of BCRi which we may incorrectly identify as having ended treatment. We cannot distinguish between patients who are in a palliative stage in their disease, or those who have stable disease and are being actively monitored between lines of therapy, as both are characterised by the absence of SACT activity. This is critical as it means we are unable to reliably identify BSC treatment switchers (see below) and those who are on an extended treatment break between cycles of BCRi.

- The CDF eligibility criteria also includes patients who are BCRi unsuitable (populations 1 and 2 in Figure 3), however, using NCRAS data we are unable to identify patients who are contraindicated for a BCRi, and therefore these patients will not enter the BSC cohort.
- Patients with small lymphocytic lymphoma (C83.0) can receive venetoclax through the CDF, however, DCA did not include these patients as part of the BSC cohort[1]. As of 2nd March 2019, there were 4 of 135 patients in the CDF cohort with a diagnosis of small lymphocytic lymphoma.

Ascertainment, data quality and completeness

SACT data collection began in April 2012 and was mandated in April 2014. Since then, data quality and completeness have been steadily improving. The SACT team feedback data to the trusts via Cancer Stats 2 (https://cancerstats.ndrs.nhs.uk/) and through the Data Liaison team, and work with trusts to develop plans to improve their data submissions. In addition, the Medicines Optimisation Commissioning for Quality and Innovation (CQUIN) scheme 2017/18 included targets to incentivise trusts to improve SACT data.

The DCA specified that PHE would investigate data quality and completeness, with a view to determining whether the proposed analyses would be feasible. The following section summarises the the relevant data quality issues and their impact on the analysis.

Patient level ascertainment

In routinely collected SACT data, we are only aware of data on patients which trusts submit to us, and there is no ‘gold standard’ against which we can benchmark this to ascertain whether all of this has been submitted. In the event of the SACT being provided as a written

[1] SLL patients can be included in the BSC cohort if it is felt that this would improve the analytical design.

prescription, or the patient being excluded from the SACT upload (e.g. because information for some of the mandatory fields is not available), we will not be aware of these patients.

The cancer registry dataset (COSD) contains summary information regarding the treatment a patient received. In contrast to the SACT database, this will only include whether or not the patient has received SACT, the drug name, and this is typically limited to a short period following diagnosis, rather than the detailed information on regimen, cycle and administration dates over an extended period which is submitted to the SACT dataset.

We have used the treatment information submitted to COSD to cross-reference to the SACT dataset in an attempt to determine the ascertainment of the SACT dataset and the estimated proportion of treatment records which are missing and received.

Table 1: The number of CLL patients (C91.10) in with a treatment record in COSD and activity recorded in the SACT database from 1st January to 31st December 2016. There are no restrictions on patient diagnosis dates.

Total C91.10 patient treatment records in COSD	**Total C91.10 patient treatment records in SACT**	**NHS number and C91.10 match in both SACT and COSD**	**NHS number match in SACT and COSD C91.10 recorded in only one database**
1,217	2,877	754	145

Examination of the overlap between treatment records in the COSD dataset and the SACT database reveals that there are discrepancies between the two datasets, with a minority of cases appearing in both databases with an exact match on the ICD10 diagnosis of C91.10. There are 145 patient records where the NHS number matches between the different databases, but the ICD10 code does not. This may reflect that the patient had the incorrect ICD10 code submitted to the SACT database (either a different haematological malignancy or other cancer), or that the patient has a second independent primary tumour.

It is hoped that ascertainment will improve over time, however, this time period was selected to represent the period over which data for the BSC cohort will be collected.

We have additionally used the Hospital Episode Statistics (HES) database to try to benchmark ascertainment. HES collects data on all episodes of care delivered in the NHS. Table 2 compares the number of patients receiving either inpatient or outpatient care recorded in HES, to data recorded in the SACT database to further investigate ascertainment. The data demonstrates that the HES database substantially under-estimates the volume of leukaemia patients receiving SACT.

Table 2: Comparison between the number of patients in the SACT database with the number of patients recorded through Hospital Episode Statistics (HES) (in and out-patients) for Leukaemia patients (C91-C95, C962, C964, C968) over the period 01/03/17 – 28/02/18.

Appendix A details the OPCS codes which we have used to identify the SACT related appointments in HES.

	Hospital Episode Statistics	SACT
Leukaemia	6,473	12,051

Tables 1 and 2 highlight that comparisons which attempt to estimate the ascertainment for haematological malignancies in the SACT database are problematic. This is a significant limitation, as if we are not able to understand ascertainment, we cannot determine the extent to which missing data issues may affect the representativeness of the SACT cohort. It is possible that there is variation between how different trusts manage CLL, and if we are only receiving an unknown proportion of this data, we cannot be confident it is representative.

CDF Ascertainment

To receive a treatment funded by the CDF, consultants have to complete a Blueteq application form and submit this to NHS England. We can therefore identify the full cohort of patients who have received venetoclax through the CDF. In the event that we receive notification of a patient who has an application for a CDF drug but does not appear in the SACT data, we are able to contact directly the trust who made the application (and where the patient should be treated) to request that the data be submitted to the SACT system. Contacting trusts means that ascertainment is better for CDF patients in routinely collected SACT data, and that we are fully aware of our ascertainment.

The limitations highlighted above (tables 1 and 2) mean that it is not possible to be similarly confident in the ascertainment of the BSC cohort. There may be systematic reasons underpinning why the BCRi data (as an eligibility criteria to the BSC cohort) was not reported. These discrepancies between the two cohorts may bias any comparative analysis.

Data Completeness

Table 3: Data completeness for key variables for the venetoclax and BSC cohorts.

	Venetoclax		Best Supportive Care	
Characteristic	**Number**	**% of total tumours with data**	**Number**	**% of total tumours with data**
Sex	135	100	982	100
Age	135	100	982	100
Binet stage	25	19	140	14
Ethnicity	135	100	958	98
Performance status	106	79	685	70

Table 3 demonstrates that there is insufficient data to be able to generate matched cohorts beyond 'age', 'sex' and 'ethnicity'. These data are inadequate to capture the patients clinical picture.

Methods such as propensity score matching, which can be used to compare the efficacy of treatments from observational data, require that all potential confounders are known. This means that all the factors (e.g. test results) considered by clinicians in their treatment decision would need to be accounted for in the statistical model. The baseline co-variates in NCRAS data on CLL patients are insufficient to support such analytical approaches.

This poor data completeness for key variables will also impact our ability to provide informative baseline characteristics for the BSC cohort.

First cycle only reporting

First cycle only (FCO) reporting is a data completeness issue whereby only the first cycle of a patient's treatment is submitted to the SACT database. No subsequent cycles are submitted although the patient may continue on the treatment for several weeks or months. This data artefact is thought to arise as a result of cancer waiting times (CWT) targets. There is a significant incentive to upload the first treatment cycle in order to meet CWT targets. However, once these targets have been met, subsequent data is less likely to be reported. This was a greater issue before the widespread implementation of e-prescribing. Before e-prescribing, reporting SACT data required significant manual intervention and given limited time and resources, subsequent cycles of SACT were more likely to be de-prioritised.

Extent of FCO reporting

Table 4: BSC cohort, proportion of patients who have received a single cycle or administration of either ibrutinib or idelalisib only.

	Ibrutinib		Idelalisib	
	N patients	**% FCO**	**N patients**	**% FCO**
1st April 2012 – 31st Dec 2012	5	0.0%	2	0.0%
1st Jan 2013 – 31st Dec 2013	25	0.0%	1	0.0%
1st Jan 2014 – 31st Dec 2014	183	2.2%	27	3.7%
1st Jan 2015 – 31st Dec 2015	336	4.2%	101	4.0%
1st Jan 2016 – 22nd Aug 2016	240	3.3%	91	9.9%

From table 4, it may appear that FCO reporting is increasing over time. As noted above, we believe that this is not the case as the roll-out of e-prescribing is addressing this issue. Instead, the apparent increases are likely to be conflated with increased patient ascertainment over time. Amongst the FCO patients there are likely to be patients who only received a single cycle of treatment before their treatment was discontinued (for example due to toxicity, disease progression or patient choice), as well as those who continued to receive these treamtents for a longer period without this information being submitted to the SACT database. From the SACT database, we cannot discern the proportion of patients who only received a single cycle of BCRi, and the proportion who receive multiple cycles which were not submitted to the SACT database.

Impact of FCO reporting on analysis

For other CDF evaluations and typically for RCTs, overall survival (OS) is calculated from when a patient starts to take the drug under investigation. For the BSC cohort, overall survival will be calculated from the point when a patient ends their course of ibrutinib or idelalisib. This corresponds to the start of BSC. If treatment duration (tx dur) on ibrutinib and idelalisib are truncated due to FCO reporting, this will have a significant impact on the current evaluation, as we will assume patients have started on BSC at an earlier date, estimates of OS on BSC will include a time period when patients are still receiving a BCRi and analysis will be systematically biased to over-estimate OS of patients for the BSC cohort.

Patient accrual on venetoclax

The DCA forecast that there would be approximately 20 new applications per month for patients to receive venetoclax through the CDF, corresponding to approximately 240 over the period when venetoclax is in the CDF (see recommendation section 5.4 below). This number of patients was thought to be sufficient to give greater confidence to the extrapolations applied to the data in AbbVie's economic model. As of 2nd March 2019, the total number of patients in the venetoclax cohort is 135, and 3 of these patients received this drug through EAMS[2].

The eligibility criteria for CDF venetoclax state that this should be provided as a single agent. Of the 135 patients in the venetoclax cohort, 12 patients have received a further therapy whilst on venetoclax. Of these 12, 8 have received rituximab. These patients will be analysed as 'venetoclax treatment switchers' (see below). We will exclude the 4 patients who received additional therapies to venetoclax or rituximab from analyses. Including these patients would only complicate the estimation of the benefit of venetoclax monotherapy, as any benefits of additional drugs will be incorrectly attributed to venetoclax.

Treatment Switching Patients

For this analysis, there are 2 potential groups of treatment switching (crossover) patients.

1. **BSC treatment switchers**: patients who have ended treatment with a BCRi and receive BSC for a period of at least 6 weeks, then subsequently start venetoclax[3]. This corresponds to a treatment gap of 6 weeks between a BCRi and venetoclax. It should be noted that because of

[2] There may be different eligibility criteria between EAMS and CDF venetoclax cohorts.
[3] This is an arbitrary threshold which is required because the BSC cohort are defined from the end of treatment with BCRi's. As noted in the 'Differences in the venetoclax and BSC comparator cohort' section on the report, patients do not only end treatment with BCRi's because of progression or toxicity, but also because the patient is stable. As such, patients in the BSC cohort may be in several different diseases states, and for some, the 6 week threshold may be inappropriate. These patients may be on a treatment break between different lines of active therapy.

the FCO issue, patients may appear to be BSC treatment switchers, when in fact they have received consecutive BCRi and venetoclax treatments (and therefore are eligible for the venetoclax cohort).

2. **Venetoclax treatment switchers**: patients who receive venetoclax, and then have switched on to venetoclax and rituximab[4].

BSC treatment switchers

Based on the above definition, from the BSC cohort, 62/982 patients 'treatment switch' to venetoclax after a period of at least 6 weeks on BSC. This corresponds to 42 patients who received ibrutinib, and 20 patients who received idelalisib as a BCRi.

Correspondingly, this means 62/135 (current cohort: 23rd August 2016-2nd March 2019) of the current venetoclax cohort are BSC treatment switchers. It it likely these patients switched when venetoclax first became available on the CDF.

Venetoclax treatment switchers

Since venetoclax monotherapy entered the CDF, venetoclax with rituximab has been approved for use in CLL and has entered routine commissioning. The Final Appraisal Document (FAD) published on the 18th January 2019. It is likely that the approval of venetoclax with rituximab will reduce the number of patients receiving venetoclax monotherapy through the CDF. Patients may directly start combination therapy and never receive the monotherapy. Alternatively "venetoclax treatment switchers" may move from the monotherapy to rituximab combination therapy. Patients who are in the initial titration period (typically 5 weeks) of taking venetoclax are able to switch to venetoclax and rituximab combination therapy, provided their consultant makes NHS England aware of this. However, as demonstrated above, it is evident from the data that some consultants are prescribing venetoclax and rituximab to their patients without making NHS England aware of this.

From 21st January 2019 to 28th February 2019, 20 patients had a successful application for venetoclax & rituximab . Of these 20 patients, 1 had previously received venetoclax monotherapy on the CDF. This patient will be analysed as a 'venetoclax treatment switcher'.

Approaches to analysing treatment switching patients

An appropriate methodology is needed to manage treatment switching and ensure patients are assigned to the correct cohort to provide baseline characteristics, and for overall survival and treatment duration calculations.

Left censoring

The left censoring (LC) approach would exclude all BSC treatment switchers from the BSC cohort, and only include them in the venetoclax cohort.

[4] Only patients who move on to venetoclax and rituximab following venetoclax will be considered as 'venetoclax treatment switchers'. No further active SACT treatments should be used following venetoclax. We will provide details of what further treatments patients have had in reports.

Advantages

- This is the only method whereby the 62/135 of the venetoclax cohort who are BSC treatment switchers could be analysed as part of the venetoclax cohort.

Disadvantages

- This approach may introduce bias as the cohort in which patients are analysed is likely to be influenced by prognosis. Specifically, it is likely that the fittest patients be considered for venetoclax and would switch. These patients would not be included in the BSC cohort which will bias the analysis to make BSC OS worse.

Intention To Treat

The Intention to Treat (ITT) would analyse all patients in the cohort in which they started out.

Advantages

- This approach is widely used in the clinical literature.

Disadvantages

- 62/135 patients in the venetoclax cohort are BSC treatment switchers. Analysing these patients as BSC patients would substantially reduce the number of patients in the venetoclax cohort.
- Any additional benefit BSC treatment switchers received from venetoclax would be incorrectly attributed to BSC.

Per Protocol

The Per Protocol (PP) approach would censor all patients from the analysis when they switch treatments.

Advantages

- This approach is widely used in the clinical literature.

Disadvantages

- 62/135 patients in the venetoclax cohort are BSC treatment switchers. Censoring these patients from the analysis would substantially reduce the number of patients in the venetoclax cohort.
- Bias is likely in this design as BSC treatment switchers have survived long enough and are well enough for their clinicians to consider a course of venetoclax. Censoring them at the point at which the receive venetoclax may underestimate the benefit of BSC. The treatment decision (for patients to receive venetoclax) is strongly related to their prognosis. A PP design is particularly inappropriate when treatment switching is strongly related to prognosis (Morden, Lambert, Latimer, Abrams, & Wailoo, 2011).

Complex approaches to treatment switching

There is insufficient baseline co-variate information on the patients to use more complex approaches to manage treatment switching. Such approaches adjust for the impact of receiving either treatment on overall survival when comparing cohorts.

Treatment switching conclusion

Sensitivity analysis will be conducted using each of these approaches. This will provide a range of values, however, all estimates are likely to be biased and it is not clear which method is preferable. Therefore interpretation of the results is likely to be problematic.

It should be noted that depending on which approach is selected to deal with treatment switching, there may be insufficient patients in the venetoclax monotherapy cohort to address committee uncertainty. This issue will become particularly critical should patients continue to switch to venetoclax and rituximab, or less new patients are accrued to the venetoclax monotherapy cohort.

Conclusion

Venetoclax treatment for CLL entered the CDF as there was uncertainty around clinical and cost effectiveness. One of the key reasons for the uncertainty was that the clinical trials used in the evidence submission to NICE for review presented data from uncontrolled trials, and there were doubts as to the appropriateness of the comparator cohorts.

The NICE committee advised they would need results from the following analyses to be able to make a decision regarding whether venetoclax was appropriate for routine commissioning in the NHS;

- Matched cohort analysis comparing venetoclax and BSC
- Overall survival on ventoclax
- Overall survival on BSC

This report has examined the feasibility of providing these analyses. The following key issues have been identified;

Study design:

- The eligibility requirments for the BSC and venetoclax cohorts are different, which means any comparison of outcomes between these cohorts will be confounded.
- Patients in the BSC cohort may be in a variety of different stages of disease.

SACT ascertainment, data quality and completeness:

- The lack of baseline co-variate information on these patients means matched cohort analyses is not a possibility.
- Ascertainment issues do not allow the accurate calculation of treatment duration for ibrutinib or idelalisib, which in turn will undermine OS calculations for the BSC cohort.

Patient accrual on venetoclax:

- Venetoclax and rituximab entering routine commissioning may reduce patient accrual to the venetoclax monotherapy cohort.
- Treatment switching means it is not clear which cohort patients should be assigned to for analysis. Each approach to handling this issue is likely to introduce bias.
- Depending on the methods used to handle treatment switching, there may be significant reductions to the number of patients in the venetoclax monotherapy cohort.

Recommendations

For each of the analysis requirements set out in the DCA, we have outlined whether the SACT dataset can provide appropriate information and whether the proposed analysis is feasible.

Given the challenges identified in this report, we recommend that consideration is given to assess whether the analyses which can be provided by the SACT dataset and PHE would be sufficient to resolve uncertainty and inform the NICE committee decision on whether venetoclax should enter routine commissioning.

TableX: Detailed consideration of feasibility of analysis set out in the venetoclax DCS

Item	From DCA	Feasibility: Yes (Y) No (N) Caveated (C)	Notes
		Data	
2.1	Venetoclax. SACT will prospectively capture data on venetoclax use within the CDF. If patients can be identified, it is expected that SACT would also capture patients who initiated venetoclax as part of the EAMS program and the AbbVie 'free of charge' supply.	**Y**	We have excluded N=3 venetoclax patients receiving AbbVie's 'free of charge' supply before venetoclax entered EAMS funding, as the analysis requires the cohorts to be temporally non-overlapping. These patients received venetoclax several years previously and fall within the BSC cohort time period.
2.2	Comparator BSC. It is anticipated that retrospective analyses using the SACT dataset will capture the use of BSC after the following treatments: • Ibrutinib • Idelalisib with rituximab	**C**	We have broadened the eligibility criteria for the BSC cohort to include patients following treatment with ibrutinib or idelalisib, +/- rituximab This mirrors the eligibility criteria for venetoclax. Patients in our BSC cohort may have been prescribed ibrutinib or idelalisib on their own, or in combination with any other drug.
2.3	Providing that the follow-up is long enough, survival data may be available for patients on BSC following failure of ibrutinib or idelalisib in combination with rituximab.	**C**	Data completeness issues (FCO reporting) undermine our ability to adequately characterise treatment duration (tx dur) on BCRi's, which may affect BSC OS calculations.
		Outcomes	
3.1	Outcomes of interest are patients' time on treatment and overall survival along with baseline characteristics of patients included in the SACT	**C**	We can provide the following baseline characteristics for BSC and venetoclax cohorts; • Age (at diagnosis) • Age (treatment start)

	dataset. It is noted that characteristics and prognostic factors will not be available for BSC.		• Gender • Ethnicity We can provide the following additional baseline characteristics for the venetoclax cohort; • 17p/TP53 deletion status • Performance status • Whether the patient is contraindicated for BCRi Treatment switching will affect estimates of OS and tx dur for the venetoclax cohort. We will provide LC, ITT and PP analyses although all will be subject to bias. FCO reporting means we are unable to accurately identify patients who are 'treatment switchers', as they may have missing data. For BSC, tx dur and OS are the same. Data completeness issues (FCO reporting) undermine our ability to adequately characterise tx dur on BCRi's, which will affect OS calculations on BSC.
3.2	Collection of time on treatment and overall survival for venetoclax will reduce the uncertainty associated with the extrapolation of the survival outcomes in AbbVie's submission.	**C**	Treatment switching will affect estimates of OS and tx dur for the venetoclax cohort. We will provide LC, ITT and PP analyses although all will be subject to bias. FCO reporting means we are unable to accurately identify patients who are 'treatment switchers', as they may have missing data.
3.3	Outcome data will also be collected for BSC (following failure to ibrutinib and idelalisib in combination with rituximab) as the comparator in the appraisal of venetoclax. Similarly to venetoclax, collection of time on treatment and overall survival for BSC in the NHS population in England will reduce the uncertainty associated with the	**C**	For BSC, tx dur and OS are the same. Data completeness issues (FCO reporting) undermine our ability to adequately characterise tx dur on BCRi's, which will affect BSC OS calculations. Additionally, there are concerns regarding the ascertainment of SACT data, particularly for more historic data. Not understanding the

	extrapolation of the survival outcomes in AbbVie's submission. The availability and quality of retrospective data on BSC will be investigated to support data collection. However, older BSC data being collected routinely in SACT rather than current data linked to use within the CDF means that a difference in data quality is anticipated between venetoclax and BSC.		extent of missing data, or the reasons why the data is missing means that we cannot be confident that the data we have is representative of the entire NHS population. Treatment switching will affect estimates of OS and tx dur for the venetoclax cohort. We will provide LC, ITT and PP analyses although all will be subject to bias.
Venetoclax			
4.1	The total number of patients initiating treatment, patients' characteristics, overall survival, time on treatment	**C**	Treatment switching will affect estimates of OS and tx dur for the venetoclax cohort. We will provide LC, ITT and PP analyses although all will be subject to bias.
4.2	PHE will investigate the possibility of reporting mean dose received; and, if patients received any other SACT regimen prior to meeting the eligibility criteria and receiving venetoclax (this will not include detail on what, if any, prior regimens were received or when they were received).	**Y**	We can provide information on mean dose received by venetoclax patients following the initial titration period (35 days). The eligibility criteria for venetoclax on the CDF require patients to have had previous treatment with either chemo-immunotherapy or a BCRi, provided they are not contraindicated for BCRi. We will provide the analyses by these breakdowns (see 4.3 below).
4.3	Analyses will be undertaken for the following populations: • all the venetoclax patients who entered the CDF, • the venetoclax patients who have failed a BCRi, with a split between those presenting or not with 17p deletion/TP53 mutation • the venetoclax patients presenting with 17p deletion/TP53 mutation	**Y**	Breakdowns will be provided for each of these sub-cohorts.

	and unsuitable for a BCRi.		
		BSC	
5.1	the total number of patients initiating treatment, overall survival, time on treatment	**C**	We will provide details on how many patients are analysed as part of the BSC cohort. For BSC, tx dur and OS are the same. Data completeness issues (FCO reporting) undermine our ability to adequately characterise tx dur on BCRi's, which will affect BSC OS calculations.
5.2	PHE will investigate the possibility of reporting patients' characteristics; mean dose received; and, if patients received any other SACT regimen prior to meeting the eligibility criteria and receiving venetoclax (this will not include detail on what, if any, prior regimens were received or when they were received).	**N**	We believe this information has been carried over inappropriately from the venetoclax section of the form. It is not meaningful to provide mean dose received of BSC, as BSC is defined only in terms of having ended treatment with a BCRi. These patients may not be actively treated.
5.3	As highlighted (see 3.1), there will be a difference in past data availability and quality in data being collected routinely in SACT rather than current data for use with in the CDF.		
5.4	It is anticipated that approximately 240 new venetoclax patients will be enrolled in the CDF during the 1st year, in addition to existing patients who started venetoclax as part of the EAMS program or AbbVie 'free of charge' supply. As hypotheses will not be tested and data from a naïve comparison between venetoclax and BSC will be incorporated into the economic model, it is AbbVie's position that in addition to the ~ 100 existing patients, the 240 new patients enrolled over	**N**	Patient accrual may not be sufficient to reach this target of 240 patients. Venetoclax and rituximab (V&R) has recently been approved for routine commissioning which may affect recruitment to the current venetoclax monotherapy cohort, and some patients in the current cohort may switch to V&R. Numbers may be insufficient to give confidence in this analysis.

	12 months and followed up for approximately 24 months should give confidence in the survival data for venetoclax and confidence in showing a difference in survival between BSC and venetoclax, because much lower survival is anticipated for the BSC comparator.		
5.5	PHE will attempt undertake an analysis of the data collected on venetoclax vs BSC in the SACT dataset. It is important to attempt to match the venetoclax and the BSC populations to ensure a fair comparison can be drawn. However it is AbbVie's understanding that limited demographic and prognostic factors will be available for the comparator arm. AbbVie will therefore only be able to undertake a naïve comparison of venetoclax vs. BSC.	**N**	It is not possible to create matched cohorts of these patient groups as there is insufficient baselines co-variate data on patients.
5.6	In order to attempt to match patients who received Venetoclax or BSC, PHE and NICE will explore the potential for this process to be undertaken.	**N**	It is not possible to create matched cohorts of these patient groups as there is insufficient baselines co-variate data on patients.

Appendix A

OPCS codes in HES	Description
X352	Intravenous chemotherapy
X373	Intramuscular chemotherapy
X384	Subcutaneous chemotherapy
X701	Procurement of drugs for chemotherapy for neoplasm for regimens in band 1

X702	Procurement of drugs for chemotherapy for neoplasm for regimens in band 2
X703	Procurement of drugs for chemotherapy for neoplasm for regimens in band 3
X704	Procurement of drugs for chemotherapy for neoplasm for regimens in band 4
X705	Procurement of drugs for chemotherapy for neoplasm for regimens in band 5
X708	Other specified procurement of drugs for chemotherapy for neoplasm in bands 1-5
X709	Unspecified procurement of drugs for chemotherapy for neoplasm in bands 1-5
X711	Procurement of drugs for chemotherapy for neoplasm for regimens in band 6
X712	Procurement of drugs for chemotherapy for neoplasm for regimens in band 7
X713	Procurement of drugs for chemotherapy for neoplasm for regimens in band 8
X714	Procurement of drugs for chemotherapy for neoplasm for regimens in band 9
X715	Procurement of drugs for chemotherapy for neoplasm for regimens in band 10
X718	Other specified procurement of drugs for chemotherapy for neoplasm in bands 6-10
X719	Unspecified procurement of drugs for chemotherapy for neoplasm in bands 6-10
X721	Delivery of complex chemotherapy for neoplasm including prolonged infusional treatment at first attendance
X722	Delivery of complex parenteral chemotherapy for neoplasm at first attendance
X723	Delivery of simple parenteral chemotherapy for neoplasm at first attendance
X724	Delivery of subsequent element of cycle of chemotherapy for neoplasm
X728	Other specified delivery of chemotherapy for neoplasm
X729	Unspecified delivery of chemotherapy for neoplasm
X731	Delivery of exclusively oral chemotherapy for neoplasm
X738	Other specified delivery of oral chemotherapy for neoplasm
X739	Unspecified delivery of oral chemotherapy for neoplasm
X748	Other specified other chemotherapy drugs
X749	Unspecified other chemotherapy drugs

References

Morden, J. P., Lambert, P. C., Latimer, N., Abrams, K. R., & Wailoo, A. J. (2011). Assessing methods for dealing with treatment switching in randomised controlled trials: a simulation study. *BMC Med Res Methodol, 11*, 4. doi:10.1186/1471-2288-11-4

SACT. (2019). Partnership on Cancer Data and the Cancer Drugs Fund.

Table 1. Patient characteristics CDF cohort by mutation status, ABSENCE of 17p deletion (N=245)

Patient characteristics[1]			
		N	**%**
Sex	Male	172	70%
	Female	73	30%
Age	<40	1	Less than 1%
	40 to 49	4	2%
	50 to 59	25	10%
	60 to 69	67	27%
	70 to 79	102	42%
	80+	46	19%
Performance status	0	58	24%
	1	88	36%
	2	20	8%
	3	1	Less than 1%
	4	0	0%
	Missing	78	32%

[1] Figures may not sum to 100% due to rounding.

Table 2. Patient characteristics CDF cohort by mutation, PRESENCE of 17p deletion or TP53 mutation (N=161)

Patient characteristics[2]			
		N	**%**
Sex	Male	103	64%
	Female	58	36%
Age	<40	0	0%
	40 to 49	3	2%
	50 to 59	19	12%
	60 to 69	42	26%
	70 to 79	63	39%
	80+	34	21%
Performance status	0	26	16%
	1	58	36%
	2	20	12%
	3	6	4%
	4	0	0%
	Missing	51	32%

[2] Figures may not sum to 100% due to rounding.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Venetoclax for treating chronic lymphocytic leukaemia (CDF review of TA487) [ID3886]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Joint Submission from Leukaemia Care and CLL Support
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	**Leukaemia Care** is a national blood cancer charity, founded in 1969. We are dedicated to ensuring that anyone affected by blood cancer receives the right information, advice and support. Approximately 85-90% of our income comes from fundraising activities – such as legacies, community events, marathons etc. Leukaemia Care also receives funding from a wide range of pharmaceutical companies, but in total those funds are less than 15% of our annual income. Leukaemia Care has undertaken a voluntary commitment to adhere to specific policies that regulate our involvement with the pharmaceutical industry set out in our code of practice here: https://media.leukaemiacare.org.uk/wp-content/uploads/Leukaemia-CARE-Code-of-Practice-pdf.pdf. **CLL Support** is the only UK CLL specific support charity which was formed in 2005 and is run entirely by volunteers. The charity's remit is to provide support to people affected by CLL and its subtypes by keeping them informed of recent and relevant developments in CLL treatment and research and to provide opportunities for awareness raising and mutual support. This requires the association to support and aid empowerment through education while advocating for improving outcomes and access to better treatments. CLLSA provides support to the UK CLL community and CLLSA membership of 2,000+ association members who live with CLL or are carers and the 15,000+ CLLSA on-line community members on the Health Unlocked CLL Support platform (not all UK based). CLLSA provides up to 6 patient conferences a year including a regular Scottish patient's conference. Since 2020 the meeting have been via Webinars because of COVID19 and have been topical and more frequent.

	CLLSA support patients through telephone and email, one to one at meetings, literature in the form of patient information packs, newsletters and the websites: http://www.cllsupport.org.uk and their online presence on Health Unlocked https://healthunlocked.com/cllsupport . The association is supported and generously funded by member's donations, legacies, members' fund raisers and unrestricted educational grants from various pharmaceutical companies.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	**Leukaemia Care:** Pfizer £10,000 support services **CLL Support:** • Janssen - £7,500 Core funding of member services • Astra Zeneca - £14,000 Core funding of member services • Astra Zeneca - £10,000 Wellbeing App development • Roche - £15,000 Core funding of member services • Gilead - £15,000 Core funding of member services • Abbvie - £12,000 Core funding of member services
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

5. How did you gather information about the experiences of patients and carers to include in your submission?	Quotes were obtained from one-on-one discussions with CLL patients. Clinical advisers, including CNS's and consultants, also shared some insight into the patient experience and changes since the original appraisal. Data was also included from a survey we conducted for CLL patients before the original submission.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with the condition has not changed since the original appraisal. CLL remains the most common form of leukaemia, and a CLL diagnosis has a significant physical, mental and financial impact on patients and their families, which affects the CLL patient's quality of life. CLL patients are especially prone to relapsing-remitting and, as CLL is incurable, patients will often be thinking about their next treatment and worrying about what challenges this will bring, including whether it will work in bringing about a response. A CLL patient we spoke to who has had multiple lines of treatment said, *"To live with CLL, every day you know you cannot be cured of this cancer*". This highlights the ongoing stress and mental health impact of CLL treatment on the patient as well as their family, friends and carers.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments	Since the original appraisal venetoclax combinations have been approved in 2 other settings. Venetoclax obinutuzumab (Ven-O) was approved in 1st line treatment and venetoclax rituximab (Ven-R) was approved

and care available on the NHS?	in the relapsed/refractory setting. Acalabrutinib was also approved in both 1st line and in the relapsed/refractory setting. Patients typically welcome more treatment options in CLL. One patient describes what increased treatment options mean to them by saying "*I am a relatively young CLL patient and see living with CLL as a series of treatment stepping stones to achieve as normal a life expectancy as is possible. Knowing there will be other treatments available when my current treatment fails gives me hope for a future and the strength to live with this insidious disease".*
8. Is there an unmet need for patients with this condition?	Whilst the newly approved drugs in this setting have increased treatment options in CLL since NICE's original appraisal, they don't eradicate the need for venetoclax monotherapy. Below are the scenarios where there is still an unmet need in CLL treatment, and where venetoclax monotherapy could be used. Firstly, not every CLL patient is suitable to have the venetoclax combination treatments, such as those who are unable to tolerate or are unsuitable for monoclonal antibodies (including both obinutuzumab and rituximab). Secondly, there is an unmet need in those who have reduced 1st line treatment options due to an ineligibility for FCR or who started treatment before Ven-O was approved in 1st line. Finally, there is an unmet need for all those patients who have run out of other treatment options, including those who have previously had venetoclax combination treatments and relapsed subsequently. This is because as both venetoclax combinations are fixed duration treatments, our clinical adviser suggested patients are unlikely to build up resistance to venetoclax whilst taking the combinations and might therefore still be eligible to receive venetoclax monotherapy treatment. There therefore remains a strong unmet need in this population to provide more suitable treatment options and prolong patient's lives, especially given how common relapse is in CLL and that the alternative is likely to be best supportive care and ultimately death (in a matter of months).

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	As previously mentioned, venetoclax monotherapy provides another option for those who are unsuitable for the venetoclax combinations, for those who have reduced 1st line treatment options (due to an ineligibility for FCR or not having the option of Ven-O at the time), and for all those who have run out of other options including patients who have previously had venetoclax combinations and relapsed subsequently. As a result, venetoclax monotherapy could prolong the life of CLL patients. A key advantage of venetoclax is the removal of a previous safety issue that was present during the original submission and has since been significantly reduced. Previously patients often experienced tumour lysis syndrome when starting out on high doses of venetoclax. However, it has since been acknowledged that gradual increases in the dosage of venetoclax over time would avoid this. This has alleviated the previous concern over tumour lysis syndrome, which resulted often from patients being placed immediately on high dose and their immune systems 'overreacting', rather than increasing the dose over time. Venetoclax monotherapy is a continuous treatment and our clinical adviser, who has experience of caring for those on venetoclax, informed us that as patients are likely to have had multiple other lines of treatment, some patients, particularly elderly patients, feel safer/reassured staying on one treatment for a continued duration. Another advantage which has emerged recently, is the movement towards more outpatient rather than inpatient delivery of venetoclax in most centres during the dose escalation stages. One of our clinical advisers commented that with venetoclax, almost 100% of their patients are outpatients now. This is advantageous from both a patient and a clinician perspective. For the clinician and the hospital, the level of care, time and space required is reduced as fewer patients are admitted for treatment. For the patient this means that while they have to come into hospital during dose escalation, they do not have to stay in which enables them to spend more time with family and loved ones and to lead a more "normal" life.

	Venetoclax offers a clinically effective treatment, with tolerable side effects, high response rates and symptom control. Of the 248 patients surveyed for the original submission, 6 had received venetoclax. Of these, 5 said that it *"managed all of my symptoms*". A significant proportion of patients from original trial data were achieving MRD negativity, which is a recognised surrogate in CLL for depth of remission and likely endurance. Our clinical advisor also told us that they have continued to see MRD negative responses with venetoclax based therapies since the original submission. During the original submission when asked about their experience with venetoclax and whether it had changed their long-term health and well-being patients commented: *"Have my normal life back. No fatigue. Feel great."* *"Still early in trial but fatigue/energy has improved significantly. I have hope for a good future"* (highlighting how quickly symptoms have improved). *"Kept me alive with hope that I may have a long remission so I can lead a normal life (apart from check-ups at hospitals and while I am on the trial drug, I can only get it from the London Base of the trial)."* *"Positive experience as do not feel ill or severely fatigued."*
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	*As mentioned, venetoclax monotherapy is a continuous treatment. This means in some cases any side effects of being on treatment might be sustained long-term. However, as mentioned above, the majority of CLL patients we surveyed who had tried venetoclax commented that venetoclax actually "managed all of my symptoms" and the side effects appear not to be severe enough as to negatively impact patients' experience of "normal" life.*

	Our clinical adviser informed us that they noticed a difference in preference of continuous treatment depending on the age of the patient. While some patients, typically older patients, can feel safer/reassured on continuous treatment, other patients, typically younger patients, favour having an end point of treatment and see this as a time where they can revert back to some sort of normality without the constant reminder of daily medication. *The continuous nature of venetoclax treatment also renders it more expensive compared to fixed duration treatments. However, the more treatments which are becoming available in this setting, the fewer patients will need venetoclax monotherapy. Whilst venetoclax monotherapy is still required to satisfy a strong unmet need in patients who have run out of other options, the cost can hopefully be mitigated due to increased treatment options. The increased number of patients who are now outpatients receiving venetoclax also reduces overall cost of treatment.* *However, our clinical adviser shared with us that patients who are typically elderly and may be more frail find it difficult to attend the regular outpatient visits required during the dose escalation phase of venetoclax.* *Another disadvantage of venetoclax monotherapy is the potential side effects. Of the six patients surveyed who had received venetoclax, the side effects they had experienced include: nausea (2 patients), anaemia or neutropenia (2), diarrhoea (2) and fatigue (2). Two patients said that they had experienced none of these. However, the patients all commented that these were side effects that they were willing to tolerate.* *"Very benign experience. Fatigue from stepwise dose increases. Some slight nausea early-on, indigestion/gas/diarrhoea which has improved significantly."* *"Additional fatigue is only lasting a couple of days after dose increase. No other side effects."*

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	All those who have run out of other treatment options in the relapsed setting could benefit from venetoclax monotherapy. This includes those who are unsuitable for/unable to tolerate Ven-O and Ven-R, those who have previously had venetoclax combinations and subsequently relapsed, and those who have one less option than other patients if they are ineligible for FCR in 1st line treatment or they started 1st line treatment before Ven-O was introduced in this setting.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**N/a**

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- CLL has high relapse rates and a strong unmet need for more treatment options before best supportive care because of the range of comorbidities in this population.
- Whilst venetoclax combinations and acalabrutinib have increased treatment options since the original appraisal, they do not eradicate the need for venetoclax monotherapy.
- The safety issue of tumour lysis syndrome has been significantly improved since the original submission.
- Many patients who are receiving venetoclax monotherapy are now able to receive their dosage escalation as outpatients.
- All the patients we spoke to who had received venetoclax monotherapy said that the side effects were tolerable.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Venetoclax for treating chronic lymphocytic leukaemia (CDF review of TA487) [ID3886]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Lymphoma Action
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Lymphoma Action is a national charity, established in 1986, registered in England and Wales and in Scotland. We provide high quality information, advice and support to people affected by lymphoma – the 5th most common cancer in the UK. We also provide education, training and support to healthcare practitioners caring for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the only charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone. Lymphoma Action is not a membership organisation. We are funded from a variety of sources predominantly fundraising activity with some limited sponsorship and commercial activity. We have a policy for working with healthcare and pharmaceutical companies – those that provide products, drugs or services to patients on a commercial or profit-making basis. The total amount of financial support from healthcare companies will not exceed 20% of our total budgeted income for the financial year (this includes donations, gifts in kind, sponsorship etc) and a financial cap of £50,000 of support from individual healthcare companies per annum (excluding employee fundraising), unless approval to accept a higher amount is granted by the Board of Trustees. The policy and approach ensures that under no circumstances will these companies influence our strategic direction, activities or the content of the information we provide to people affected by lymphoma. https://lymphoma-action.org.uk/about-us-how-we-work-policies-and-terms-use/working-healthcare-and-pharmaceutical-companies

4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	AbbVie: £12,000 (support for information and education activities) Roche Products: £21,000 (support for information and education activities)
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and	n/a

carers to include in your submission?	
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Lymphoma Action supports the submission made by Leukaemia Care
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Lymphoma Action supports the submission made by Leukaemia Care
8. Is there an unmet need for patients with this condition?	Lymphoma Action supports the submission made by Leukaemia Care

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Lymphoma Action supports the submission made by Leukaemia Care
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Lymphoma Action supports the submission made by Leukaemia Care
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Lymphoma Action supports the submission made by Leukaemia Care

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Lymphoma Action supports the submission made by Leukaemia Care
Other issues	
13. Are there any other issues that you would like the committee to consider?	Lymphoma Action supports the submission made by Leukaemia Care
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • Lymphoma Action supports the submission made by Leukaemia Care	

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Drs** [redacted], [redacted], [redacted], [redacted]
2. Name of organisation	UK CLL Forum

<table>
<tr><td>3. Job title or position</td><td></td></tr>
<tr><td>4. Are you (please tick all that apply):</td><td>☒ an employee or representative of a healthcare professional organisation that represents clinicians?
☒ a specialist in the treatment of people with this condition?
☒ a specialist in the clinical evidence base for this condition or technology?
☐ other (please specify):</td></tr>
<tr><td>5a. Brief description of the organisation (including who funds it).</td><td>The UK CLL Forum is umbrella organisation for CLL in the UK which aims to bridge the gap between the clinical and scientific aspects of the disease. It provides framework where the UK CLL community, can input into issues such as guidelines, clinical trials and translational science. UK CLL Forum is a charity organisation and does receive support from interested Pharma companies.</td></tr>
<tr><td>4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]</td><td>. The funding listed below has been used to support the ongoing educational activities of the organisation.
<table>
<tr><th></th><th>2019</th><th>2020</th><th>2021</th></tr>
<tr><td>Roche</td><td>£10,000.00</td><td>£10,000.00</td><td>£6,000.00</td></tr>
<tr><td>Janssen</td><td>£7,000.00</td><td>£3,500.00</td><td>£7,000.00</td></tr>
<tr><td>Gilead</td><td>£10,000.00</td><td>n/a</td><td>n/a</td></tr>
<tr><td>AbbVie</td><td>£13,000.00</td><td>£10,000.00</td><td>£10,000.00</td></tr>
<tr><td>AstraZeneca</td><td>n/a</td><td>£10,000.00</td><td>£10,000.00</td></tr>
<tr><td>BeiGene</td><td>n/a</td><td>£1,000.00</td><td>£10,000.00</td></tr>
<tr><td>Novalgen</td><td>n/a</td><td>£250.00</td><td>n/a</td></tr>
<tr><td>Lipomed</td><td>n/a</td><td>£250.00</td><td>n/a</td></tr>
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If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	CLL is a cancer characterised by uncontrolled proliferation of lymphocytes within the bone marrow and/or lymph nodes. This leads to progressive bone marrow failure and/or worsening lymphadenopathy. The aim of treatment is to induce remission by clearing disease within the bone marrow and nodes and improve both progression free and overall survival. There is no cure currently for CLL and treatments have limited efficacy and associated toxicities. A regime with greater efficacy leads to resolution and maintenance of normal marrow function, control of lymphadenopathy and improved overall survival. In addition, as survival improves, the impact of therapies on longer term effects such as secondary cancer, cardiovascular health and Richter's transformation are increasingly important.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	In addition to resolution of lymphadenopathy and bone marrow function, we now can now also look for very deep remissions in the blood and bone marrow, using flow cytometry or next generation sequencing. We know that inducing these very deep remissions leads to improved PFS and OS.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, specifically for CLL patients with relapsed disease
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	CLL is treated with B cell receptor pathway inhibitors (principally BTKi such as ibrutinib and acalabrutinib) and venetoclax (in combination with anti-CD20 monoclonal antibodies or as monotherapy) in sequence. Chemo-immunotherapy is now rarely used following studies showing major superiority of non-chemotherapy regimens over these newer treatments, which have been assessed in a number of previous technology appraisals (TA359, TA429, TA487, TA561, TA663, TA 689). Updated guidelines from the BCSH are in press, and include Venetoclax Monotherapy for certain indications at each line of therapy. The current proposed BCSH first line recommendations are: • Venetoclax-obinutuzumab (VenO) or acalabrutinib are recommended and NICE-approved options as initial therapy in patients unsuitable for CIT irrespective of *TP53* status. • Bendamustine or chlorambucil-based CIT are no longer recommended. • NICE-approved treatment options for fit patients with *TP53* disruption include acalabrutinib, ibrutinib or venetoclax monotherapy for those with a contra-indication to B-cell receptor inhibitor. • Acalabrutinib is recommend for patients who have intact *TP53* and for whom FCR or BR are considered unsuitable.

	• For fit patients with intact *TP53*, VenO may be obtained via CDF. • For fit patients with intact *TP53* and with mutated *IGHV*, chemo-immunotherapy with FCR remains an acceptable initial therapy Relapsed patients are recommended to be treated as follows: • Targeted inhibitors (BTKi or BCL2i alone or in combination with rituximab) are the treatment of choice for relapsed CLL. • For patients relapsing after BTKi offer venetoclax-based regimens, irrespective of *TP53* status • For patients relapsing following fixed-duration venetoclax-based therapy consider either a BTKi (Grade III) or venetoclax re-treatment depending on duration of PFS1 • For relapsed patients who are intolerant to ibrutinib, offer either venetoclax-based therapy or acalabrutinib depending on the reason for intolerance • For patients relapsing on BTKi, continue treatment until alternative therapy is initiated • Idelalisib-rituximab remains an option for relapsed patients who are unsuitable for or who are refractory to BTKi and BCL2i-based treatment. • Patients with double refractory CLL after BTKi and BCL2i should be considered for clinical trials
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	• Guideline for the treatment of chronic lymphocytic leukaemia**, 2021 ;** on **behalf of the Haemato-Oncology** Task Force of the British Society for Haematology**, in press BJHaem, this is an update on the published 2018 guidelines (2018:** Treatment of chronic lymphocytic leukaemia | British Society for Haematology (b-s-h.org.uk)) • Clinical Practice Guidelines – Chronic Lymphocytic Leukaemia (esmo.org) • iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL | Blood | American Society of Hematology (ashpublications.org)
• Is the pathway of care well defined? Does it	TA487 approved continuous Venetoclax monotherapy, within the conditions of the managed access agreement, for CLL patients with

vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	• 17p deletion or TP53 mutation and when a B-cell receptor pathway inhibitor is unsuitable • disease progression 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 This initial technology appraisal for Venetoclax was approved based on evidence from Phase 1 and 2 single arm clinical trials and the treatment landscape for CLL has evolved and expanded significantly since its publication in 2017. Phase 3 trials followed, using Venetoclax in combination with immunotherapy (either Obinutuzumab or Rituximab) and the majority for a fixed duration rather than continuous therapy. There is now evidence of Venetoclax (plus antibody) superiority over conventional CIT in the setting of untreated, high risk and relapse/ refractory disease. Current trials should help further define the optimal sequencing, drug partners and duration (fixed vs intermittent vs continuous) of both Venetoclax and the B-cell receptor inhibitors. The VENICE 1 study, a phase 3 b study comparing Venetoclax Rituximab to Venetoclax Monotherapy alone has been published in abstract form and shows equivalence between the two regimens. Patient factors such as co-existent cardiac disease, renal function, bleeding risk, drug interactions and ease/ desirability of hospital visits are already part of patient and physician treatment discussions and decisions.
• What impact would the technology have on the current pathway of care?	Technology already in use, and has an important role in CLL pathway and has been used in patients who relapsed post fixed duration of Venetoclax Obinutuzumab or Venetoclax Rituximab, it is important to add there is a sizeable group of patients that have received Venetoclax monotherapy based on the indications above and that are still on therapy.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	In 2021, Venetoclax is more commonly used in combination with Rituximab (for R/R disease – Murano data) for 24 months or with Obinutuzumab in the upfront setting (CLL 14 data) for 12 months. Nonetheless, extended, fixed-duration venetoclax treatment is well tolerated, with potential for mild myelosuppression and infrequent need for dose-adjustment for toxicity (most commonly neutropenia). Efficacy following intolerance of or progression on BTKi is well documented. Venetoclax monotherapy is specifically recommended as a treatment option in the clinical guidelines referenced above for: • BCSH: o 2nd line with p53 deletion or disruption o Consider 3rd line with progression after fixed-term Ven-R • ESMO o 1st line with p53 deletion or disruption o R/r with p53 deletion or disruption
• How does healthcare resource use differ between the technology and current care?	In current practice
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist Haematology Clinics, as per current standard of care in the frontline and relapsed setting
• What investment is needed to introduce the technology? (For	None

example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Important option of treatment or re-treatment especially for patients with intolerance or contraindication for BTKi

The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Already in use. Initial dose escalation requires multiple hospital visits over a 5 week period, but in the longer term is well tolerated with few emerging later effects, in contrast to longer term BTKis.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Will follow current guideline recommendations

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	There is no doubt that Venetoclax therapy has made a huge contribution to PFS, quality and quantity of life in CLL. It will continue to be used either alone or in combination with other small molecules or antibodies at all stages of disease. Current trials should help further define the optimal sequencing, drug partners and duration (fixed vs intermittent vs continuous) of both Venetoclax and the B-cell receptor inhibitors.
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any	

particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict	

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No significant emerging late effects with ongoing follow-up
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Efficacy of venetoclax monotherapy in patients with relapsed chronic lymphocytic leukaemia in the post-BCR inhibitor setting: a UK wide analysis - Eyre - 2019 - British Journal of Haematology - Wiley Online Library Venetoclax Effectiveness, Safety, and Treatment Patterns in Chronic Lymphocytic Leukemia Patients: Results from the CLL Collaborative Study of Real-World Evidence (CORE) | Blood | American Society of Hematology (ashpublications.org)
20. How do data on real-world experience compare with the trial data?	Yes UK data: provides the first evidence in the non-trial setting of equivalent efficacy and survival in patients exposed to BTKi, PI3Ki or both classes of BCRi US data: consistent with trial experiences, venetoclax demonstrates high response rates, including high-risk groups, and a manageable safety profile with low rates of TLS in clinical practice

Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	No

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.

- Venetoclax is a targeted therapy that is extremely potent in CLL, including high-risk del(17p)/mutated-*TP53* CLL and CLL refractory to CIT and has improved both PFS and OS in treatment naïve and relapse/refractory patients
- Data on continuous Venetoclax monotherapy as described in TA487 was, and still is, limited to Phase 1 and 2 clinical trials
- Randomised data against CIT regimens is based on Venetoclax used in combination with monoclonal antibodies to CD20 in a time-limited fashion, but the optimum treatment partner and therapy duration remains to be determined.
- There is very good evidence for the efficacy of Venetoclax after BTKi intolerance or failure
- Venetoclax monotherapy remains an important therapy option for patients who may be unable to tolerate monoclonal antibodies, or in those who lose response after fixed term Venetoclax combination therapy regimens.

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Public Health England

Protecting and improving the nation's health

Venetoclax for treating chronic lymphocytic leukaemia – data review

Commissioned by NHS England and NHS Improvement

Contents

Executive summary

Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of venetoclax for chronic lymphocytic leukaemia. The appraisal committee highlighted clinical uncertainty around estimates of overall survival (OS) and duration of treatment in the evidence submission. As a result, they recommended the commissioning of venetoclax through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England and NHS Improvement commissioned Public Health England (PHE) to evaluate the real-world treatment effectiveness of venetoclax in the CDF population, during the managed access period. This report presents the results of the use of venetoclax in clinical practice in England, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The NHS England and NHS Improvement and PHE partnership for collecting and following up real-world SACT data for patients treated through the CDF in England has resulted in analysis being carried out on 100% of patients and 75% of patient outcomes reported in the SACT dataset. PHE also analysed a cohort of patients that were treated via an Early Access to Medicine Scheme (EAMS) where analysis was carried out on 99% of patients and 77% of patient outcomes reported in the SACT dataset. PHE and NHS England and NHS Improvement are committed to providing world first, high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

NHS England and NHS Improvement's Blueteq® system was used to provide a reference list of all patients with an application for venetoclax for chronic lymphocytic leukaemia in the CDF. Patient NHS numbers were used to link Blueteq applications to PHE's routinely collected SACT data to provide SACT treatment history.

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

(see Figures 2 and 5), 406 unique patients who received treatment were included in these analyses. 105 unique patients were identified as EAMS, following appropriate exclusions (see Figures 1 and 4), 102 patients who received treatment were included in these analyses.

All patients were traced to obtain their vital status using the personal demographics service (PDS)[1].

Results

406 (100%) unique patients with CDF applications were reported in the SACT dataset and 102 (99%) of EAMS patients were included in the final cohort.

Median treatment duration amongst the CDF cohort was 21.2 months [95% CI: 18.6, 24.7] (645 days). The median treatment duration amongst the EAMS cohort was 19.1 months [95% CI: 11.7, 27.0] (581 days) and for the combined cohort (CDF and EAMS) the median treatment duration was 21.2 months [95% CI: 17.9, 24.6] (645 days).

Table 1: Treatment duration at 6, 12, 18, 24 and 36-month intervals, combined cohort

Treatment duration (%)			
Time period	**CDF cohort**	**EAMS cohort**	**Combined cohort**
6 months	73% [95% CI: 68%, 77%]	74% [95% CI: 64%, 81%]	73% [95% CI: 69%, 77%]
12 months	63% [95% CI: 58%, 68%]	60% [95% CI: 50%, 69%]	63% [95% CI: 58%, 67%]
18 months	56% [95% CI: 50%, 61%]	51% [95% CI: 41%, 60%]	55% [95% CI: 50%, 59%]
24 months	47% [95% CI: 41%, 52%]	47% [95% CI: 37%, 56%]	47% [95% CI: 42%, 52%]
36 months	27% [95% CI: 21%, 34%]	28% [95% CI: 20%, 37%]	28% [95% CI: 23%, 33%]

At data cut off, 54% (N=220) of patients included in the CDF cohort and 82% (N=84) of EAMS patients were identified as no longer being on treatment. Of these 304 patients (220 CDF, 84 EAMS), 27% (N=53 CDF, N=30 EAMS) of patients stopped treatment due to progression, 8% (N=20 CDF, N=3 EAMS) of patients stopped treatment due to acute toxicity, 6% (N=16 CDF, N=3 EAMS) of patients chose to end their treatment, 32% (N=74 CDF, N=23 EAMS) of patients died not on treatment, 12% (N=24 CDF, N=13 EAMS) of patients died on treatment, 3% (N=6 CDF, N=3 EAMS) of patients completed treatment as prescribed and 12% (N=27 CDF, N=9 EAMS) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment.

Median OS amongst the CDF cohort was 43.1 months[a] (1,311 days). The median OS amongst the EAMS cohort was 32.5 months [95% CI: 20.3, 41.8] (989 days) and for the combined cohort the median OS was 38.5 months [95% CI: 31.3, 44.1] (1,171 days).

Table 2: OS at 6, 12, 18, 24 and 36-month intervals, combined cohort

OS (%)			
Time period	**CDF cohort**	**EAMS cohort**	**Combined cohort**
6 months	83% [95% CI: 79%, 86%]	80% [95% CI: 71%, 87%]	82% [95% CI: 79%, 85%]
12 months	75% [95% CI: 70%, 79%]	73% [95% CI: 63%, 80%]	74% [95% CI: 70%, 78%]
18 months	68% [95% CI: 63%, 73%]	65% [95% CI: 55%, 73%]	68% [95% CI: 63%, 72%]
24 months	63% [95% CI: 57%, 68%]	60% [95% CI: 50%, 69%]	62% [95% CI: 58%, 66%]
36 months	55% [95% CI: 49%, 60%]	46% [95% CI: 36%, 55%]	51% [95% CI: 46%, 56%]

Sensitivity analysis was carried out on treatment duration to evaluate a cohort for which all patients had a minimum follow-up of six months in SACT. Results for treatment duration showed a difference of 0.3 months (full cohort = 21.2 months; sensitivity analysis cohort = 20.9 months).

A secondary sensitivity analysis was carried out on the CDF cohort, splitting treatment duration and OS by mutation status. Results for treatment duration showed a difference of 4.4 months (presence of 17p deletion or TP53 mutation = 17.9 months; absence of 17p deletion or TP53 mutation = 22.3 months). Results for OS showed those without a 17p deletion or TP53 mutation was not reached. OS amongst those with a 17p deletion or TP53 mutation was 33 months (1,004 days).

A third sensitivity analysis was carried out to establish treatment duration and OS when removing patients that received rituximab on or after a patient's first venetoclax treatment, regardless of the time from a patient's first venetoclax treatment to their first rituximab treatment. Results for treatment duration showed a difference of 3.5 months amongst the CDF cohort (full cohort = 21.2 months; third sensitivity analysis cohort = 24.7 months). There was a difference amongst the EAMS cohort of 2.9 months (full cohort = 19.1 months; third sensitivity analysis cohort = 16.2 months) and the difference amongst the combined cohort was 3.4 month (full cohort = 21.2 months; third sensitivity analysis cohort = 24.6 months).

Results for OS showed no difference amongst the CDF cohort (full cohort = 43.1 months; third sensitivity analysis cohort = 43.1 months). The difference amongst the EAMS cohort was 2.3

[a] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced

months (full cohort = 32.5 months; third sensitivity analysis cohort = 34.8 months) and the difference amongst the combined cohort was 4.6 months (full cohort = 38.5 months; third sensitivity analysis cohort = 43.1 months).

Conclusion

This report analysed SACT real-world data for patients treated with venetoclax for chronic lymphocytic leukaemia in the CDF. It evaluates treatment duration, OS and treatment outcomes for all patients treated with venetoclax for this indication.

Introduction

Chronic lymphocytic leukaemia (ICD-10: C91) accounts for 1.3% of all cancer diagnoses in England. In 2018, 4,238 patients were diagnosed with chronic lymphocytic leukaemia (males 2,665, females 1,573)[2].

- Venetoclax is recommended for use within the Cancer Drugs Fund, within its marketing authorisation, as an option for treating chronic lymphocytic leukaemia, that is, in adults:
    - with a 17p deletion or TP53 mutation and when a B-cell receptor pathway inhibitor is unsuitable, or whose disease has progressed after a B-cell receptor pathway inhibitor **or**
    - without a 17p deletion or TP53 mutation, and whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor **and**
    - only if the conditions in the managed access agreement are followed[3].

Background to this report

The Public Health England and NHS England and NHS Improvement partnership on cancer data – using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England and NHS Improvement and Public Health England's (PHE's) ambitions of monitoring cancer care and outcomes across the patient pathway. The objective of the PHE and NHS England and NHS Improvement partnership on cancer data is to address mutually beneficial questions using Systemic Anti-Cancer Therapy (SACT) data collected by PHE. This includes NHS England and NHS Improvement commissioning PHE to produce routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access.

The CDF is a source of funding for cancer drugs in England[4]. From 29 July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical effectiveness. During this period of managed access, ongoing data collection is used to answer the clinical uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period[5].

PHE analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Cancer Registration and Analysis Service, which is part of PHE.

NICE Appraisal Committee review of venetoclax for treating chronic lymphocytic leukaemia [TA487].

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of venetoclax (AbbVie Inc.) in treating chronic lymphocytic leukaemia and published guidance [TA487] for this indication in November 2017[6].

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended the commissioning of venetoclax through the CDF for a period of 38 months, from October 2017 to December 2020.

For this indication, SACT is the primary source of data and will be used to answer clinical uncertainties raised by the NICE committee.

Analysis of the SACT dataset provides information on real-world treatment patterns and outcomes for venetoclax treating chronic lymphocytic leukaemia in England, during the CDF funding period.

The committee identified the key areas of uncertainty below for re-appraisal at the end of the CDF data collection;

- **Overall survival** from the start of a patient's first treatment with venetoclax
- **Matched cohort analyses** comparing the overall survival of best supportive care (BSC) and venetoclax patients[b].

Treatment duration was not an area of clinical uncertainty but has been included in this report.

Public health England have calculated treatment duration and overall survival for this indication. The BSC cohort was not included due to the under reporting of haematological malignancies in the SACT dataset at the time the BSC treatment option was available.

Approach

Upon entry to the CDF, representatives from NHS England and NHS Improvement, NICE, PHE and the company (AbbVie Inc.) formed a working group to agree the Data Collection Agreement (DCA)[6]. The DCA set out the real-world data to be collected and analysed to support the NICE re-appraisal of venetoclax. It also detailed the eligibility criteria for patient access to venetoclax through the CDF, and CDF entry and exit dates.

This report includes patients with approved CDF applications for venetoclax, approved through Blueteq® and followed up in the SACT dataset collected by PHE.

Methods

CDF applications – identification of the cohort of interest

NHS England and NHS Improvement collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

[b] During the period of managed access PHE conducted a feasibility assessment to investigate the ability of the SACT database to provide the data required to support these analyses. The SACT Operational Group determined that a matched cohort analyse would not provide meaningful analyses, and these analyses have not been produced.

Consultants must complete a Blueteq application form for every patient receiving a CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. PHE has access to the Blueteq database and key data items such as NHS number, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the United Kingdom (UK) General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). The processing of special categories of personal data is also covered under article 9(2)(h) of UK GDPR (processing is necessary for the purposes of preventive or occupational medicine). As NHS England and NHS Improvement do not have an exemption to the Common Law Duty of Confidentiality, NHS England and NHS Improvement cannot access the identifiable data directly. PHE, through the National Cancer Registration and Analysis Service, have permission to process confidential patient information though Regulation 2 of The Health Service (Control of Patient Information) Regulations 2002.

PHE collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Venetoclax clinical treatment criteria

- Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
- Confirmed diagnosis of chronic lymphocytic leukaemia or small lymphocytic lymphoma that requires treatment
- Patient has a performance status of 0-2
- Patient has been assessed specifically for potential drug interactions with venetoclax
- Venetoclax is to be used as a single agent
- Patient has been prospectively assessed for the risk of the development of tumour lysis syndrome following the start of venetoclax
- Venetoclax is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment
- No treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve)
- Venetoclax to be otherwise used as set out in its Summary of Product Characteristics

In the absence of 17p deletion or TP53 mutation the patient eligibility criteria also include the following:

- Patient has been tested for 17p deletion and TP53 mutation and both results are negative
- Patient must have progressive disease on or after chemoimmunotherapy
- Patient has 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.
- Patient must also either have progressive disease on or after treatment with a B-cell receptor pathway inhibitor: a Bruton's tyrosine kinase inhibitor (BTKi e.g. ibrutinib) or a PI3K inhibitor (PI3Ki e.g. idelalisib) or have a contraindication to receiving both a BTKi and a PI3Ki.

In the presence of 17p deletion or TP53 mutation the patient eligibility criteria also include the following:

- Patient is positive for testing for 17p deletion or TP53 mutation
- 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.

CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

1. If two trusts apply for venetoclax for the treatment of chronic lymphocytic leukaemia for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

2. If two trusts apply for venetoclax for the treatment of chronic lymphocytic leukaemia for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.

3. If two applications are submitted for venetoclax for the treatment of chronic lymphocytic leukaemia and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

Initial CDF cohorts

The CDF applications included in these analyses are from 5 October 2017 to 4 December 2020. A snapshot of SACT data was taken 5 June 2021 and made available for analysis on 11 June 2021 and includes SACT activity up to the 28 February 2021. Tracing the patients' vital status was carried out on 2 July 2021 using the Personal Demographics Service (PDS)[1].

There were 454 applications for CDF funding for venetoclax for the treatment of chronic lymphocytic leukaemia between 5 October 2017 and 4 December 2020 in the NHS England and NHS Improvement Blueteq database. Following de-duplication this relates to 429 unique patients.

Early Access to Medicine (EAMS) cohort

A further 105 unique patients were identified as receiving venetoclax for chronic lymphocytic leukaemia prior to the drug entering the CDF. These patients received treatment through the Early Access to Medicines Scheme (EAMS) that ran from 23 August 2016 to 5 December 2016, or other compassionate access programmes and were identified as any venetoclax treatment for chronic lymphocytic leukaemia recorded in the SACT dataset before 5 October 2017; or as EAMS applications recorded by NHS England and NHS Improvement. The eligibility of these patients at treatment start cannot be determined. The EAMS patients were required to meet the following eligibility criteria:

- Adult patient with chronic lymphocytic leukaemia in the presence of 17p deletion or TP53 mutations or who is unsuitable for or has failed a BCRi or
- Adult patient with CLL in the absence of 17p deletion or TP53 mutation, who is unsuitable for or has failed both chemo-immunotherapy and a BCRi

There is no record of eligibility criteria or the reason for receiving treatment for non-EAMS, early access patients in this cohort.

As a result of the uncertainly around patient eligibility, the CDF and EAMS cohorts will be analysed as two separate cohorts and as a single combined cohort.

Figure 1: Derivation of the early access cohort of interest.
23 August 2016 – 4 October 2017

All early access venetoclax[a,b] **(N=105)**

Figure 2: Derivation of the CDF cohort of interest
5 October 2017 - 4 December 2020

All venetoclax CDF applications[c] **(N=454)**

Exclusions Duplicate CDF applications **(N=25)**

CDF cohort of interest **(N=429)**

Figure 3: Derivation of the combined cohort of interest (CDF and early access)
23 August 2016 - 4 December 2020

All CDF and EAMS applications[d] **(N=559)**

Exclusions Duplicate CDF and EAMS applications **(N=25)**

Combined cohort of interest **(N=534)**

[c] Early access cohort identified as either:

[d] Patients identified as EAMS by NHSE-I (via NHSE-I Blueteq system or pre-Blueteq records)
[e] Patients with a CDF Blueteq application for venetoclax (5 October 2017 to 4 December 2020) and a venetoclax treatment record in SACT before the CDF start date (pre-5 October 2017)
[f] Patients with a C91.1 diagnosis in SACT and a venetoclax treatment record from 23 August 2016 onward (start of EAMS for venetoclax monotherapy). Patients with venetoclax before 23 August 2016 were excluded as they are likely to represent trial patients.

Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for venetoclax in NHS England and NHS Improvement's Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Addressing clinical uncertainties

Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT.

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest. Data items[7] used to determine a patient's earliest treatment date are:

- Start date of regimen – SACT data item #22
- Start date of cycle – SACT data item #27
- Administration date – SACT data item #34

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34)[7] are used to identify a patient's final treatment date. The latest of these three dates is used as the patient's final treatment date.

Additional explanation of these dates is provided below:

Start date of regimen
A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

Start date of cycle
A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example; a patient may be on a 3-weekly cycle with treatment being administered on the 1st and 8th day, but nothing on days 2 to 7 and days 9 to 20. The 1st day would be recorded as the "start day of cycle". The patient's next cycle would start on the 21st day.

Administration date
An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week

cycle would be on the 1st and 8th day. The next administration would be on the 21st day, which would be the start of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment.

All patients are then allocated a 'prescription length', which is a set number of days added to the final treatment date to allow for the fact that they are effectively still 'on treatment' between administrations. The prescription length should correspond to the typical interval between treatment administrations.

If a patient dies between administrations, then their censor date is their date of death and these patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database confirming that the patient ended treatment, for example, due to disease progression or toxicity before death.

Venetoclax is administered orally, treatment is generally prescribed in a healthcare facility and healthcare professionals are able to confirm that the prescribing of treatment has taken place on a specified date. A duration of 7-days (if within 35 days of commencing treatment) or 28-days has been added to the final treatment date for all patients; this represents the duration from a patient's last cycle to their next[8]. Venetoclax is a 28-day cycle consisting of one administration of 28 tablets.

Treatment duration is calculated for each patient as:
Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days). This date would be the patients censored date, unless a patient dies in between their last treatment and the prescription length added, in this case, the censored date would be the patients date of death.

Once a patient's treatment duration has been calculated, the patient's treatment status is identified as one of the following:

No longer receiving treatment (event), if:

- the patient has died.
- the outcome summary, detailing the reason for stopping treatment has been completed:
    - SACT v2.0 data item #41
    - SACT v3.0 data item #58 - #61.
- there is no further SACT records for the patient following a three-month period.

If none of the above apply, the patient is assumed to still be on treatment and is censored.

Overall survival (OS)

OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, as described above, and the patient's date of death or the date the patient was traced for their vital status.

All patients in the cohort of interest are submitted to the PDS to check their vital status (dead or alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

OS (days) = Date of death (or follow up) - treatment start date

The patient is flagged as either:

Dead (event):
At the date of death recorded on the PDS.

Alive (censored):
At the date patients were traced for their vital status as patients are confirmed as alive on this date.

Results

Cohort of interest

Of the 429 applications for CDF funding for venetoclax for the treatment of chronic lymphocytic leukaemia, seven patients did not receive treatment and 16 patients died before treatment. Of the 105 early access patients, two patients did not have a treatment record in SACT and one patient died before treatment[g] (see Figures 4, 5 and 6).

The SACT data liaison officers followed up patients that received venetoclax and were identified as EAMS patients, but the process was challenging. There are two main reasons for this:

- Trusts are being asked to retrieve and submit data on treatments prescribed 2-3 years ago, often on paper. This requires extensive trust resource to find the information, input it into e-prescribing systems and submit to the SACT dataset. Trusts often do not have the time to complete this process.
- The standard SACT upload portal is unable to accept data submission at such a long-time delay after treatment activity. The SACT team have to use alternative routes for trusts to submit data to us.

Of the two patients that did not have a treatment record in SACT, one patient could not be found on the trust's e-prescribing system.

[g] Of the seven CDF patients that did not receive treatment, two were confirmed by the relevant trust. The remaining five patients did not receive venetoclax monotherapy but received venetoclax plus rituximab. Of the 16 CDF patients that died before treatment, all were confirmed by the relevant trust by the PHE data liaison team. The EAMS patient that died before treatment was confirmed by the relevant trust by the PHE data liaison team.

Figure 4: Matched early access cohort - SACT data to EAMS applications for venetoclax for CLL 23 August 2016 – 4 October 2017

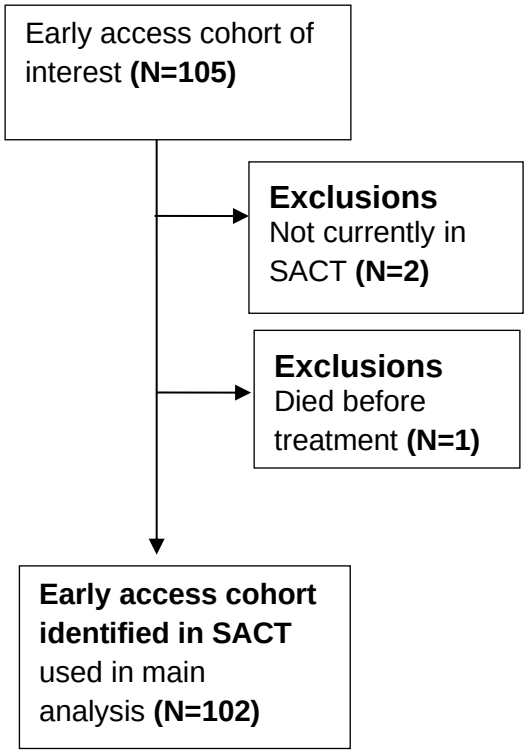


Figure 5: Matched CDF cohort - SACT data to CDF (Blueteq) applications for venetoclax for CLL 5 October 2017 - 4 December 2020

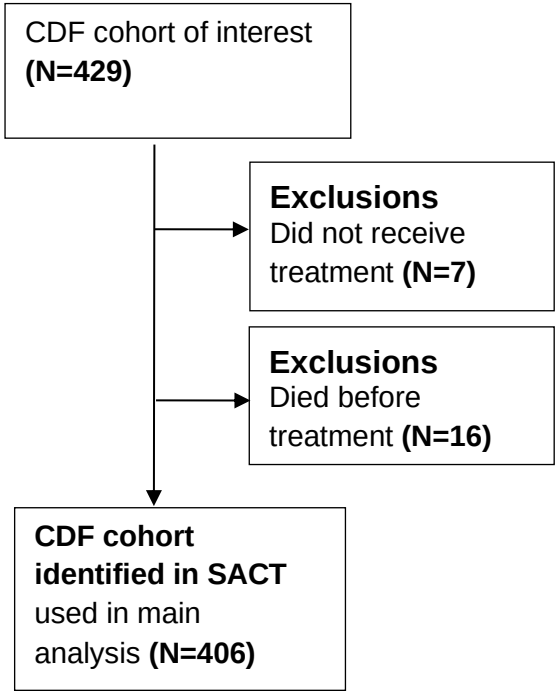
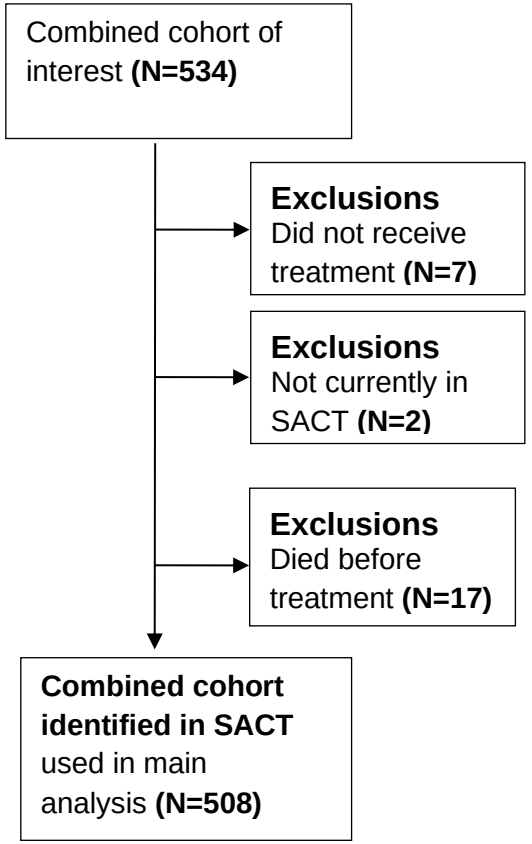


Figure 6: Combined cohort – SACT data to CDF and EAMS applications for venetoclax for CLL 23 August 2016 - 4 December 2020



A maximum of 406 venetoclax records, who had a CDF application between 5 October 2017 and 4 December 2020 were expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 5). 100% (406/406) of these applicants for CDF funding have a treatment record in SACT.

A maximum of 104 venetoclax records, who received venetoclax via EAMS are expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 4). 98% (102/104) of these applicants for EAMS funding have a treatment record in SACT.

Completeness of SACT key variables

Table 3 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender and treatment dates. Performance status at the start of a patient's regimen is 68% complete for the CDF cohort and 79% for the EAMS cohort.

Table 3. Completeness of key SACT data items for the venetoclax cohorts (N=508)

Variable	CDF cohort completeness (%) (N=406)	Early access cohort completeness (%) (N=102)
Primary diagnosis	100%	100%
Date of birth (used to calculate age)	100%	100%
Sex	100%	100%
Start date of regimen	100%	100%
Start date of cycle	100%	100%
Administration date	100%	100%
Performance status at start of regimen	68%	79%

Table 4 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with venetoclax in at least three months[8]. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 220 CDF patients and 84 early access

patients. 75% (165/220) of CDF patients have an outcome summary recorded in the SACT dataset. 77% (65/84) of early access patients have an outcome summary recorded in the SACT dataset.

Table 4. Completeness of outcome summary for patients that have ended treatment (N=304)

Variable	CDF cohort outcomes completeness (%) (N=220)	Early access cohort outcomes completeness (%) (N=84)
Outcome summary of why treatment was stopped	75%	77%

Blueteq application forms

Table 5 presents a breakdown of mutation status, as recorded on the Blueteq application, for CDF patients.

Table 5: Mutation status, Blueteq application form CDF cohort (N=406)

Variable	N (%)
Venetoclax treatment in the ABSENCE of 17p deletion	245 (60)
Venetoclax treatment in the PRESENCE of 17p deletion or TP53 mutation	161 (40)
Total	**406**

Patient characteristics

The median age of the 406 CDF patients receiving venetoclax for treating chronic lymphocytic leukaemia was 72 years. The median age in males and females was 72 and 73 years respectively.

Table 6. Patient characteristics CDF cohort (N=406)

Patient characteristics[h]			
		N	**%**
Sex	Male	275	68%
	Female	131	32%
Age	<40	1	<1%
	40 to 49	7	2%
	50 to 59	44	11%
	60 to 69	109	27%
	70 to 79	165	41%
	80+	80	20%
Performance status	0	84	21%
	1	146	36%
	2	40	10%
	3	7	2%
	4	0	0%
	Missing	129	32%

[h] Figures may not sum to 100% due to rounding.

The median age of the 102 early access patients receiving venetoclax for the treatment of chronic lymphocytic leukaemia was 72 years; and was consistent for both genders.

Table 7. Patient characteristics EAMS cohort (N=102)

Patient characteristics[i]			
		N	**%**
Sex	Male	67	66%
	Female	35	34%
Age	<40	0	0%
	40 to 49	2	2%
	50 to 59	19	19%
	60 to 69	23	23%
	70 to 79	47	46%
	80+	11	11%
Performance status	0	30	29%
	1	44	43%
	2	7	7%
	3	0	0%
	4	0	0%
	Missing	21	21%

[i] Figures may not sum to 100% due to rounding.

Treatment duration – CDF cohort

Of the 406 patients with CDF applications, 220 (54%) were identified as having completed treatment by 28 February 2021 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with venetoclax in at least three months (see Table 12). The median follow-up time in SACT was 12.6 months (383 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT + prescription length.

Presently, 94% (N=132) of trusts submit their SACT return to the submission portal two months after the month's treatment activity has ended; this provides a maximum follow-up period of 40.8 months. 6% (N=9) of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended; this provides a maximum follow-up period of 41.8 months. SACT follow-up ends 28 February 2021.

Table 8: Breakdown by patients' treatment status, CDF cohort[j,k,l]

Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	133	33%
Patient died – on treatment	24	6%
Treatment stopped	63	16%
Treatment ongoing	186	46%
Total	**406**	**100%**

[j] Figures may not sum to 100% due to rounding.
[k] Table 12 presents the outcome summary data reported by trusts. This includes patients from Table 8 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[l] 'Deaths on treatment' and 'deaths not on treatment' are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/.

Table 9: Treatment duration at 6, 12, 18, 24 and 36-month intervals, CDF cohort

Time period	Treatment duration (%)
6 months	73% [95% CI: 68%, 77%]
12 months	63% [95% CI: 58%, 68%]
18 months	56% [95% CI: 50%, 61%]
24 months	47% [95% CI: 41%, 52%]
36 months	27% [95% CI: 20%, 34%]

The Kaplan-Meier curve for ongoing treatment is shown in Figure 7. The median treatment duration for all patients was 21.2 months [95% CI: 18.6, 24.7] (645 days) (N=406).

Figure 7. Kaplan-Meier treatment duration, CDF cohort (N=406)

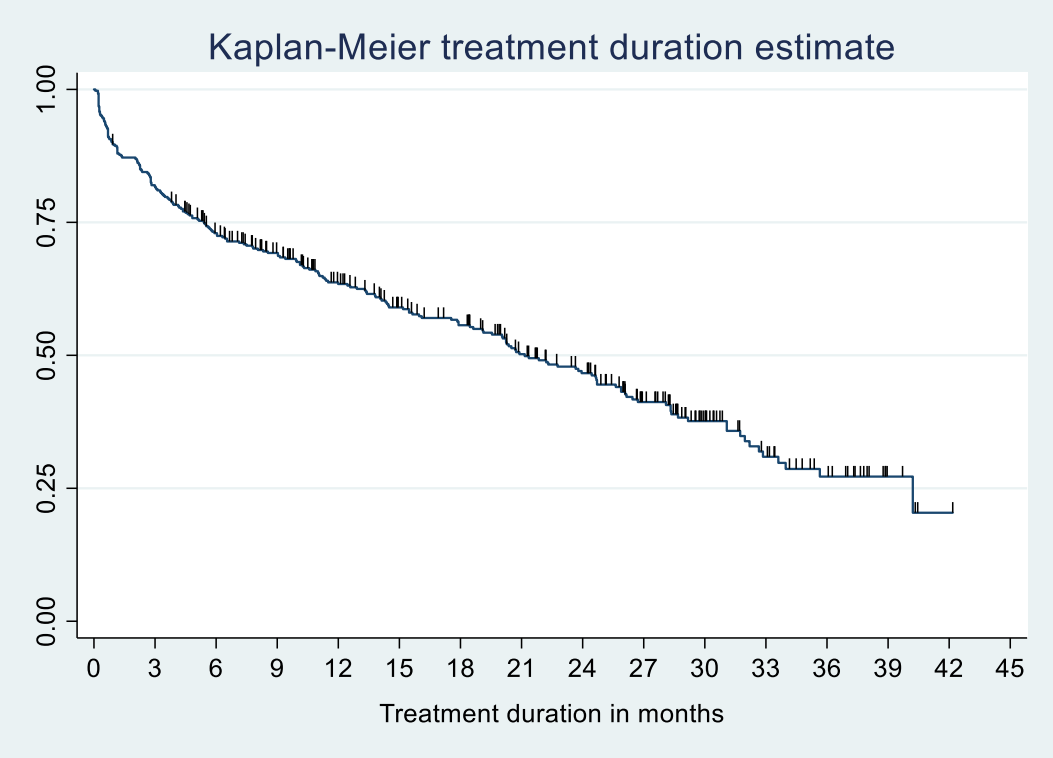


Table 10 and Table 11 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 40.8 months (1,241 days). SACT contains more follow-up for some patients.

Table 10. Number of patients at risk, by quarterly breakpoint, CDF cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Number at risk	406	331	282	248	207	181	164	134	114	80	47	30	18	5	1

Table 11 shows that for all patients who received treatment, 186 were still on treatment (censored) at the date of follow-up and 220 had ended treatment (events).

Table 11. Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored), CDF cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Censored	186	185	171	151	130	118	111	96	85	63	36	26	17	4	1
Events	220	146	111	97	77	63	53	38	29	17	11	4	1	1	0

Table 12 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 54% (N=220) of patients had ended treatment at 28 February 2021.

Table 12: Treatment outcomes for patients that have ended treatment, CDF cohort (N=220)[m,n]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – died not on treatment[o]	74	34%
Stopped treatment – progression of disease	53	24%
Stopped treatment – no treatment in at least 3 months	27	12%
Stopped treatment – died on treatment	24	11%
Stopped treatment – acute toxicity	20	9%
Stopped treatment – patient choice	16	7%
Stopped treatment – completed as prescribed	6	3%
Total	**220**	**100%**

[m] Figures may not sum to 100% due to rounding.
[n] Table 12 presents the outcome summary data reported by trusts. This includes patients from Table 8 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[o] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website.

Table 13. Treatment outcomes and treatment status for patients that have ended treatment, CDF cohort (N=220)

Outcome[p]	Patient died [q] not on treatment	Treatment stopped	Patient died on treatment
Stopped treatment – died not on treatment	74		
Stopped treatment – progression of disease	36	17	
Stopped treatment – no treatment in at least 3 months		27	
Stopped treatment – died on treatment			24
Stopped treatment – acute toxicity	11	9	
Stopped treatment – patient choice	8	8	
Stopped treatment – completed as prescribed	4	2	
Total	**133**	**63**	**24**

[p] Relates to outcomes submitted by the trust in Table 12.
[q] Relates to treatment status in Table 8 for those that have ended treatment.

Treatment duration – EAMS cohort

Of the 102 patients with CDF applications, 84 (82%) were identified as having completed treatment by 28 February 2021 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with venetoclax in at least three months (see Table 18). The median follow-up time in SACT was 19.1 months (581 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT + prescription length.

Table 14. Breakdown by patients' treatment status, EAMS cohort[r,s,t]

Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	52	51%
Patient died – on treatment	13	13%
Treatment stopped	19	19%
Treatment ongoing	18	18%
Total	**102**	**100%**

Table 15. Treatment duration at 6, 12, 18, 24 and 36-month intervals, EAMS cohort

Time period	Treatment duration (%)
6 months	74% [95% CI: 64%, 81%]
12 months	60% [95% CI: 50%, 69%]
18 months	51% [95% CI: 41%, 60%]
24 months	47% [95% CI: 37%, 56%]
36 months	28% [95% CI: 20%, 37%]

[r] Figures may not sum to 100% due to rounding.
[s] Table 18 presents the outcome summary data reported by trusts. This includes patients from Table 14 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[t] 'Deaths on treatment' and 'deaths not on treatment' are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/.

The Kaplan-Meier curve for ongoing treatment is shown in Figure 8. The median treatment duration for all patients was 19.1 months [95% CI: 11.7, 27.0] (581 days) (N=102).

Figure 8. Kaplan-Meier treatment duration, EAMS cohort (N=102)

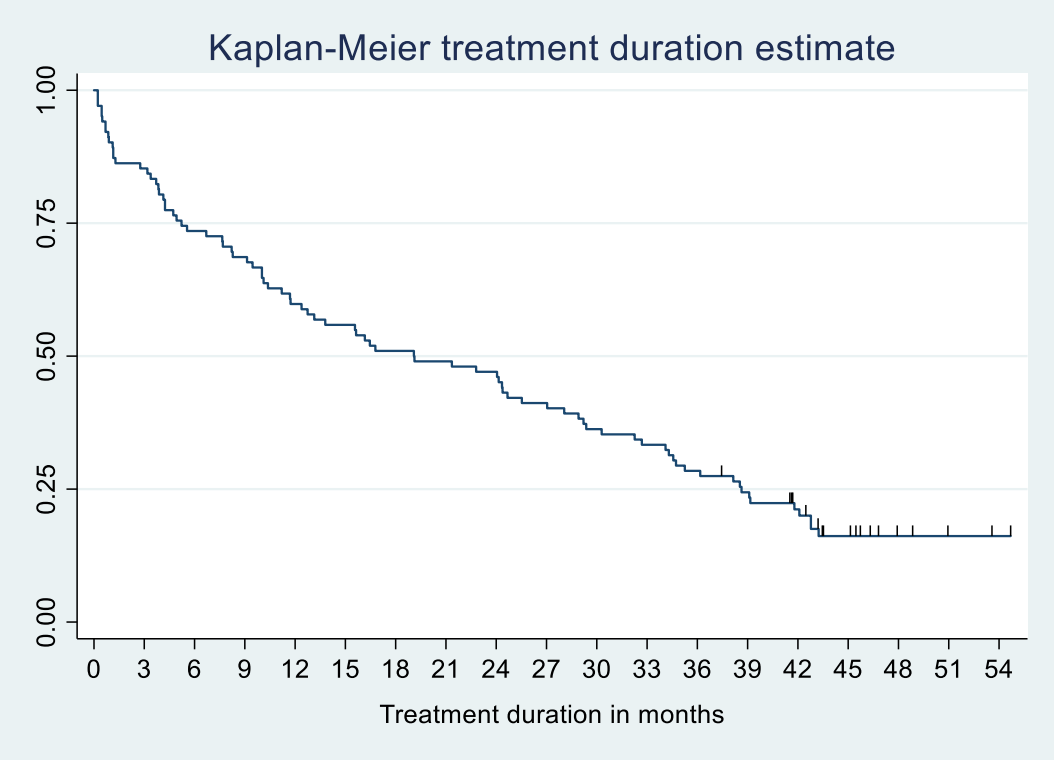


Table 16 and Table 17 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 54.2 months (1,649 days). SACT contains more follow-up for some patients.

Table 16. Number of patients at risk and number of events, by quarterly breakpoint, EAMS cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Number at risk	102	87	75	70	61	57	52	50	48	42	37	34	29	24	18	9	4	2	1

Table 17 shows that for all patients who received treatment, 18 patients were still on treatment (censored) at the date of follow-up and 84 had ended treatment (events).

Table 17. Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored), EAMS cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Censored	18	18	18	18	18	18	18	18	18	18	18	18	18	17	14	9	4	2	1
Events	84	69	57	52	43	39	34	32	30	24	19	16	11	7	4	0	0	0	0

Table 18 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 84 (82%) of patients had ended treatment at 28 February 2021.

Table 18. Treatment outcomes for patients that have ended treatment, EAMS cohort (N=84)[u],[v]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – progression of disease	30	36%
Stopped treatment – died not on treatment[w]	23	27%
Stopped treatment – died on treatment	13	15%
Stopped treatment – no treatment in at least 3 months	9	11%
Stopped treatment – acute toxicity	3	4%
Stopped treatment – patient choice	3	4%
Stopped treatment – completed as prescribed	3	4%
Total	**84**	**100%**

[u] Figures may not sum to 100% due to rounding.
[v] Table 18 presents the outcome summary data reported by trusts. This includes patients from Table 14 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[w] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website.

Table 19. Treatment outcomes and treatment status for patients that have ended treatment, EAMS cohort (N=84)

Outcome[x]	Patient died [y] not on treatment	Treatment stopped	Patient died on treatment
Stopped treatment – progression of disease	25	5	
Stopped treatment – died not on treatment	23		
Stopped treatment – died on treatment			13
Stopped treatment – no treatment in at least 3 months		9	
Stopped treatment – acute toxicity	2	1	
Stopped treatment – patient choice		3	
Stopped treatment – completed as prescribed	2	1	
Total	**52**	**19**	**13**

[x] Relates to outcomes submitted by the trust in Table 18.
[y] Relates to treatment status in Table 14 for those that have ended treatment.

Treatment duration – CDF and EAMS, combined cohort

Of the 508 patients in the combined cohort, 304 (60%) were identified as having completed treatment by 28 February 2021 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with venetoclax in at least three months (see Table 24). The median follow-up time in SACT was 13.8 months (420 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT + prescription length.

Table 20. Breakdown by patients' treatment status, combined cohort[z,aa,bb]

Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	185	36%
Patient died – on treatment	37	7%
Treatment stopped	82	16%
Treatment ongoing	204	40%
Total	**508**	**100%**

Table 21. Treatment duration at 6, 12, 18, 24 and 36-month intervals, combined cohort

Time period	Treatment duration (%)
6 months	73% [95% CI: 69%, 77%]
12 months	63% [95% CI: 58%, 67%]
18 months	55% [95% CI: 50%, 59%]
24 months	47% [95% CI: 42%, 52%]
36 months	28% [95% CI: 23%, 33%]

[z] Figures may not sum to 100% due to rounding.
[aa] Table 24 presents the outcome summary data reported by trusts. This includes patients from Table 20 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[bb] 'Deaths on treatment' and 'deaths not on treatment' are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/.

The Kaplan-Meier curve for ongoing treatment is shown in Figure 9. The median treatment duration for all patients was 21.2 months [95% CI: 17.9, 24.6] (645 days) (N=508).

Figure 9. Kaplan-Meier treatment duration, combined cohort (N=508)

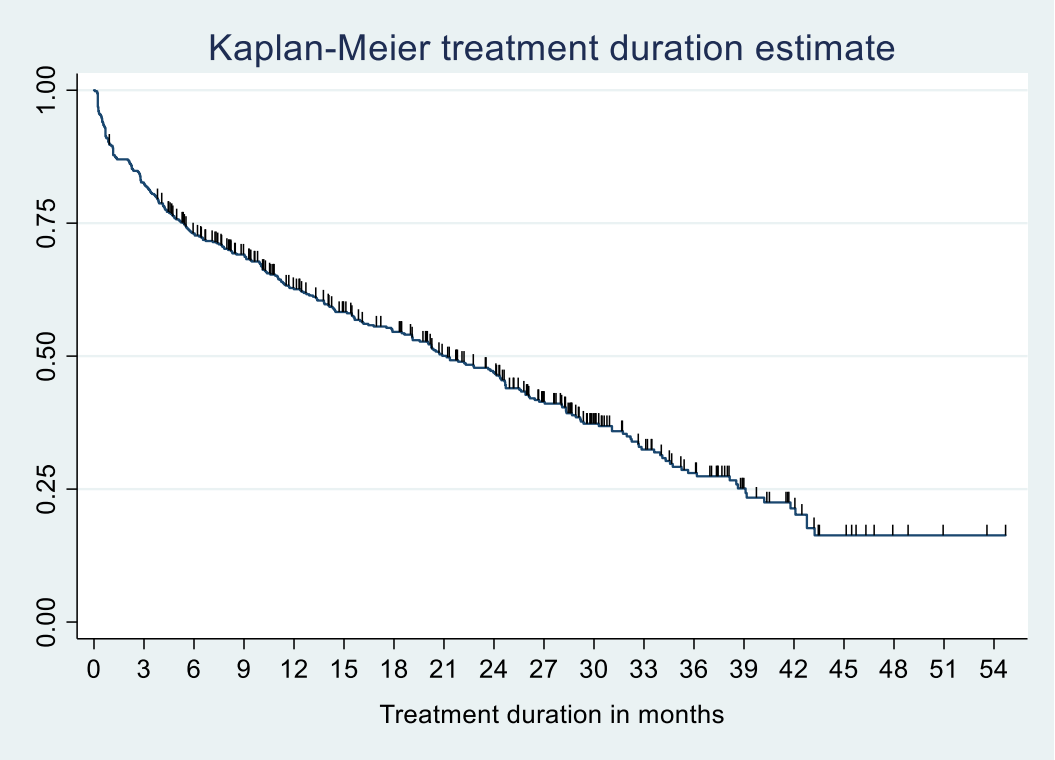


Table 22 and Table 23 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 54.2 months (1,649 days). SACT contains more follow-up for some patients.

Table 22. Number of patients at risk, by quarterly breakpoint, combined cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Number at risk	508	418	357	318	268	238	216	184	162	122	84	64	47	29	19	9	4	2	1

Table 23 shows that for all patients who received treatment, 204 were still on treatment (censored) at the date of follow-up and 304 had ended treatment (events).

Table 23. Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored), combined cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Censored	204	203	189	169	148	136	129	114	103	81	54	44	35	21	15	9	4	2	1
Events	304	215	168	149	120	102	87	70	59	41	30	20	12	8	4	0	0	0	0

Table 24 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 60% (N=304) of patients had ended treatment at 28 February 2021.

Table 24. Treatment outcomes for patients that have ended treatment, combined cohort (N=304)[cc],[dd]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – died not on treatment[ee]	97	32%
Stopped treatment – progression of disease	83	27%
Stopped treatment – died on treatment	37	12%
Stopped treatment – no treatment in at least 3 months	36	12%
Stopped treatment – acute toxicity	23	8%
Stopped treatment – patient choice	19	6%
Stopped treatment – completed as prescribed	9	3%
Total	**304**	**100%**

[cc] Figures may not sum to 100% due to rounding.
[dd] Table 24 presents the outcome summary data reported by trusts. This includes patients from Table 20 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[ee] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website.

Table 25. Treatment outcomes and treatment status for patients that have ended treatment, combined cohort (N=304)

Outcome[ff]	Patient died [gg] not on treatment	Treatment stopped	Patient died on treatment
Stopped treatment – died not on treatment	97		
Stopped treatment – progression of disease	61	22	
Stopped treatment – died on treatment			37
Stopped treatment – no treatment in at least 3 months		36	
Stopped treatment – acute toxicity	13	10	
Stopped treatment – patient choice	8	11	
Stopped treatment – completed as prescribed	6	3	
Total	**185**	**82**	**37**

[ff] Relates to outcomes submitted by the trust in Table 24.
[gg] Relates to treatment status in Table 20 for those that have ended treatment.

Overall survival (OS) – CDF cohort

Of the 406 patients with a treatment record in SACT, the minimum follow-up was 6.9 months (210 days) from the last CDF application. Patients were traced for their vital status on 2 July 2021. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time in SACT was 18.9 months (575 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Table 26: OS at 6, 12, 18, 24 and 36-month intervals, CDF cohort

Time period	OS (%)
6 months	83% [95% CI: 79%, 86%]
12 months	75% [95% CI: 70%, 79%]
18 months	68% [95% CI: 63%, 73%]
24 months	63% [95% CI: 57%, 68%]
36 months	55% [95% CI: 49%, 60%]

Figure 10 provides the Kaplan-Meier curve for OS, censored at 2 July 2021. The median OS was 43.1 months[hh] (1,311 days).

Figure 10. Kaplan-Meier survival plot, CDF cohort (N=406)

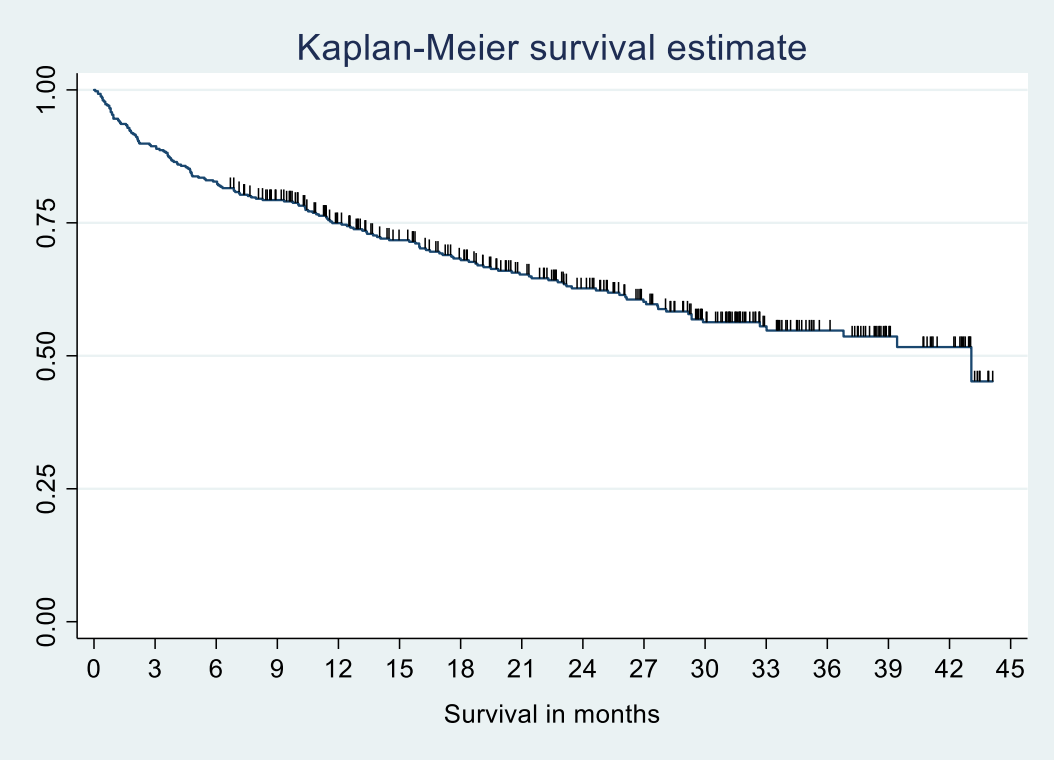


Table 27 and Table 28 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 44.9 months (1,366 days), all patients were traced on 2 July 2021.

[hh] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced

Table 27. Includes the number of patients at risk, by quarterly breakpoints, CDF cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Number at risk	406	363	336	307	266	237	213	185	161	135	103	70	50	27	19

Table 28 shows that for all patients who received treatment, 249 were still alive (censored) at the date of follow-up and 157 had died (events).

Table 28. Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints, CDF cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Censored	249	249	249	234	209	191	178	159	142	122	98	66	47	25	18
Events	157	114	87	73	57	46	35	26	19	13	5	4	3	2	1

Overall survival (OS) – EAMS cohort

Of the 102 patients with a treatment record in SACT, the minimum follow-up was 44.9 months (1,366 days) from the last access entry (4 October 2017) to the date patients were traced for their vital status. Patients were traced for their vital status on 2 July 2021. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time in SACT was 33.1 months (1,007 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Table 29: OS at 6, 12, 18, 24 and 36-month intervals, EAMS cohort

Time period	OS (%)
6 months	80% [95% CI: 71%, 87%]
12 months	73% [95% CI: 63%, 80%]
18 months	65% [95% CI: 55%, 73%]
24 months	60% [95% CI: 50%, 69%]
36 months	46% [95% CI: 36%, 55%]

Figure 11 provides the Kaplan-Meier curve for OS, censored at 2 July 2021. The median OS was 32.5 months [95% CI: 20.3, 41.8] (989 days).

Figure 11. Kaplan-Meier survival plot, EAMS cohort (N=102)

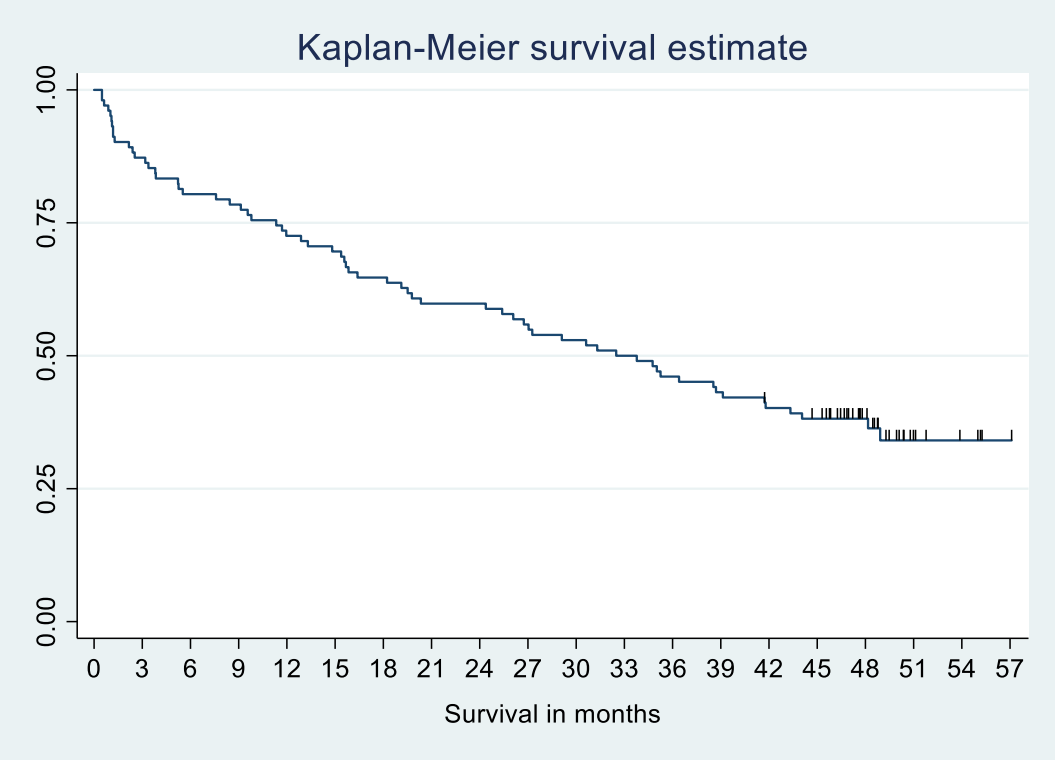


Table 30 and Table 31 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 58.3 months (1,774 days), all patients were traced on 2 July 2021.

Table 30. Includes the number of patients at risk, by quarterly breakpoints, EAMS cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Number at risk	102	89	82	80	74	71	66	61	61	57	54	51	47	44	40	37	21	6	4

Table 31 shows that for all patients who received treatment, 37 were still alive (censored) at the date of follow-up and 65 had died (events).

Table 31. Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints, EAMS cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Censored	37	37	37	37	37	37	37	37	37	37	37	37	37	37	36	35	19	6	4
Events	65	52	45	43	37	34	29	24	24	20	17	14	10	7	4	2	2	0	0

Overall survival (OS) – CDF and EAMS, combined cohort

Of the 508 patients with a treatment record in SACT, the minimum follow-up was 44.9 months (1,366 days) from the last CDF application. Patients were traced for their vital status on 2 July 2021. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time in SACT was 20.1 months (611 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Table 32: OS at 6, 12, 18, 24 and 36-month intervals, combined cohort

Time period	OS (%)
6 months	82% [95% CI: 79%, 85%]
12 months	74% [95% CI: 70%, 78%]
18 months	68% [95% CI: 63%, 72%]
24 months	62% [95% CI: 57%, 66%]
36 months	51% [95% CI: 46%, 56%]

Figure 12 provides the Kaplan-Meier curve for OS, censored at 2 July 2021. The median OS was 38.5 months [95% CI: 31.3, 44.1] (1,171 days).

Figure 12. Kaplan-Meier survival plot, combined cohort (N=508)

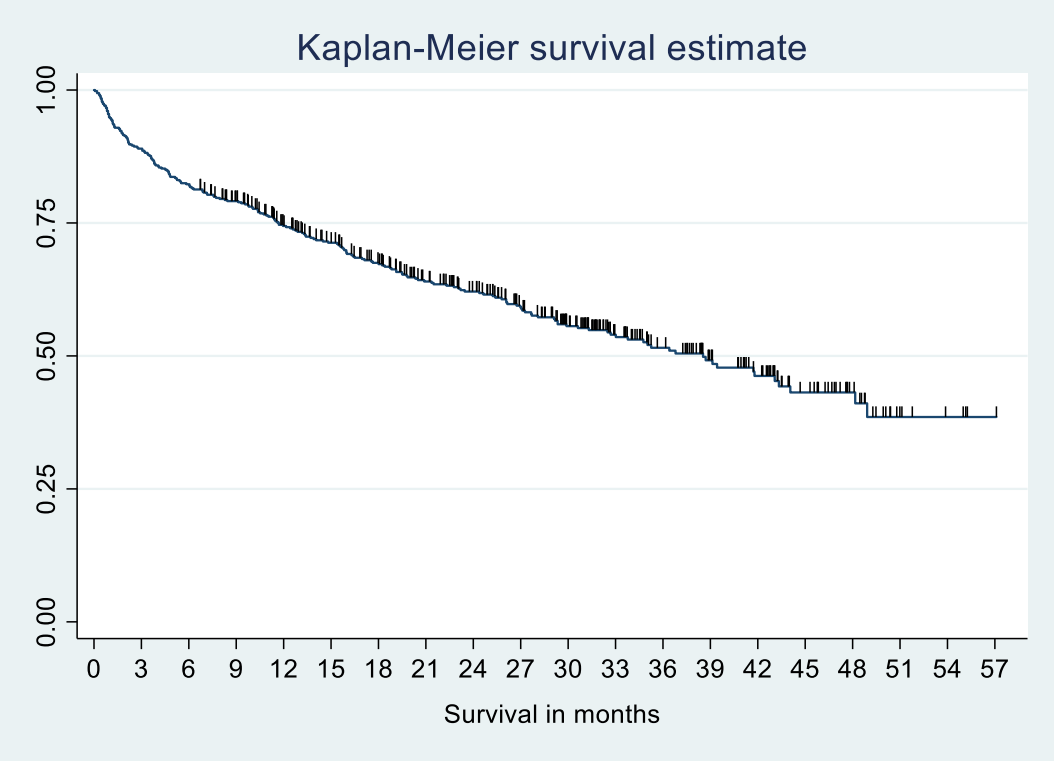


Table 33 and Table 34 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 58.3 months (1,774 days), all patients were traced on 2 July 2021.

Table 33. Includes the number of patients at risk, by quarterly breakpoints, combined cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Number at risk	508	452	418	387	340	308	279	246	222	192	157	121	97	71	59	37	21	6	4

Table 34 shows that for all patients who received treatment, 286 were still alive (censored) at the date of follow-up and 222 had died (events).

Table 34. Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints, combined cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Censored	286	286	286	271	246	228	215	196	179	159	135	103	84	62	54	35	19	6	4
Events	222	166	132	116	94	80	64	50	43	33	22	18	13	9	5	2	2	0	0

Sensitivity analysis

6-months SACT follow-up

Treatment duration – CDF cohort

Sensitivity analysis was carried out on a cohort with at least six months follow-up in SACT. To identify the treatment duration cohort, CDF applications were limited from 5 October 2017 to 28 August 2020 and SACT activity was followed up to the 28 February 2021.

Following the exclusions above, 374 patients (92%) were included in these analyses. The median follow-up time in SACT was 14.4 months (438 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT + prescription length.

The Kaplan-Meier curve for ongoing treatment is shown in Figure 13. The median treatment duration for patients in this cohort was 20.9 months [95% CI: 17.9, 24.7] (636 days) (N=374).

Figure 13. Kaplan-Meier treatment duration plot (N=374)

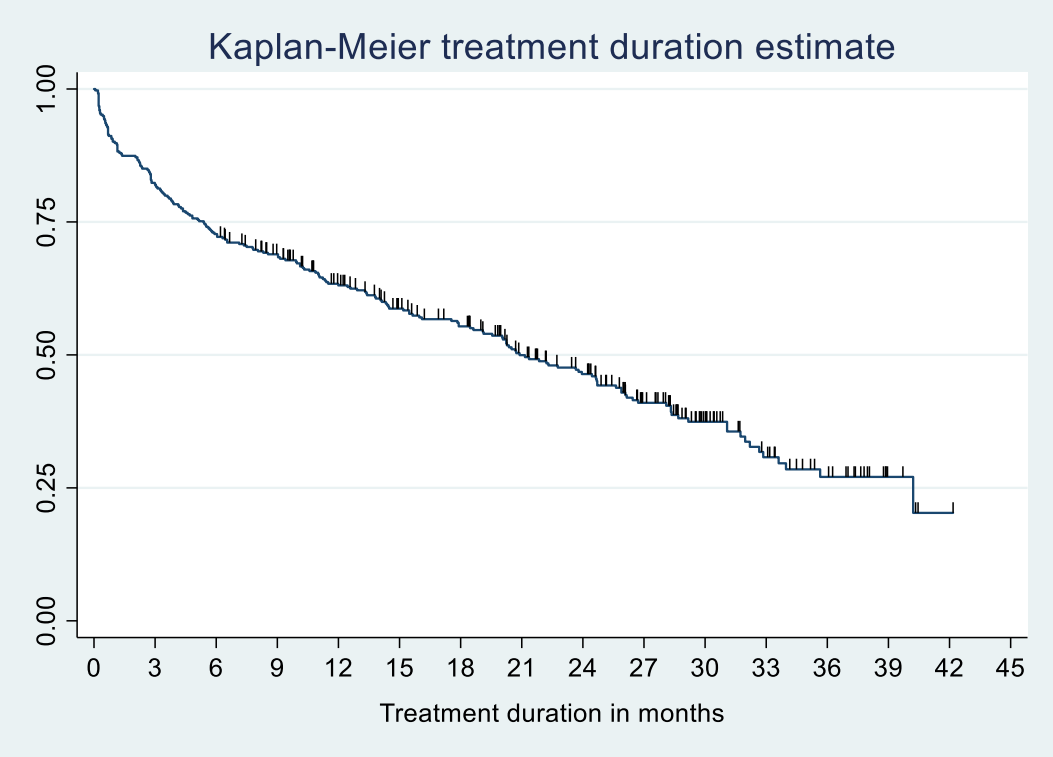


Table 35 and Table 36 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all

patients for treatment duration was 40.8 months (1,241 days). SACT contains more follow-up for some patients.

Table 35. Number of patients at risk, by quarterly breakpoint, CDF cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Number at risk	374	307	272	245	207	181	164	134	114	80	47	30	18	5	1

Table 36 shows that for all patients who received treatment, 161 were still on treatment (censored) at the date of follow-up and 213 had ended treatment (events).

Table 36. Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored), CDF cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Censored	161	161	161	148	130	118	111	96	85	63	36	26	17	4	1
Events	213	146	111	97	77	63	53	38	29	17	11	4	1	1	0

Secondary sensitivity analyses

Treatment duration and OS by mutation status

Treatment duration – CDF cohort

A secondary sensitivity analysis was carried out on the full CDF cohort to include treatment duration and OS by mutation status.

The median follow-up time in SACT amongst those without a 17p deletion or TP53 mutation was 14.6 months (445 days). The median follow-up time in SACT amongst those with a 17p deletion or TP53 mutation was 10.6 months (322 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT + prescription length.

Table 37. Treatment duration by mutation status at 6, 12, 18, 24 and 36-month intervals

Time period	ABSENCE of 17p deletion or TP53 mutation (%)	PRESENCE of 17p deletion or TP53 mutation (%)
6 months	76% [95% CI: 70%, 81%]	68% [95% CI: 60%, 75%]
12 months	67% [95% CI: 61%, 73%]	57% [95% CI: 49%, 65%]
18 months	59% [95% CI: 52%, 66%]	50% [95% CI: 41%, 58%]
24 months	48% [95% CI: 41%, 55%]	44% [95% CI: 35%, 52%]
36 months	28% [95% CI: 19%, 37%]	27% [95% CI: 17%, 38%]

The Kaplan-Meier curve for ongoing treatment is shown in Figure 14. The median treatment duration for all patients without a 17p deletion or TP53 mutation was 22.3 months [95% CI: 20.0, 28.1] (678 days) (N=245).

The median treatment duration for all patients with a 17p deletion or TP53 mutation was 17.9 months [95% CI: 11.5, 25.6] (544 days) (N=161).

Figure 14. Kaplan-Meier treatment duration by mutation status, CDF cohort (N=406)

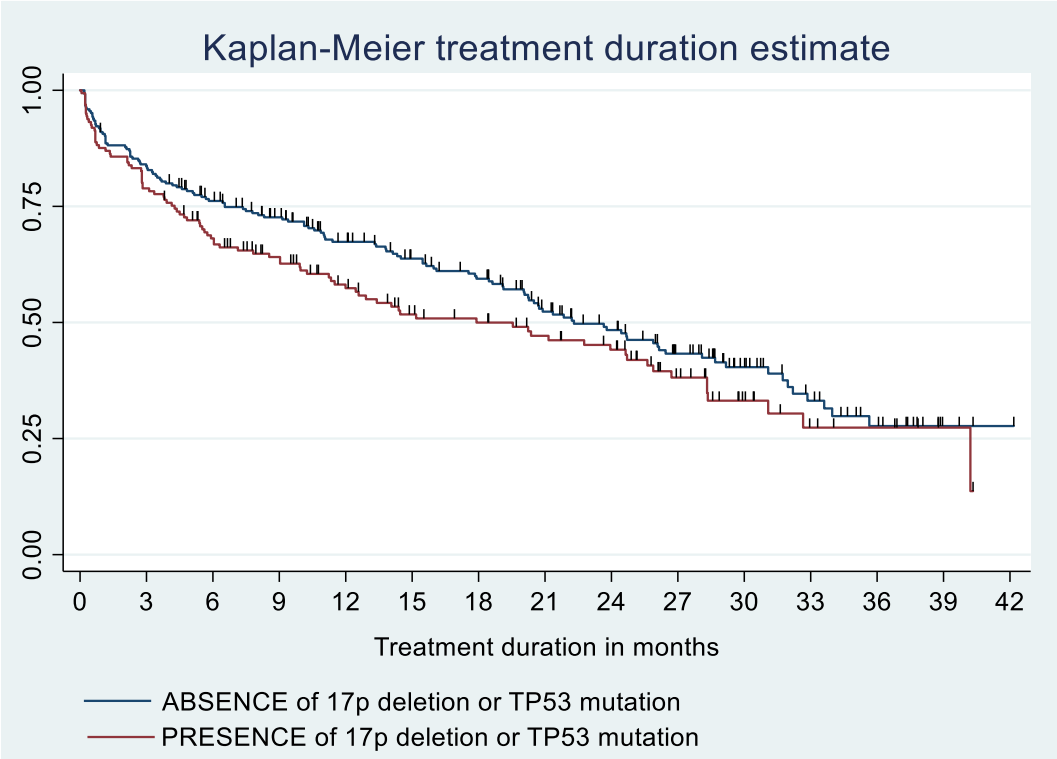


Table 38, Table 39 and Table 40 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 40.8 months (1,241 days). SACT contains more follow-up for some patients.

Table 38. Number of patients at risk, by mutation status and quarterly breakpoint, CDF cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Number at risk Absence of 17p deletion or TP53 mutation	245	204	177	158	134	120	108	85	71	53	33	22	12	3	1
Number at risk Presence of 17p deletion or TP53 mutation	161	127	105	90	73	61	56	49	43	27	14	8	6	2	0

Table 39 shows that for all patients who received treatment and do not have a 17p deletion or TP53 mutation, 117 were still on treatment (censored) at the date of follow-up and 128 had ended treatment (events).

Table 39. Number of patients at risk, amongst patients who do not have a 17p deletion or TP53 mutation, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Censored	117	116	107	96	83	76	72	61	53	42	25	19	12	3	1
Events	128	88	70	62	51	44	36	24	18	11	8	3	0	0	0

Table 40 shows that for all patients who received treatment and have a 17p deletion or TP53 mutation, 69 were still on treatment (censored) at the date of follow-up and 92 had ended treatment (events).

Table 40. Number of patients at risk, amongst patients who have a 17p deletion or TP53 mutation, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Censored	69	69	64	55	47	42	39	35	32	21	11	7	5	1	0
Events	92	58	41	35	26	19	17	14	11	6	3	1	1	1	0

OS – CDF cohort

The median follow-up time in SACT amongst those without a 17p deletion or TP53 mutation was 20.6 months (627 days). The median follow-up time in SACT amongst those with a 17p deletion or TP53 mutation was 15.5 months (471 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Table 41. OS by mutation status at 6, 12, 18, 24 and 36-month intervals

Time period	ABSENCE of 17p deletion or TP53 mutation (%)	PRESENCE of 17p deletion or TP53 mutation (%)
6 months	86% [95% CI: 81%, 90%]	78% [95% CI: 70%, 83%]
12 months	79% [95% CI: 73%, 83%]	69% [95% CI: 61%, 76%]
18 months	73% [95% CI: 66%, 78%]	61% [95% CI: 53%, 69%]
24 months	66% [95% CI: 59%, 72%]	58% [95% CI: 49%, 65%]
36 months	59% [95% CI: 51%, 66%]	48% [95% CI: 38%, 57%]

The Kaplan-Meier curve for ongoing treatment is shown in Figure 15. The median OS for all patients without a 17p deletion or TP53 mutation (N=245) was not reached.

The OS for all patients with a 17p deletion or TP53 mutation was 33 months[ii] (1,004 days) (N=161).

Figure 15. Kaplan-Meier survival plot by mutation status, CDF cohort (N=406)

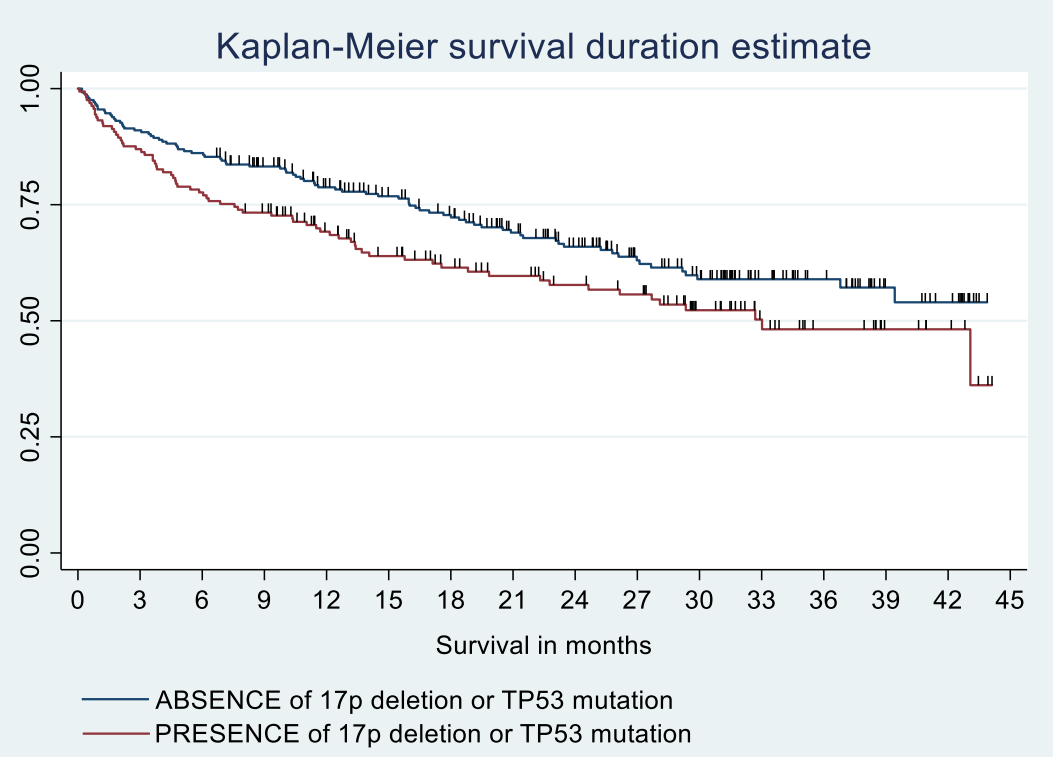


Table 42, Table 43 and Table 44 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 44.9 months (1,366 days), all patients were traced on 2 July 2021.

[ii] Confidence intervals are not shown if there was an insufficient number of events at the time this report was produced.

Table 42. Number of patients at risk, by mutation status and quarterly breakpoint, CDF cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Number at risk Absence of 17p deletion or TP53 mutation	245	223	211	191	170	154	141	120	103	81	67	46	34	18	13
Number at risk Presence of 17p deletion or TP53 mutation	161	140	125	116	96	83	72	65	58	54	36	24	16	9	6

Table 43 shows that for all patients who received treatment and do not have a 17p deletion or TP53 mutation, 159 were still alive (censored) at the date of follow-up and 86 had died (events).

Table 43. Number of patients at risk, amongst patients who do not have a 17p deletion or TP53 mutation, by quarterly breakpoints split between patients that have died (events) and patients that are still alive (censored)

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Censored	159	159	159	146	135	123	118	104	92	74	65	44	32	17	13
Events	86	64	52	45	35	31	23	16	11	7	2	2	2	1	0

Table 44 shows that for all patients who received treatment and have a 17p deletion or TP53 mutation, 90 were still alive (censored) at the date of follow-up and 71 had died (events).

Table 44. Number of patients at risk, amongst patients who have a 17p deletion or TP53 mutation, by quarterly breakpoints split between patients that have died (events) and patients that are still alive (censored)

Time intervals (months)	0-42	3-42	6-42	9-42	12-42	15-42	18-42	21-42	24-42	27-42	30-42	33-42	36-42	39-42	42
Censored	90	90	90	88	74	68	60	55	50	48	33	22	15	8	5
Events	71	50	35	28	22	15	12	10	8	6	3	2	1	1	1

Third sensitivity analyses

Venetoclax treatment switchers

Venetoclax with rituximab entered routine commissioning on 18th January 2019. Venetoclax treatment switchers are defined as patients who move from venetoclax monotherapy to venetoclax and rituximab combination therapy. Patients who are still in the initial titration period (typically 5 weeks) of venetoclax monotherapy are allowed, by NHS England and NHS Improvement, to switch to the combination therapy, provided their consultant makes NHS England and NHS Improvement aware of this.

Of the 508 patients included in these analyses, 112 patients (32 EAMS, 80 CDF) went on to receive rituximab on or after the patients earliest venetoclax regimen start date. Of the 112 patients that started rituximab, 30 (27%) started within 8 weeks (56 days) of their venetoclax regimen start date Treatment switchers are included in the main analyses[jj].

Due to the way rituximab is commissioned, trusts may use rituximab without completing a Blueteq form. There are no barriers to the use of rituximab.

Sensitivity analysis was carried out to evaluate both CDF and the EAMS cohorts for which treatment switchers were removed, results are as follows:

Treatment duration - CDF cohort

The median follow-up time in SACT was 12.1 months (368 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT + prescription length.

[jj] No further exploration has been done to establish if these are true treatment switchers. Switchers have been identified only on the basis that they have received rituximab at some point on or after a patient's earliest venetoclax treatment, some of which may be subsequent treatments rather than combination.

Table 45. Treatment duration at 6, 12, 18, 24 and 36-month intervals, CDF cohort

Time period	Treatment duration (%)
6 months	73% [95% CI: 68%, 77%]
12 months	65% [95% CI: 59%, 70%]
18 months	59% [95% CI: 53%, 64%]
24 months	52% [95% CI: 46%, 58%]
36 months	36% [95% CI: 28%, 44%]

The Kaplan-Meier curve for ongoing treatment is shown in Figure 16. The median treatment duration for all patients was 24.7 months [95% CI: 20.3, 31.1] (751 days) (N=326).

Figure 16. Kaplan-Meier treatment duration, CDF cohort (N=326)

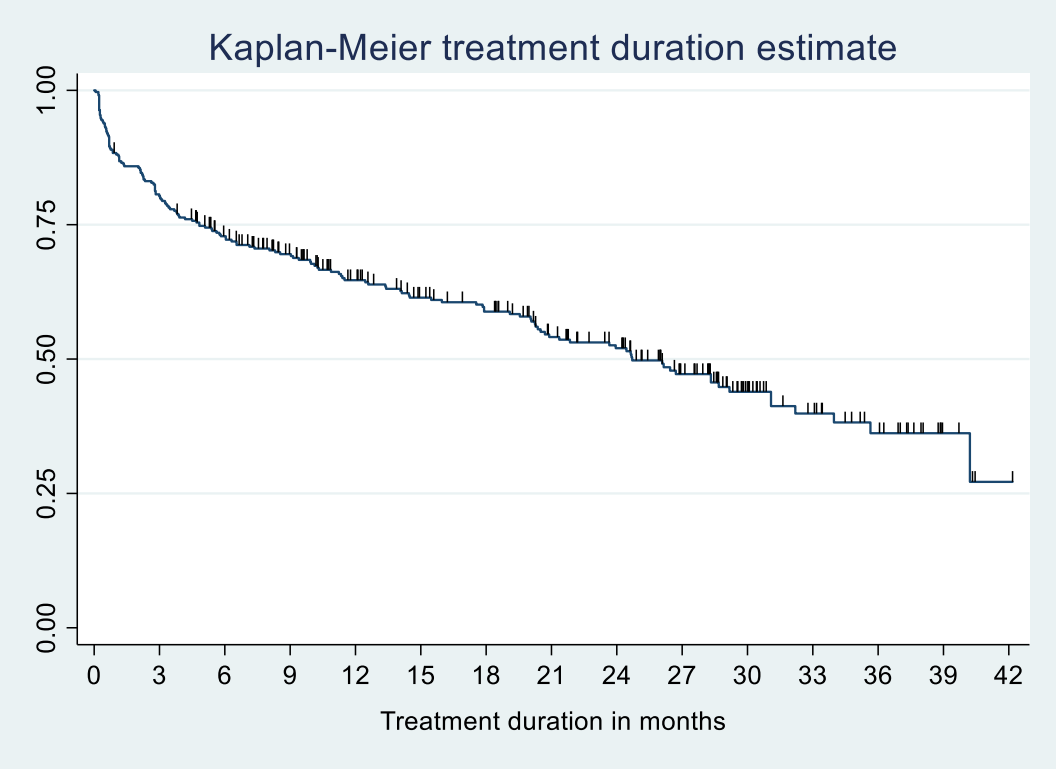


Table 46 and Table 47 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 40.8 months (1,241 days). SACT contains more follow-up for some patients.

Table 46. Number of patients at risk, by quarterly breakpoint, CDF cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Number at risk	326	261	225	196	163	146	135	111	97	70	39	27	17	5	1

Table 47 shows that for all patients who received treatment, 169 were still on treatment (censored) at the date of follow-up and 157 had ended treatment (events).

Table 47. Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored), CDF cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Censored	169	168	156	137	117	108	103	89	79	60	33	24	16	4	1
Events	157	93	69	59	46	38	32	22	18	10	6	3	1	1	0

Treatment duration - EAMS cohort

The median follow-up time in SACT was 16.5 months (502 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT + prescription length.

Table 48. Treatment duration at 6, 12 and 36-month intervals, EAMS cohort

Time period	Treatment duration (%)
6 months	67% [95% CI: 55%, 77%]
12 months	56% [95% CI: 43%, 66%]
18 months	49% [95% CI: 36%, 60%]
24 months	49% [95% CI: 36%, 60%]
36 months	31% [95% CI: 21%, 42%]

The Kaplan-Meier curve for ongoing treatment is shown in Figure 17. The median treatment duration for all patients was 16.2 months [95% CI: 9.1, 28.9] (493 days) (N=70).

Figure 17. Kaplan-Meier treatment duration, EAMS cohort (N=70)

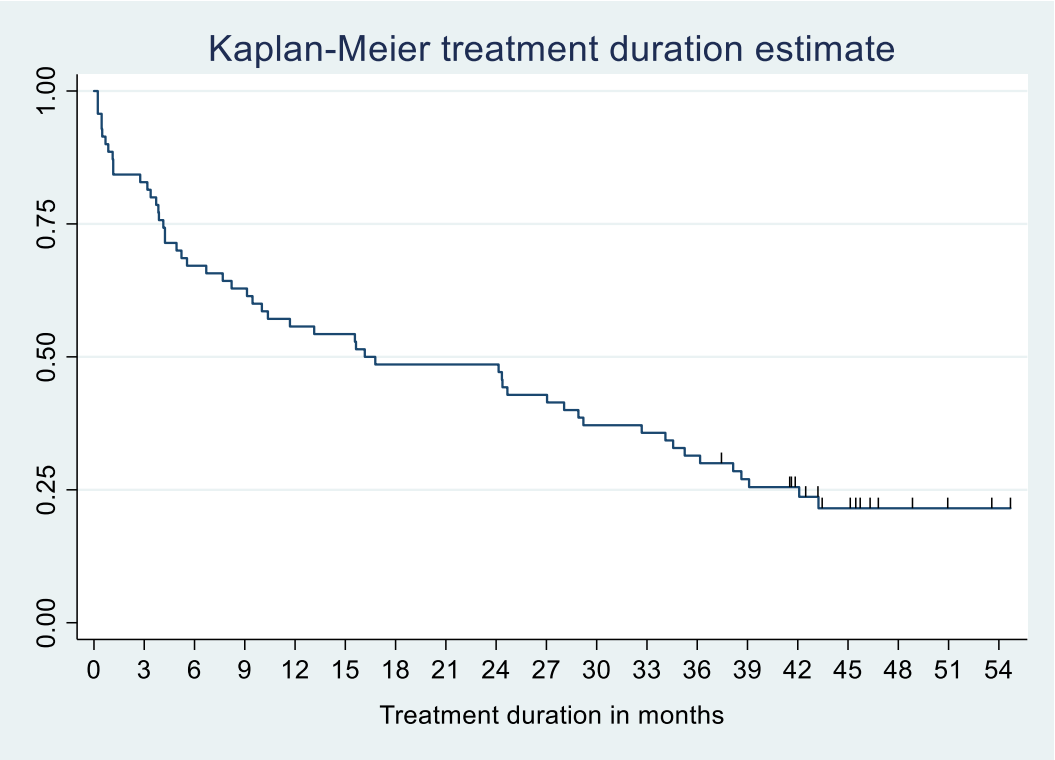


Table 49 and Table 50 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all

patients for treatment duration was 54.2 months (1,649 days). SACT contains more follow-up for some patients.

Table 49. Number of patients at risk and number of events, by quarterly breakpoint, EAMS cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
Number at risk	70	58	47	44	39	38	34	34	34	30	26	25	22	18	14	8	4	2

Table 50 shows that for all patients who received treatment, 16 patients were still on treatment (censored) at the date of follow-up and 54 had ended treatment (events).

Table 50. Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored), EAMS cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
Censored	16	16	16	16	16	16	16	16	16	16	16	16	16	15	12	8	4	2
Events	54	42	31	28	23	22	18	18	18	14	10	9	6	3	2	0	0	0

Treatment duration - Combined cohort

The median follow-up time in SACT was 12.6 months (383 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT + prescription length.

Table 51. Treatment duration at 6, 12, 18, 24 and 36-month intervals, Combined cohort

Time period	Treatment duration (%)
6 months	72% [95% CI: 67%, 76%]
12 months	63% [95% CI: 58%, 68%]
18 months	57% [95% CI: 51%, 62%]
24 months	52% [95% CI: 46%, 57%]
36 months	35% [95% CI: 29%, 42%]

The Kaplan-Meier curve for ongoing treatment is shown in Figure 18. The median treatment duration for all patients was 24.6 months [95% CI: 20.2, 28.7] (748 days) (N=396).

Figure 18. Kaplan-Meier treatment duration, combined cohort (N=396)

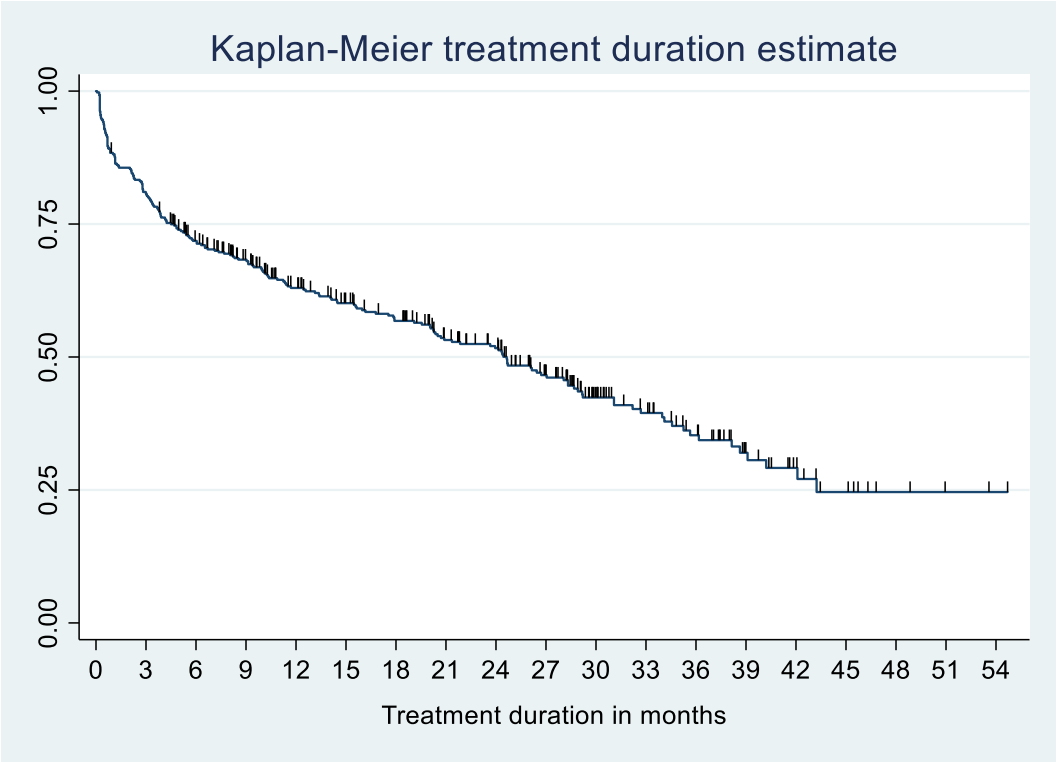


Table 52 and Table 53 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 54.2 months (1,649 days). SACT contains more follow-up for some patients.

Table 52. Number of patients at risk and number of events, by quarterly breakpoint, combined cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
Number at risk	396	319	272	240	202	184	169	145	131	100	65	52	39	23	15	8	4	2

Table 53 shows that for all patients who received treatment, 185 patients were still on treatment (censored) at the date of follow-up and 211 had ended treatment (events).

Table 53. Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored), combined cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
Censored	185	184	172	153	133	124	119	105	95	76	49	40	32	19	13	8	4	2
Events	211	135	100	87	69	60	50	40	36	24	16	12	7	4	2	0	0	0

OS - CDF cohort

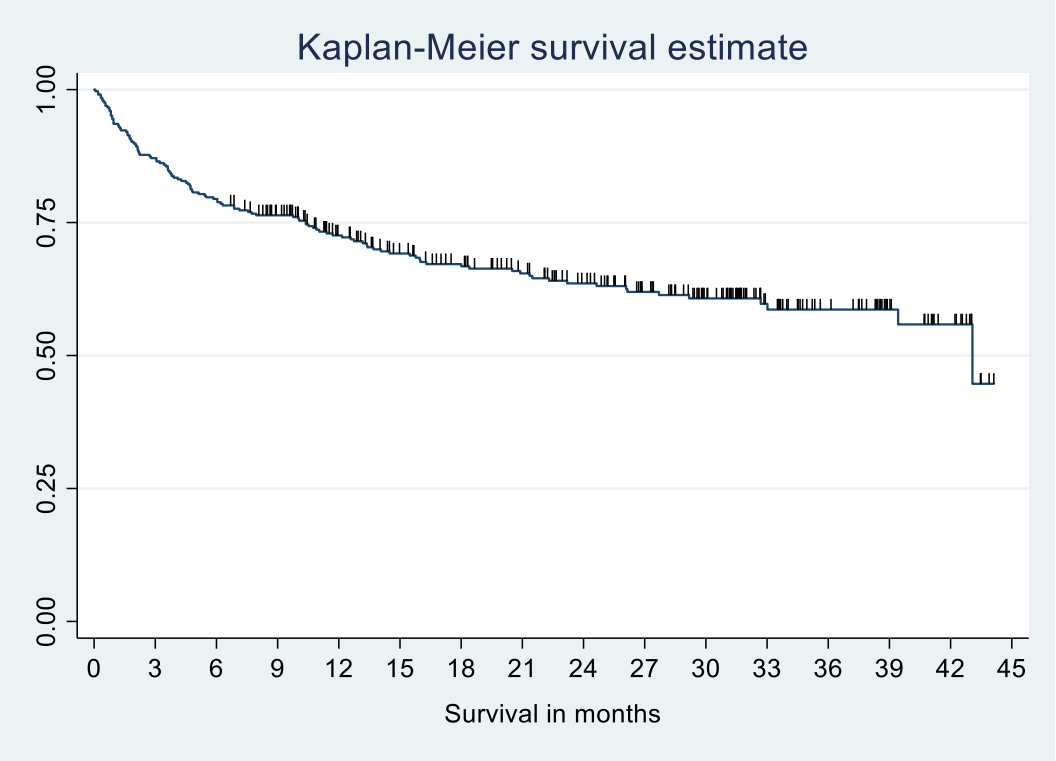
The median follow-up time in SACT was 17 months (517 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Table 54: OS at 6, 12, 18, 24 and 36-month intervals, CDF cohort

Time period	OS (%)
6 months	79% [95% CI: 75%, 83%]
12 months	73% [95% CI: 67%, 77%]
18 months	67% [95% CI: 62%, 72%]
24 months	64% [95% CI: 58%, 69%]
36 months	59% [95% CI: 52%, 65%]

The Kaplan-Meier curve for OS is shown in Figure 19. The median OS for all patients was 43.1 months[kk] (1,311 days) (N=326).

Figure 19. Kaplan-Meier survival plot, CDF cohort (N=326)



[kk] Confidence intervals are not shown if there was an insufficient number of events at the time this report was produced.

Table 55 and Table 56 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 44.9 months (1,366 days), all patients were traced on 2 July 2021.

Table 55. Number of patients at risk, by quarterly breakpoint, CDF cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Number at risk	326	284	259	236	200	176	161	145	128	108	85	56	39	21	13

Table 56 shows that for all patients who received treatment, 207 were still alive (censored) at the date of follow-up and 119 had died (events).

Table 56. Number of patients at risk, by quarterly breakpoints split between patients that have died (events) and patients that are still alive (censored), CDF cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Censored	207	207	207	194	169	154	144	132	119	102	81	53	37	19	12
Events	119	77	52	42	31	22	17	13	9	6	4	3	2	2	1

OS - EAMS cohort

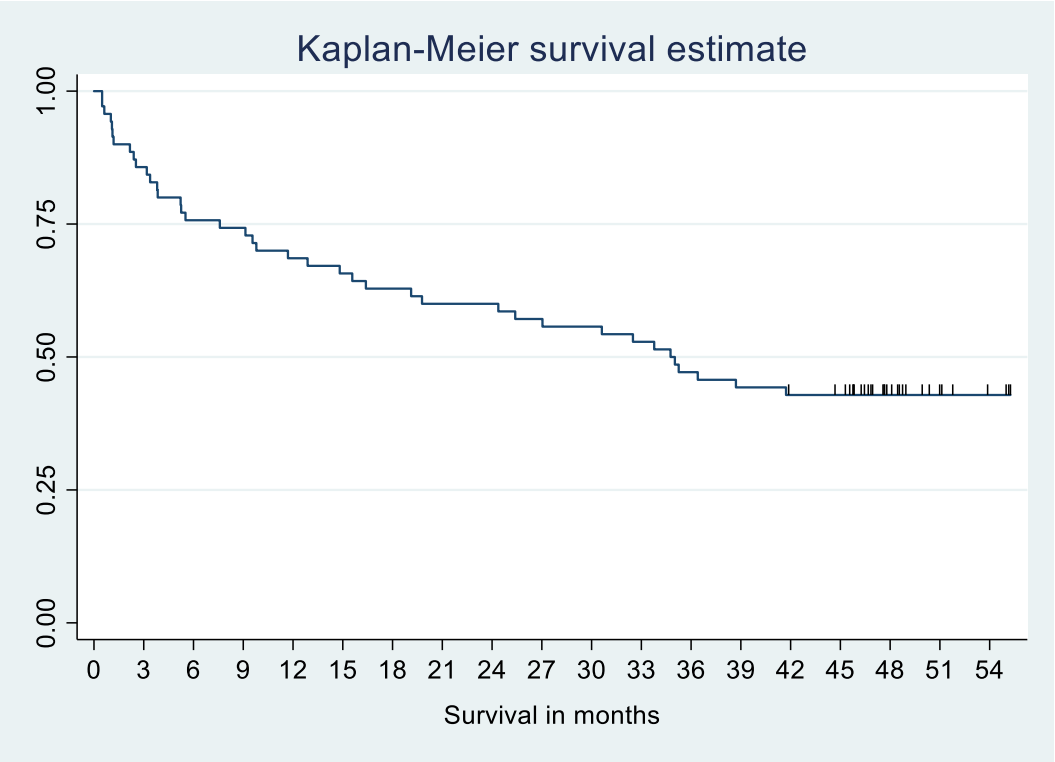
The median follow-up time in SACT was 34.9 months (1,062 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Table 57: OS at 6, 12 and 36-month intervals, EAMS cohort

Time period	OS (%)
6 months	76% [95% CI: 64%, 84%]
12 months	69% [95% CI: 56%, 78%]
18 months	63% [95% CI: 50%, 73%]
24 months	60% [95% CI: 48%, 70%]
36 months	47% [95% CI: 35%, 58%]

The Kaplan-Meier curve for OS is shown in Figure 20. The median OS for all patients was 34.8 months[ll] (1,059 days) (N=70).

Figure 20. Kaplan-Meier survival plot, EAMS cohort (N=70)



[ll] Confidence intervals are not shown if there was an insufficient number of events at the time this report was produced.

Table 58 and Table 59 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 58.3 months (1,774 days), all patients were traced on 2 July 2021.

Table 58. Includes the number of patients at risk, by quarterly breakpoints, EAMS cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Number at risk	70	60	53	52	48	46	44	42	42	40	39	37	33	31	29	28	13	5	3

Table 59 shows that for all patients who received treatment, 30 were still alive (censored) at the date of follow-up and 40 had died (events).

Table 59. Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints, EAMS cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Censored	30	30	30	30	30	30	30	30	30	30	30	30	30	30	29	28	13	5	3
Events	40	30	23	22	18	16	14	12	12	10	9	7	3	1	0	0	0	0	0

OS - combined cohort

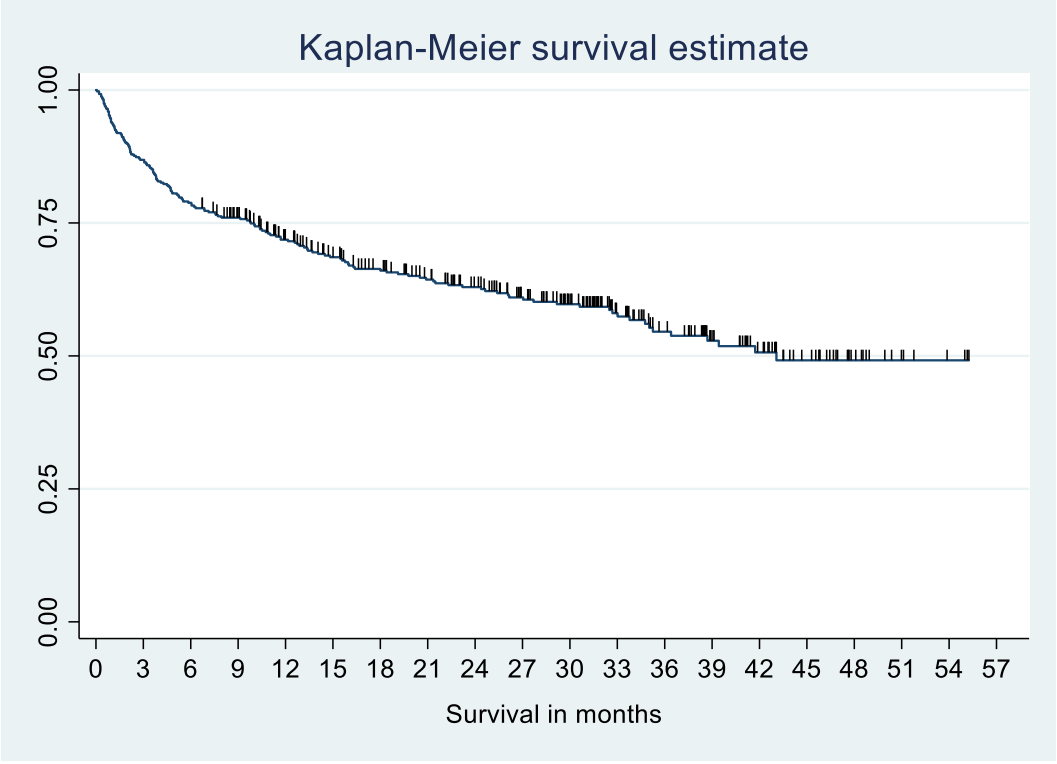
The median follow-up time in SACT was 18.8 months (572 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Table 60. OS at 6, 12, 18, 24 and 36-month intervals, Combined cohort

Time period	OS (%)
6 months	79% [95% CI: 74%, 83%]
12 months	72% [95% CI: 67%, 76%]
18 months	66% [95% CI: 61%, 71%]
24 months	63% [95% CI: 58%, 68%]
36 months	55% [95% CI: 48%, 60%]

The Kaplan-Meier curve for OS is shown in Figure 21. The median OS for all patients was 43.1 months[mm] (1,311 days) (N=396).

Figure 21. Kaplan-Meier survival plot, combined cohort (N=396)



[mm] Confidence intervals are not shown if there was an insufficient number of events at the time this report was produced.

Table 61 and Table 62 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 58.3 months (1,774 days), all patients were traced on 2 July 2021.

Table 61. Includes the number of patients at risk, by quarterly breakpoints, combined cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Number at risk	396	344	312	288	248	222	205	187	170	148	124	93	72	52	42	28	13	5	3

Table 62 shows that for all patients who received treatment, 237 were still alive (censored) at the date of follow-up and 159 had died (events).

Table 62. Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints, combined cohort

Time intervals (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Censored	237	237	237	224	199	184	174	162	149	132	111	83	67	49	41	28	13	5	3
Events	159	107	75	64	49	38	31	25	21	16	13	10	5	3	1	0	0	0	0

Table 63. Median treatment duration and median OS, CDF, EAMS and combined cohort[nn].

Metric	Cohort	Standard Analysis (full cohort)	Sensitivity analysis (minimum 6-months follow-up)	Secondary sensitivity analysis Absence of 17p deletion or TP53 mutation	Secondary sensitivity analysis Presence of 17p deletion or TP53 mutation	Third sensitivity analysis – removal of treatment switchers
N	CDF cohort	406	374	245	161	326
	EAMS cohort	102				70
	Combined cohort (CDF and EAMS)	508				396
Median treatment duration	CDF cohort	21.2 months [95% CI: 18.6, 24.7] (645 days)	20.9 months [95% CI: 17.9, 24.7] (636 days)	22.3 months [95% CI: 20.0, 28.1] (678 days)	17.9 months [95% CI: 11.5, 25.6] (544 days)	24.7 months [95% CI: 20.3, 31.1] (751 days)
	EAMS cohort	19.1 months [95% CI: 11.7, 27.0] (581 days)				16.2 months [95% CI: 9.1, 28.9] (493 days)
	Combined cohort (CDF and EAMS)	21.2 months [95% CI: 17.9, 24.6] (645 days)				24.6 months [95% CI: 20.2, 28.7] (748 days)

[nn] Confidence intervals are not shown if there was an insufficient number of events at the time this report was produced.

Metric	Cohort	Standard Analysis (full cohort)	Sensitivity analysis (minimum 6-months follow-up)	Secondary sensitivity analysis Absence of 17p deletion or TP53 mutation	Secondary sensitivity analysis Presence of 17p deletion or TP53 mutation	Third sensitivity analysis – removal of treatment switchers
Median OS	CDF cohort	43.1 months (1,311 days)		Not reached	33 months (1,004 days)	43.1 months (1,311 days)
	EAMS cohort:	32.5 months [95% CI: 20.3, 41.8] (989 days).				34.8 months (1,059 days)
	Combined cohort (CDF and EAMS)	38.5 months [95% CI: 31.3, 44.1] (1,171 days)				43.1 months (1,311 days)

Conclusions

406 patients received venetoclax for the treatment of chronic lymphocytic leukaemia [TA487] through the CDF in the reporting period (5 October 2017 and 4 December 2020), all 406 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 100%. An additional seven patients with a CDF application did not receive treatment and 16 patients died before treatment. All were confirmed by the trust responsible for the CDF application by the team at PHE.

Of the 105 patients that received venetoclax via an Early Access to Medicine Scheme, 102 were reported to the SACT dataset, giving a SACT ascertainment of 98%. One patient died before treatment, this was confirmed by the relevant trust.

Patient characteristics from the SACT dataset amongst the CDF cohort showed that 68% (N=275) of patients that received venetoclax for chronic lymphocytic leukaemia were male, 32% (N=131) of patients were female. Most of the cohort were aged 60 years and over (87%, N=354) and 67% (N=270) of patients had a performance status between 0 and 2 at the start of their regimen.

Patient characteristics from the SACT dataset amongst the EAMS cohort showed that 66% (N=67) of patients that received venetoclax for chronic lymphocytic leukaemia were male, 34% (N=35) of patients were female. Most of the cohort were aged between 50 and 79 years of age (87%, N=89) and 79% (N=81) of patients had a performance status between 0 and 2 at the start of their regimen.

At data cut off, 54% (N=220) of patients included in the CDF cohort and 82% (N=84) of EAMS patients were identified as no longer being on treatment. Of these 304 patients (220 CDF, 84 EAMS), 27% (N=53 CDF, N=30 EAMS) of patients stopped treatment due to progression, 8% (N=20 CDF, N=3 EAMS) of patients stopped treatment due to acute toxicity, 6% (N=16 CDF, N=3 EAMS) of patients chose to end their treatment, 32% (N=74 CDF, N=23 EAMS) of patients died not on treatment, 12% (N=24 CDF, N=13 EAMS) of patients died on treatment, 3% (N=6 CDF, N=3 EAMS) of patients completed treatment as prescribed and 12% (N=27 CDF, N=9 EAMS) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment.

Median treatment duration amongst the CDF cohort was 21.2 months [95% CI: 18.6, 24.7] (645 days). The median treatment duration amongst the EAMS cohort was 19.1 months [95% CI: 11.7, 27.0] (581 days) and for the combined cohort (CDF and EAMS) the median treatment duration was 21.2 months [95% CI: 17.9, 24.6] (645 days).

Median OS amongst the CDF cohort was 43.1 months[oo] (1,311 days). The median OS amongst the EAMS cohort was 32.5 months [95% CI: 20.3, 41.8] (989 days) and for the combined cohort the median OS was 38.5 months [95% CI: 31.3, 44.1] (1,171 days).

Sensitivity analysis was carried out on treatment duration to evaluate a cohort for which all patients had a minimum follow-up of six months in SACT. Results for treatment duration showed a difference of 0.3 months (full cohort = 21.2 months; sensitivity analysis cohort = 20.9 months).

A secondary sensitivity analysis was carried out on the CDF cohort, splitting treatment duration and OS by mutation status. Results for treatment duration showed a difference of 4.4 months (presence of 17p deletion or TP53 mutation = 17.9 months; absence of 17p deletion or TP53 mutation = 22.3 months). Results for OS showed those without a 17p deletion or TP53 mutation was not reached. OS amongst those with a 17p deletion or TP53 mutation was 33 months (1,004 days).

A third sensitivity analysis was carried out to establish treatment duration and OS when removing patients that received rituximab on or after a patient's first venetoclax treatment, regardless of the time from a patient first venetoclax treatment to their first rituximab treatment. Results for treatment duration showed a difference of 3.5 months amongst the CDF cohort (full cohort = 21.2 months; third sensitivity analysis cohort = 24.7 months). There was a difference amongst the EAMS cohort of 2.9 months (full cohort = 19.1 months; third sensitivity analysis cohort = 16.2 months) and the difference amongst the combined cohort was 3.4 month (full cohort = 21.2 months; third sensitivity analysis cohort = 24.6 months).

Results for OS showed no difference amongst the CDF cohort (full cohort = 43.1 months; third sensitivity analysis cohort = 43.1 months). The difference amongst the EAMS cohort was 2.3 months (full cohort = 32.5 months; third sensitivity analysis cohort = 34.8 months) and the difference amongst the combined cohort was 4.6 months (full cohort = 38.5 months; third sensitivity analysis cohort = 43.1 months).

[oo] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced

References

1. The Personal Demographics Service (PDS). NHS Digital: 2020 [cited 2021 Jul]. Available from: https://digital.nhs.uk/Demographics

2. National Statistics. Cancer Registration Statistics, England: 2018. 2020 [cited 2021 Jul]. Available from: https://www.gov.uk/government/statistics/cancer-registration-statistics-england-2018-final-release

3. National Institute for Health and Care Excellence: 2017 [cited 2021 Jul]. Available from: https://www.nice.org.uk/guidance/ta487/chapter/1-Recommendations

4. Cancer Drugs Fund. [Internet]. NHS England and NHS Improvement: 2016 [cited 2021 Jul]. Available from: https://www.england.nhs.uk/cancer/cdf/

5. Appraisal and funding of Cancer Drugs. NHS England and NHS Improvement: 2016 [cited 2021 Jul]. Available from: https://www.england.nhs.uk/wp-content/uploads/2013/04/cdf-sop.pdf

6. National Institute for Health and Care Excellence: 2017 [cited 2021 Jul]. Available from: https://www.nice.org.uk/guidance/ta487/chapter/4-Committee-discussion

7. Systemic Anti-Cancer Therapy [Internet]: SACT: 2019 [cited 2021 Jul]. Available from: http://www.chemodataset.nhs.uk/home

8. CDF analytical methods. [Internet]. PHE: 2019 [cited 2021 Jul]. Available from: http://www.chemodataset.nhs.uk/nhse_partnership/

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Evidence Review Group's 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.

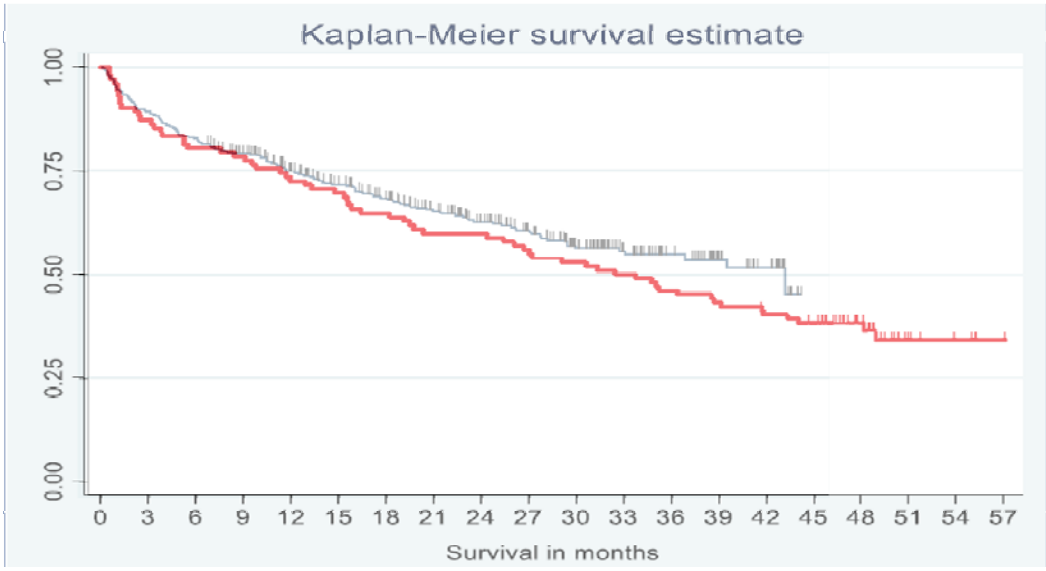


Figure 1: Comparison of SACT CDF (blue) and SACT EAMS (red) overall survival data

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.

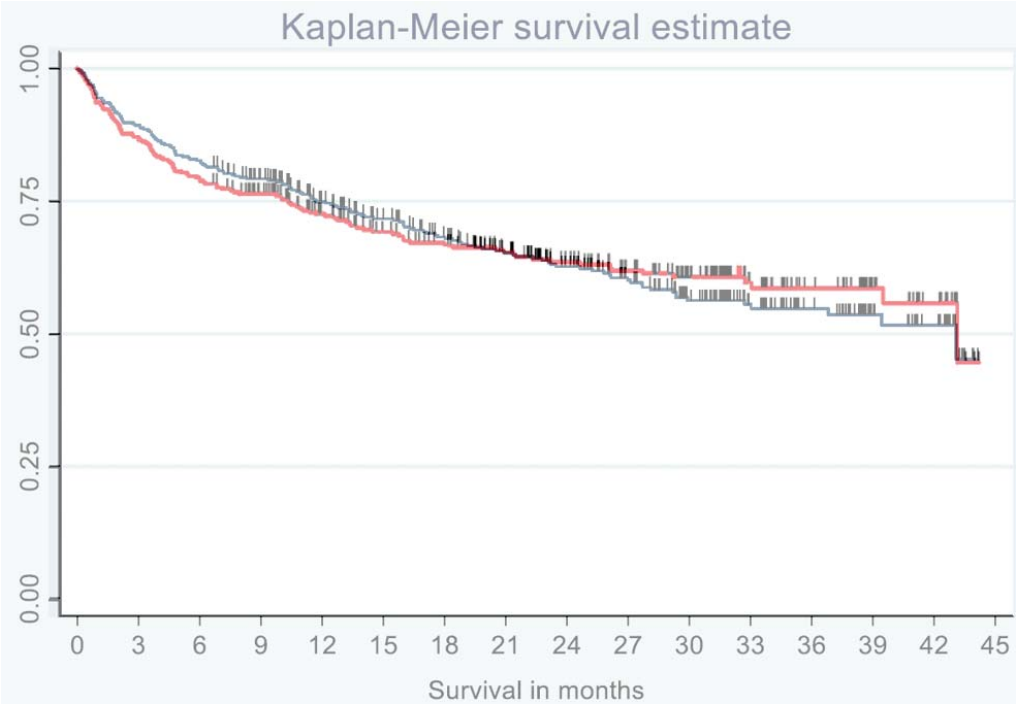


Figure 2: Comparison of CDF overall survival including (blue) and excluding (red) patients who received rituximab.

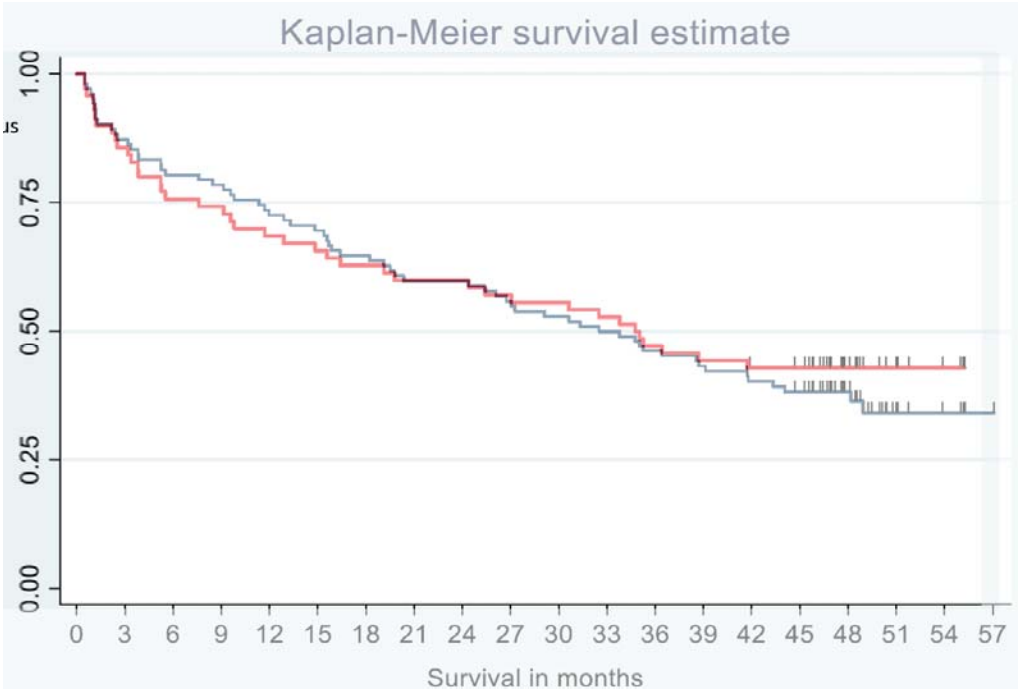


Figure 3: Comparison of EAMS overall survival including (blue) and excluding (red) patients who received rituximab.

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).

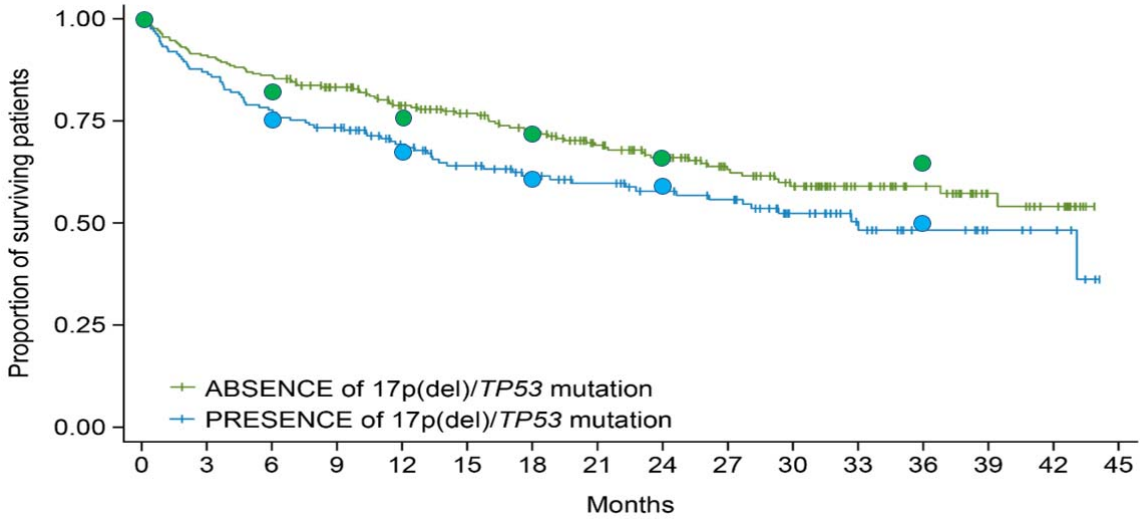


Figure 4: Overall survival for venetoclax patients from CDF SACT, comparing the effect of removing patients who received rituximab (dots) from the wider population (lines).

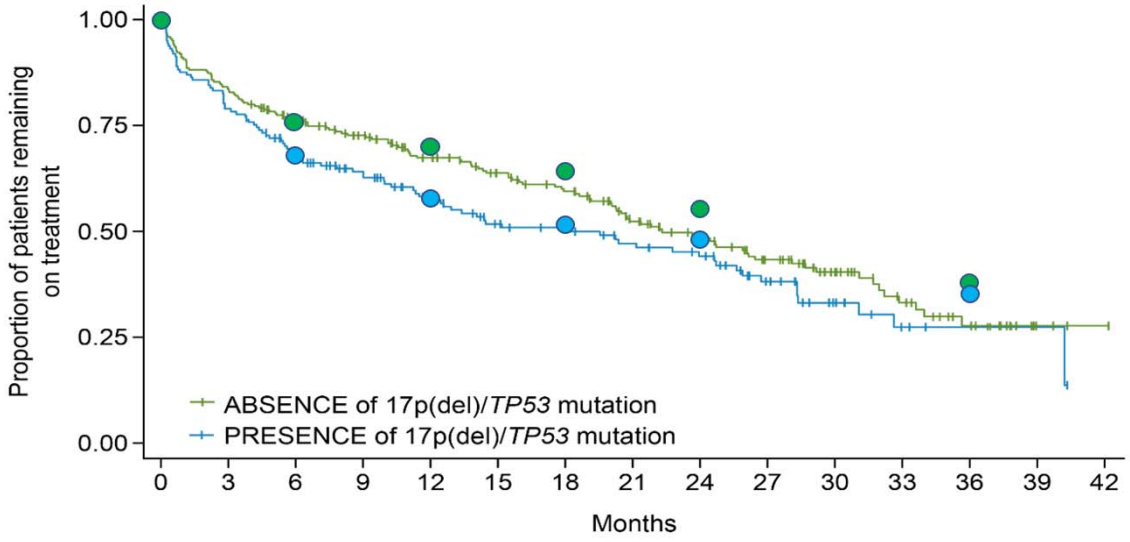


Figure 5:Time on treatment for venetoclax patients from CDF SACT, comparing the effect of removing patients who received rituximab (dots) from the wider population (lines).

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).

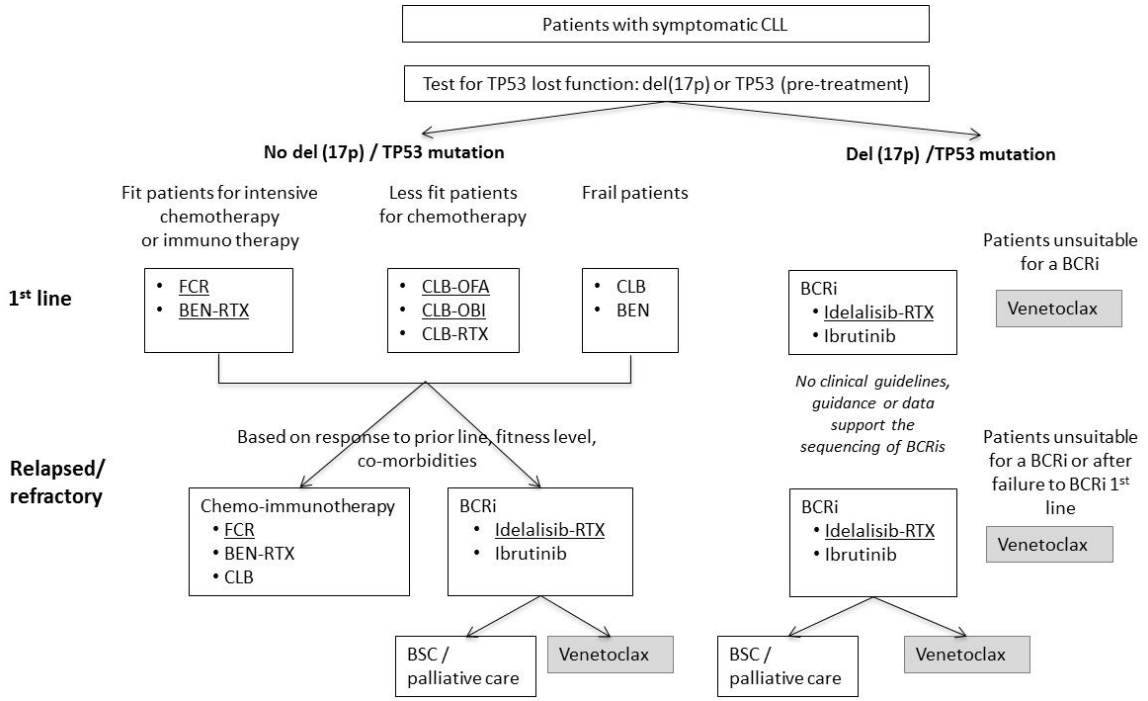
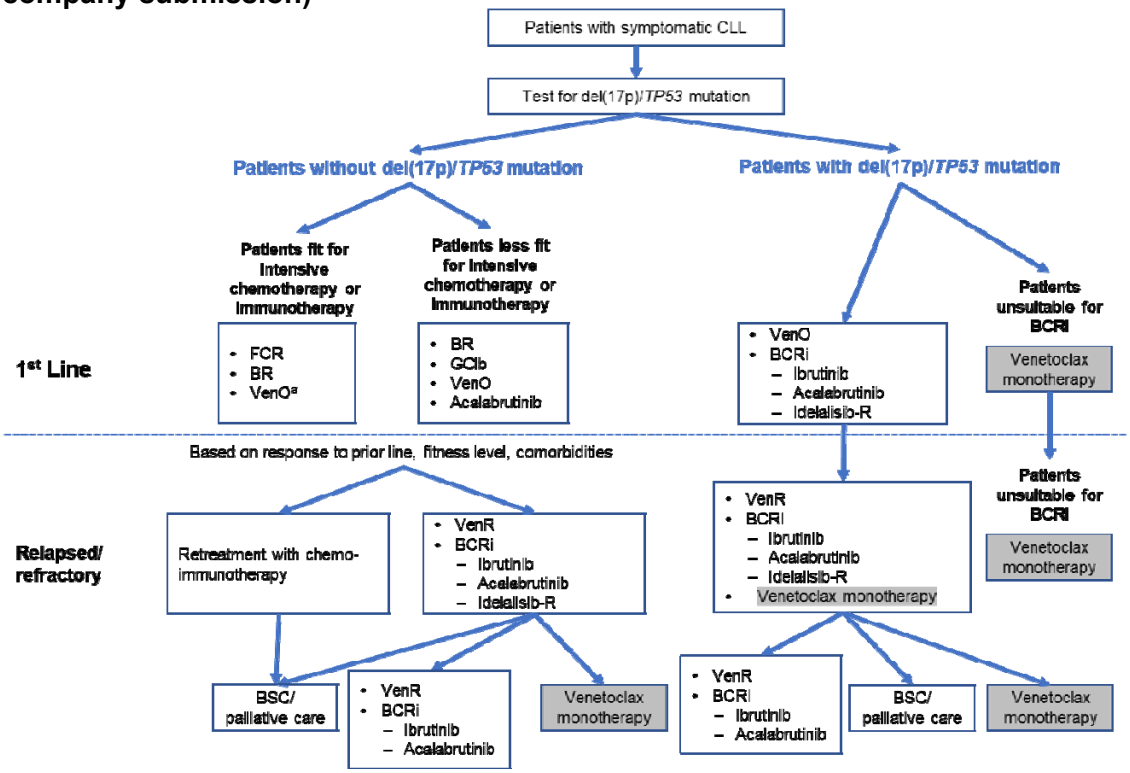


Figure 6: Treatment pathway at point of original appraisal (taken from original company submission)



[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; GCIb: 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.

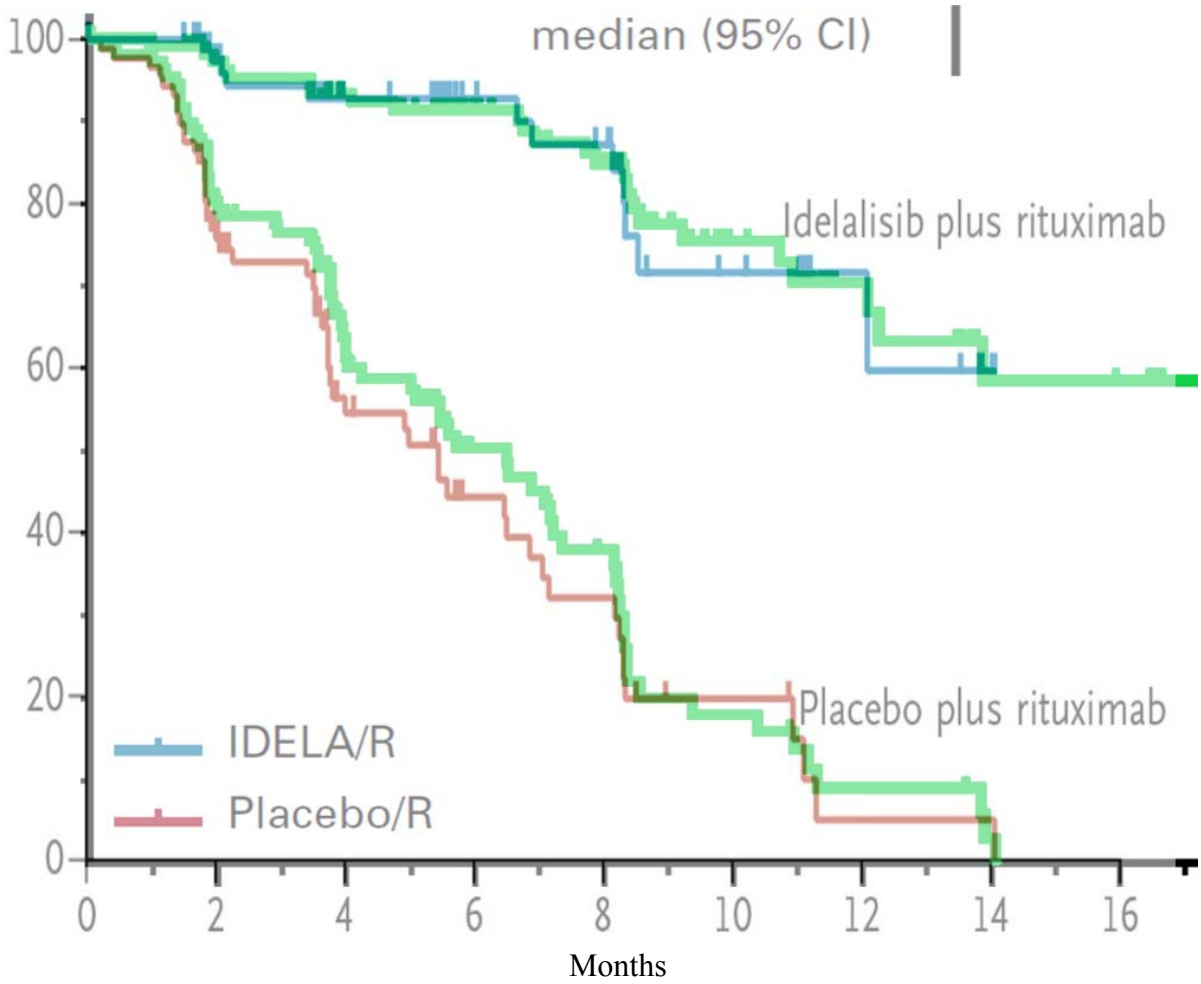


Figure 8: Updated (green) vs old follow-up of progression-free survival from Trial 116 demonstrating slightly improved PFS for the placebo arm. (Overlayed figures from Furman et al. 2014 [12] and Sharman et al. 2019 [11]).

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.

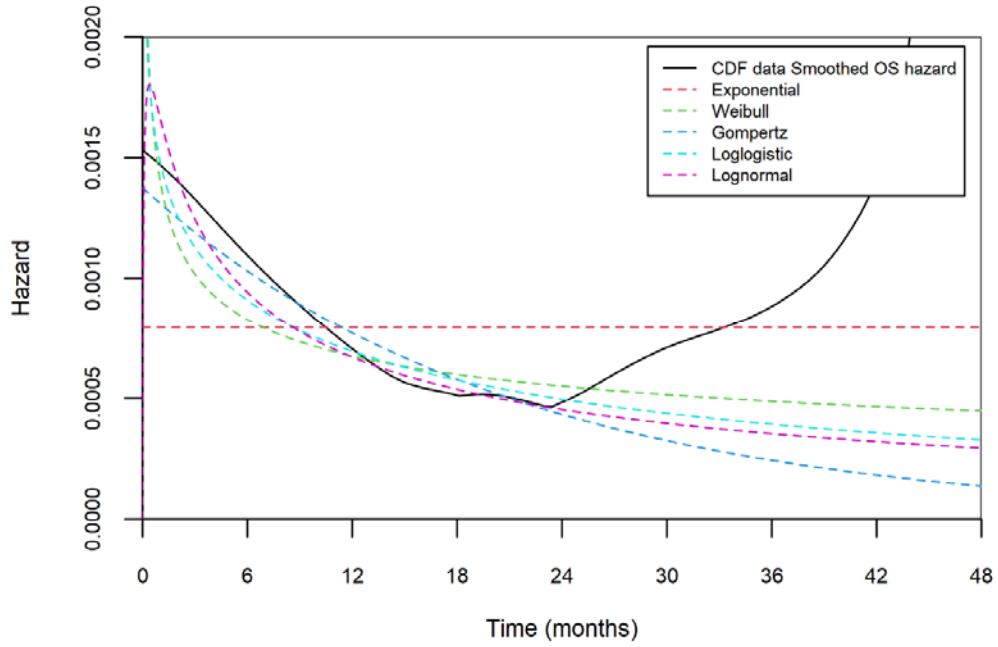


Figure 9: OS hazard rate for deletion/mutation population (from CS Figure 8)

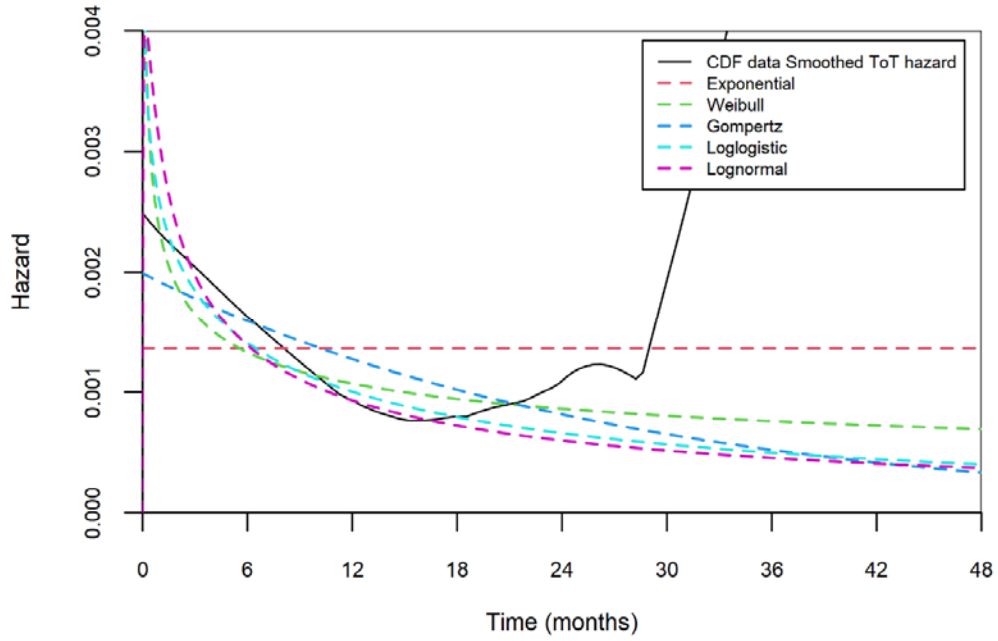


Figure 10: TOT hazard rate for deletion/mutation population (from CS Figure 11)

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.

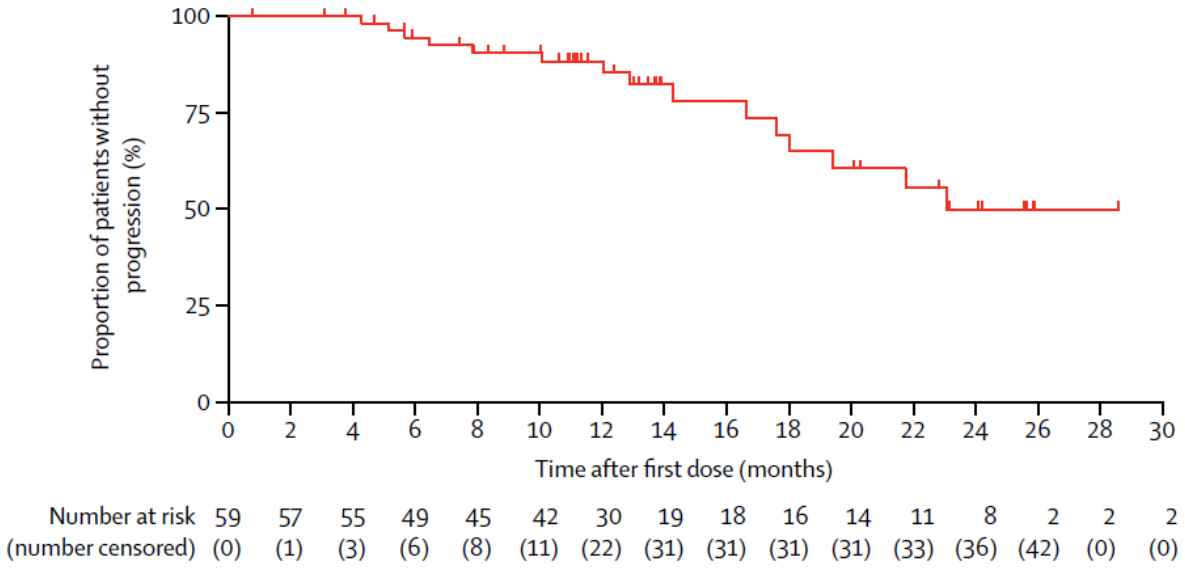


Figure 11: Duration of response for venetoclax, taken from Jones 2018.[26]

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 ***[redacted]

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				

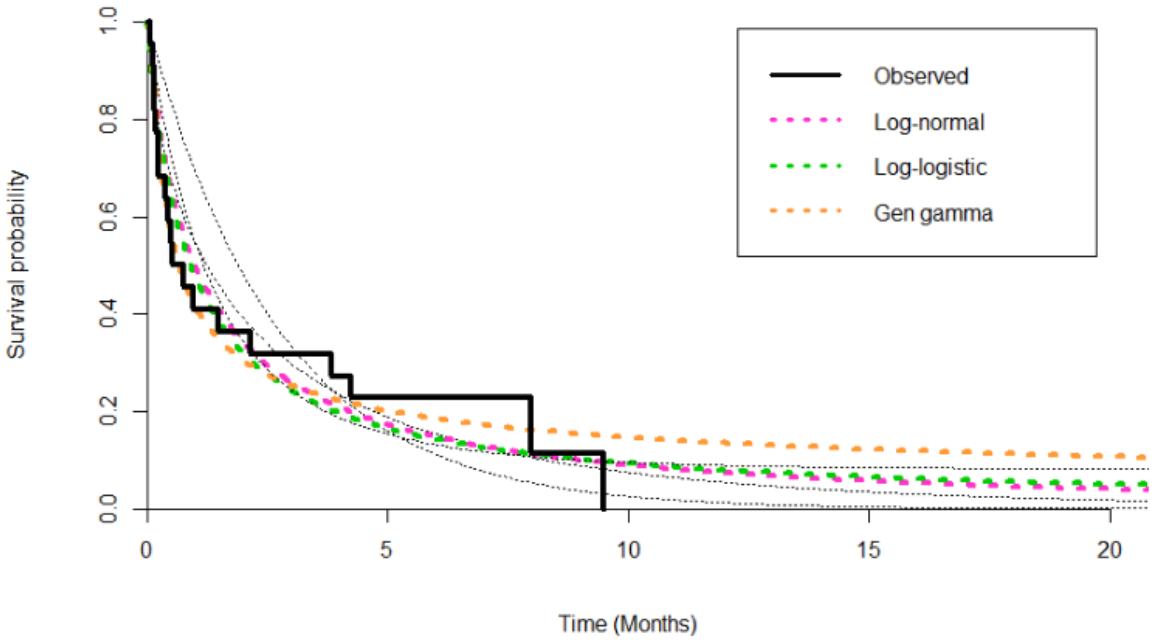


Figure 14: Observed survival from Eyre[6], and the best fitting ERG-fitted parametric curves

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.

8 REFERENCES

1. Gilead Sciences Ltd. Single technology appraisal: Idelalisib for treating chronic lymphocytic leukaemia [ID764]: Company evidence submission. In: Leukaemia (chronic lymphocytic, previously treated) - idelalisib [ID764]: committee papers [AC1]. National Institute for Health and Care Excellence; 2015. URL: https://www.nice.org.uk/guidance/ta359/documents/leukaemia-chronic-lymphocytic-previously-treated-idelalisib-id764-committee-papers (Accessed 15 December 2021).

2. National Institute for Health and Care Excellence. Venetoclax for treating chronic lymphocytic leukaemia: Technology appraisal guidance [TA487]: 1 Recommendations. 2017. URL: https://www.nice.org.uk/guidance/ta487/chapter/1-Recommendations (Accessed 20 December 2021).

3. National Institute for Health and Care Excellence. Venetoclax for treating chronic lymphocytic leukaemia [TA487]: Final appraisal determination. 2017. URL: https://www.nice.org.uk/guidance/ta487/documents/final-appraisal-determination-document (Accessed 5 January 2022).

4. Public Health England (PHE). Venetoclax for treating chronic lymphocytic leukaemia – data review; 2021.

5. National Institute for Health and Care Excellence. Venetoclax for treating chronic lymphocytic leukaemia [TA487]: Committee papers [AC1]. 2017. URL: https://www.nice.org.uk/guidance/ta487/documents/committee-papers (Accessed 15 December 2021).

6. Eyre TA, Kirkwood AA, Gohill S, Follows G, Walewska R, Walter H, et al. Efficacy of venetoclax monotherapy in patients with relapsed chronic lymphocytic leukaemia in the post-BCR inhibitor setting: a UK wide analysis. Br J Haematol 2019;**185**(4):656-69. http://dx.doi.org/10.1111/bjh.15802

7. NHS England Cancer Drugs Fund Team. National Cancer Drugs Fund list. NHS England; 2021. URL: https://www.england.nhs.uk/publication/national-cancer-drugs-fund-list/ (Accessed 20 December 2021).

8. Cancer Research UK. Chronic lymphocytic leukaemia (CLL) incidence statistics. 2021. URL: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-cll/incidence#heading-One (Accessed 20 December 2021).

9. National Institute for Health and Care Excellence. Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia: Technology appraisal guidance [TA561]. 2019. URL: https://www.nice.org.uk/guidance/ta561 (Accessed 20 December 2021).

10. National Institute for Health and Care Excellence. Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia: Technology appraisal guidance [TA663]. 2020. URL: https://www.nice.org.uk/guidance/ta663 (Accessed 20 December 2021).

11. Sharman JP, Coutre SE, Furman RR, Cheson BD, Pagel JM, Hillmen P, et al. Final Results of a Randomized, Phase III Study of Rituximab With or Without Idelalisib Followed by Open-Label Idelalisib in Patients With Relapsed Chronic Lymphocytic Leukemia. J Clin Oncol 2019;**37**(16):1391-402. http://dx.doi.org/10.1200/jco.18.01460

12. Furman RR, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P, et al. Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia. N Engl J Med 2014;**370**(11):997-1007. http://dx.doi.org/10.1056/NEJMoa1315226

13. Rigolin GM, Cavazzini F, Piciocchi A, Arena V, Visentin A, Reda G, et al. Efficacy of idelalisib and rituximab in relapsed/refractory chronic lymphocytic leukemia treated outside of clinical trials. A report of the Gimema Working Group. Hematol Oncol 2021;**39**(3):326-35. http://dx.doi.org/10.1002/hon.2861

14. Aarup K, Rotbain EC, Enggaard L, Pedersen RS, Bergmann OJ, Thomsen RH, et al. Real-world outcomes for 205 patients with chronic lymphocytic leukemia treated with ibrutinib. Eur J Haematol 2020;**105**(5):646-54. http://dx.doi.org/10.1111/ejh.13499

15. Kater AP, Wu JQ, Kipps T, Eichhorst B, Hillmen P, D'Rozario J, et al. Venetoclax Plus Rituximab in Relapsed Chronic Lymphocytic Leukemia: 4-Year Results and Evaluation of Impact of Genomic Complexity and Gene Mutations From the MURANO Phase III Study. J Clin Oncol 2020;**38**(34):4042-54. http://dx.doi.org/10.1200/jco.20.00948

16. Seymour JF, Kipps TJ, Eichhorst B, Hillmen P, D'Rozario J, Assouline S, et al. Venetoclax–Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. N Engl J Med 2018;**378**(12):1107-20. http://dx.doi.org/10.1056/NEJMoa1713976

17. Thompson MC, Allan JN, Sail K, Manzoor BS, Pu JJ, Barr PM, et al. Venetoclax Re-Treatment of Chronic Lymphocytic Leukemia (CLL) Patients after a Previous Venetoclax-Based Regimen. Blood 2020;**136**:39-41. http://dx.doi.org/10.1182/blood-2020-138725

18. Harrup RA, Owen C, D'Rozario J, Robak T, Kater AP, Montillo M, et al. Efficacy of Subsequent Novel Targeted Therapies, Including Repeated Venetoclax-Rituximab (VenR), in Patients (Pts) with Relapsed/Refractory Chronic Lymphocytic Leukemia (R/R CLL) Previously Treated with Fixed-Duration Venr in the Murano Study. Blood 2020;**136**:44-5. http://dx.doi.org/10.1182/blood-2020-137415

19. Tausch E, Close W, Dolnik A, Bloehdorn J, Chyla B, Bullinger L, et al. Venetoclax resistance and acquired BCL2 mutations in chronic lymphocytic leukemia. Haematologica 2019;**104**(9):e434-e7. http://dx.doi.org/10.3324/haematol.2019.222588

20. Jain P, Keating M, Wierda W, Estrov Z, Ferrajoli A, Jain N, et al. Outcomes of patients with chronic lymphocytic leukemia after discontinuing ibrutinib. Blood 2015;**125**(13):2062-7. http://dx.doi.org/10.1182/blood-2014-09-603670

21. Jain P, Thompson PA, Keating M, Estrov Z, Ferrajoli A, Jain N, et al. Long-term outcomes for patients with chronic lymphocytic leukemia who discontinue ibrutinib. Cancer 2017;**123**(12):2268-73. http://dx.doi.org/10.1002/cncr.30596

22. UK CLL Forum. Ibrutinib for relapsed/refractory chronic lymphocytic leukemia: a UK and Ireland analysis of outcomes in 315 patients. Haematologica 2016;**101**(12):1563-72. http://dx.doi.org/10.3324/haematol.2016.147900

23. Iskierka-Jażdżewska E, Puła B, Szeremet A, Hus M, Gołos A, Hołojda J, et al. Ibrutinib discontinuation in patients with relapsed or refractory chronic lymphocytic leukemia treated in a compassionate use program: A report from the Polish Adult Leukemia Study Group (PALG). Adv Clin Exp Med 2019;**28**(8):1051-7. http://dx.doi.org/10.17219/acem/99911

24. O'Brien SM, Byrd JC, Hillmen P, Coutre S, Brown JR, Barr PM, et al. Outcomes with ibrutinib by line of therapy and post-ibrutinib discontinuation in patients with chronic lymphocytic leukemia: Phase 3 analysis. Am J Hematol 2019;**94**(5):554-62. http://dx.doi.org/10.1002/ajh.25436

25. Maddocks KJ, Ruppert AS, Lozanski G, Heerema NA, Zhao W, Abruzzo L, et al. Etiology of Ibrutinib Therapy Discontinuation and Outcomes in Patients With Chronic Lymphocytic Leukemia. JAMA Oncol 2015;**1**(1):80-7. http://dx.doi.org/10.1001/jamaoncol.2014.218

26. Jones JA, Mato AR, Wierda WG, Davids MS, Choi M, Cheson BD, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. The Lancet Oncology 2018;**19**(1):65-75. http://dx.doi.org/https://doi.org/10.1016/S1470-2045(17)30909-9

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG response to the factual accuracy check and confidential information check

Venetoclax for treating chronic lymphocytic leukaemia (CDF review of TA487) [ID3886]

Issue 1 Factually Inaccurate Errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 8 of the ERG report states: *"No additional data for BSC was presented by the company."* Page 9 of the ERG report states: *"Issue 2: The uncertainty around BSC efficacy and the company's failure to consider alternative sources of data for BSC"* Page 10 of the ERG report states: *"The company has not considered any alternative sources of BSC data and repeated its use of data from the rituximab arm of trial 116."* Page 19 of the ERG report states: *"The company has not presented any evidence to suggest they have considered any alternative sources of data for BSC or conducted any formal literature search."* Page 39 of the ERG report states: *"The company failed to fully explore alternative sources of BSC data as recommended in the scope."*	The statement on Page 8 should be amended as follows: *"No additional data for BSC was **provided by PHE or** presented by the company."* The statement on Page 9 should be amended as follows: *"Issue 2: The uncertainty around BSC efficacy and **the company not identifying and presenting** alternative sources of data for BSC"* The statement on Page 10 should be amended as follows: *"The company has not **identified and therefore not presented** any alternative sources of BSC data and repeated its use of data from the rituximab arm of trial 116."* The statement on Page 19 should be amended as follows: *"The company **did not identify and therefore present** any alternative sources of data for BSC or conducted any formal literature search."* The statement on Page 39 should be amended as follows:	These statements are factually inaccurate and potentially misleading. Firstly, they do not consider all factors relating to why no new data were presented for BSC, namely the inability of SACT to provide BSC data as agreed. AbbVie was only made aware of the failure of SACT to provide BSC data in February 2021, therefore leaving limited opportunities to attempt to capture additional BSC data. Secondly, the company did consider alternative sources of BSC data (clarification question A8). However, as there were no robust data sources identified, none were presented.	P8 – not a factual error. P9 – not a factual error P10 – text has been amended for clarification P19 – not a factual error P39 – text has been amended for clarification P40a – text has been amended for clarification P40b – not a factual error P56 – not a factual error

Page 40 of the ERG report states: *"In their CDF submission, the company have not considered any alternative approaches to modelling for the BSC arm and maintained their original modelling approach.* Page 40 of the ERG report states: *"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."* Page 56 of the ERG report states: *"The only exception is the modelling of BSC arm because of the company failed to fully explore alternative sources of BSC data."*	"*The company **did not identify and therefore present** alternative sources of BSC data as recommended in the scope."* The statement on Page 40 should be amended as follows: *"Notwithstanding the inability of SACT CDF to collect BSC data as recommended by the committee, in their CDF submission, the company have not presented any alternative approaches to modelling for the BSC arm and maintained their original modelling approach."* The statement on Page 40 should be amended as follows: *"In review, the ERG note that the company have not **identified and therefore presented** any other sources of information."* The statement on Page 56 should be amended as follows: *"The only exception is the modelling of BSC arm because the company **had not identified and therefore presented** alternative sources of BSC data."*		
Page 9 of the ERG report states: *"The company implemented the same approach as they did in the original appraisal (TA487) without any consideration of alternative modelling, such as the ERG's preferred approach in the original appraisal to use post-progression*	The statement on Page 9 should be amended as follows: *"The company implemented the same approach as they did in the original appraisal (TA487) **and did not present alternative modelling approaches** such as the ERG's preferred approach in the original appraisal to*	This statement is factually incorrect and potentially misleading. AbbVie did consider alternative modelling approaches, including the ERG's preferred approach in the original appraisal, which was considered inappropriate as described in Section A.14 of the CS.	The ERG report has been amended for clarity.

survival information from the idelalisib arm of trial 116."	*use post-progression survival information from the idelalisib arm of trial 116."*		
Page 10 of the ERG report states: *"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."*	The statement on Page 9 should be removed or amended as follows: *"The SACT CDF data are also more optimistic than the SACT EAMS data;* ***however, the ERG concluded that the SACT CDF data was the appropriate cohort for this submission****."*	This statement is potentially misleading and does not reflect the conclusions of the ERG, as noted in the following statement on Page 26 of the ERG report: *"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. "*	Not a factual error.
Page 10 of the ERG report states: *"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."* Pages 17–18 of the ERG report states: *"Within this CDF review, an updated treatment pathway was submitted by the company in*	These statements should be removed or heavily caveated.	The CDF submission provided by the company aligned with the previous decision problem of TA487 as per the terms of engagement agreed with NICE. Consideration of the updated treatment pathway is therefore outside the scope of this review, and discussion of this as an issue is misleading.	Not a factual error.

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" Section 3.4.2 also discusses this point.			
Page 19 of the ERG report states: *"Company did not consider any alternative methods of extrapolation that may better represent the data."*	The statement on Page 19 should be removed.	This statement is factually inaccurate. Section A.8.1 of the CS explains the survival extrapolation approach taken and fully considered the methods as described in the NICE DSU guide.	Not a factual error.
Page 19 of the ERG reports states: *"New and extended follow-up from trials of ibrutinib and of study 116 but it does not appear the company attempted to obtain or use this data."* Page 33 of the ERG report states: *"The ERG notes that extended follow-up from trial 116 is now available, however, it was not publicly reported to the detail necessary for inclusion in this*	The statement on Page 19 should be amended as follows: *"New and extended follow-up from trials of ibrutinib and of study 116 but it does not appear the company* ***were able*** *to obtain or use this data."* The statement on Page 33 should be amended as follows: *"The ERG notes that extended follow-up from trial 116 is now available, however, it was not publicly reported to the detail necessary for inclusion in this appraisal.* ~~*The company did not*~~	These statements are potentially misleading. As Trial 116 is not an AbbVie trial, we would not have been able to obtain unpublished follow-up data and so were reliant on publicly available data to support the submission; efforts were made to identify any useful published updates to Trial 116, but none were appropriate (as the ERG acknowledge). It would not have been appropriate for AbbVie, as a manufacturer, to request IPD	In question A6, the ERG specifically asked about the extent of effort made by the company to obtain updated information from Trial 116. As the company did not mention contacting the authors, the ERG presume no attempt was made to obtain this information in a useable format. Not a factual error.

appraisal. The company did not make any attempt to obtain useable information from the authors." Page 42 of the ERG report states: *"The company do not appear to have attempted to use or obtain this extended follow-up (clarification A6)."*	~~*make any attempt to obtain useable information from the authors.*~~*"* The statement on Page 42 should be amended as follows: *"The company* ***were unable*** *to use or obtain this extended follow-up (clarification A6)."*	from Gilead, nor would this have been successful.	
Page 21 of the ERG report states: *"The company did not provide updated data for the M12-175 trial in this submission, nor following the request for further updated data in the clarification question A7."*	The statement on Page 21 should be amended as follows: *"The company did not provide updated data for the M12-175 trial in this submission* ***and following the request for further updated data in the clarification question A7, confirmed that no further follow-up trial data for M12-175 are available since the original submission****."*	This statement is factually inaccurate and potentially misleading. As confirmed in the clarification questions (A7), no further follow-up for trial M12-175 is available since the original appraisal.	The ERG report has been amended for clarity.
Table 14, Page 24 of the ERG report contains the following footnote: *"Mean and median age with CI for SACT data were not available in the PHE report but provided by the company (clarification latter A11&12). Patients age within SACT data is age at the start of treatment. SACT OS by mutation was provided by company (clarification letter, appendix A)."*	The footnote of Page 24 should be amended as follows: *"Mean and median age with CI for SACT data were not available in the PHE report but provided by* ***NHSD*** *(clarification latter A11&12). Patients age within SACT data is age at the start of treatment. SACT OS by mutation was provided by* ***NHSD*** *(clarification letter, appendix A)."*	This statement is factually inaccurate. These responses were part of the clarification question answers provided by NHS Digital, rather than those provided by AbbVie.	The ERG report has been corrected.

Page 26 of the ERG report states: *"If the EAMS OS data were broken down by deletion/mutation status and pooled with the CDF data, the efficacy of venetoclax would decrease."*	The statement on Page 26 should be amended as follows: *"**We predict that** if the EAMS OS data were broken down by deletion/mutation status and pooled with the CDF data, the efficacy of venetoclax would decrease."*	As these analyses have not been conducted, this statement represents a theory from the ERG rather than known fact, and as such is currently misleading.	The ERG report has been amended for clarity.
Page 27 of the ERG report states: *"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. It is uncertain if this update had*	The statement on Page 27 should be amended as follows: *"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.* ***Following the ERG's request for clarification directed to PHE, in relation to the SACT data, in question A15 it was confirmed that included patients with 17p deletion or TP53 mutation "must never [have] received venetoclax before or [have] been previously treated with the combination of venetoclax with an anti-CD20 antibody (obinutuzumab or rituximab), in which case the patient must not have progressed during such treatment with venetoclax."****"*	This paragraph is potentially misleading. Whilst this inclusion criteria was not reported in the PHE SACT report for patients with 17p deletion or *TP53* mutation, this was confirmed in the clarification questions (A15). The remainder of this paragraph is therefore no longer relevant, following this clarification.	The ERG has removed the final sentence from the original paragraph, improving the accuracy of the ERG report.

influenced the information collected within the PHE SACT report."			
Page 30 of the ERG report states: *"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."*	The statement on Page 30 should be amended as follows: *"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.* ***However, median OS was the same amongst the relevant CDF cohort (full cohort = 43.1 months; sensitivity analysis cohort = 43.1 months)."***	This statement is potentially misleading as it does not consider all available data. Although there was some variation in Kaplan–Meier curves when rituximab patients were removed from the CDF cohort, the median overall survival remained the same.	Not a factual error.
Page 33 of the ERG report states: *"No updated information on the 116 trial was presented by the company in the current submission (clarification question A6) nor was a search for an alternative source of BSC data performed (clarification question A8)."*	The statement on Page 33 should be amended as follows: *"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)."*	This statement is factually inaccurate. The company did investigate alternative sources of BSC data, but a systematic literature search was not conducted.	The ERG report has been amended for clarity.
Page 35 of the ERG report states: *"The ERG sought to do a statistical comparison of venetoclax to BSC, as the company failed to provide one."*	The statement on Page 35 should be amended as follows: *"The ERG sought to do a statistical comparison of venetoclax to BSC, as the company* ***were unable*** *to provide one."*	This statement is factually incorrect. As noted in the clarification questions (A2), a naïve comparison between the SACT data and AbbVie's choice of BSC was not possible due to a lack of	Not a factual error.

Page 39 of the ERG report states: *"The company did not perform any form of matching analysis to account for the identified differences…"*	The statement on Page 39 should be amended as follows: *"The company **were unable to** perform any form of matching analysis to account for the identified differences…"*	access to suitable data to be able to generate this analysis.	
Page 39 of the ERG report states: *"The company did not discuss in detail the data and extrapolations for BSC in their CDF submission."*	The statement on Page 39 should be amended as follows: *"The company did not discuss in detail the data and extrapolations for BSC in their CDF submission **as it had already been covered in the original submission**."*	This statement is potentially misleading and implies an omission by the company. As the data and extrapolations for BSC were already covered in detail in the original submission, the information was not repeated in the CDF exit submission.	Not a factual error.
Page 61 of the ERG report states: *"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)."*	The statement on Page 61 should be amended as follows: *"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 **may** be considerably higher than as presented in the ERG base case (Table 29)."*	As the ERG were unable to conduct other scenarios, the current statement is based on assumption and is therefore misleading. The ERG has acknowledged that there are limitations to the alternative approaches, and as such chosen not to include them in their base case; it is therefore inappropriate to make a claim about the likely impact on the ICERs for these unconducted scenarios.	Not a factual error.

Issue 2 General Errors

Description of problem	Description of proposed amendment	Justification for amendment	
Table 14, Page 22 of the ERG report describes the baseline characteristics and key outcomes for relevant studies. The following data are reported incorrectly: *"Mean age, years (STD) for the 'Total pooled population M12-175/ M14-032 (without del(17p)/TP53 patients) –original appraisal': 65.44 (9.68)."* *"Rai stage at screening, n (%) for the 'Trial 116 (rituximab arm)': 0.5."* Also, in this table, data for the total pooled populations both with and without del(17p)/*TP53* have been reported to 0dp rather than the 2dp given in the original submission.	These data values should be corrected to the following values: *"Mean age, years (STD) for the 'Total pooled population M12-175/ M14-032 (without del(17p)/TP53 patients) –original appraisal';* ***65.25 (8.79)****."* *"Rai stage at screening, n (%) for the 'Trial 116 (rituximab arm)'; 0.9."* For clarity, all amendments to Table 14 of the ERG report have been indicated in bold and blue text in the table in Appendix A of this response. The rounding from the original submission have also been implemented in this table.	These values were incorrect in the ERG report.	The ERG report has been corrected. The ERG have used rounded values for consistency across the table.
Table 21, Page 55 of the ERG report describes the company's one way sensitivity analyses for the patient population with deletion/mutation. The following data are reported incorrectly: *"Starting age, low value, value: 65.216"* *"Starting age, high value, value: 67.292"*	These data values should be correct to the following values: *"Starting age, low value, value: 64.396"* *"Starting age, high value, value: 66.472"*	These values were incorrect in the ERG report.	The ERG report has been corrected.
Page 26 of the ERG report cites Eyre et al. (2019), with the reference provided being 'Eyre TA, Walter HS, Iyengar S, Follows G, Cross M,	The citation should be updated to the following: 'Eyre TA, Kirkwood AA, Gohill S, et al. Efficacy of venetoclax monotherapy in	We believe that the citation used is incorrect as it relates to a study of mantle cell	The ERG report has been corrected.

Fox CP, et al. Efficacy of venetoclax monotherapy in patients with relapsed, refractory mantle cell lymphoma after Bruton tyrosine kinase inhibitor therapy. Haematologica 2019;104(2):e68-e71. http://dx.doi.org/10.3324/haematol.2018.198812'	patients with relapsed chronic lymphocytic leukaemia in the post-BCR inhibitor setting: a UK wide analysis. Br J Haematol. 2019;185(4):656-669. doi:10.1111/bjh.15802'	lymphoma. The updated citation refers to what we believe to be the correct Eyre et al. (2019) study of relapsed CLL patients treated with venetoclax monotherapy.	

Issue 3 Typographical Errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 17 of the ERG report states: *"For this CDF review, venetoclax is used for adults with CLL who have 17p deletion or **TP52** 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 **T17p** deletion or TP53 mutation and whose disease has progressed following both chemo-immunotherapy and a B-cell receptor pathway inhibitor."*	The statement on Page 17 should be amended as follows: *"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."*	The statement contains two typographical errors.	The ERG report has been corrected.
Page 24 of the ERG report states: "*SCAT: Systemic Anti-Cancer Therapy"*	The statement on Page 24 should be amended as follows: *"SACT: Systemic Anti-Cancer Therapy"*	The statement contains a typographical error.	The ERG report has been corrected.
Page 29 of the ERG report states: *"TOT and OS by mutation status were presented in CS section*	The statement on Page 29 should be amended as follows:	This statement contains two typographical errors.	The ERG report has been corrected.

A.6.6.2 to A.6.6.3 and summarised in Table 14."	*"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."*		

NICE National Institute for Health and Care Excellence

Technical engagement response form

Venetoclax for treating chronic lymphocytic leukaemia (CDF review of TA487) [ID3886]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Tuesday 15 February 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	AbbVie Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Key issue	Does this response contain new evidence, data or analyses?	Response
1. Generalisability of venetoclax data to UK practice	No	The generalisability of the venetoclax trial data was a key uncertainty of the original appraisal; in TA487, the committee considered that the patients included in the venetoclax trials may be younger and have a lower burden of disease compared with patients who would be expected to receive venetoclax in clinical practice.[1] To address this uncertainty, data collected from SACT rather than updated data from the venetoclax trials have been used to inform the model for this appraisal. Although SACT data were provided separately for the Cancer Drug Fund (CDF) and Early Access to Medicine Scheme (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 were presented within the submission. As noted on Page 26 of the ERG report, the *"ERG agrees with this statement"*. A clinical expert in CLL consulted by AbbVie further agreed with this approach. Additionally, as presented in the company submission (CS), patients in the SACT CDF cohort are closer in age to the mean age of patients with CLL at diagnosis in England (71 years), compared with a mean age of 65 years in the venetoclax trials.[2-4] When excluding patients with missing Eastern Cooperative Oncology Group (ECOG) scores in the SACT CDF cohort, there is a trend towards more advanced disease compared with the patients in the venetoclax trials, with a higher proportion of patients with a ECOG score of 2 or above.[1] Additionally, AbbVie's clinical expert highlighted that the EAMS cohort was a more heavily pre-treated cohort when compared with patients in the CDF cohort. Therefore, considering both the improved

		generalisability of the SACT CDF data to UK clinical practice, and the relevance of the cohort to the economic model by providing separate data split by del(17p)/*TP53* mutation status, the SACT CDF cohort is considered the most appropriate source of efficacy data for this submission. The ERG noted that since the original appraisal, venetoclax combinations have been made available to patients as both front line and relapsed/refractory options; this means that the patients within this indication today will have followed a different treatment pathway to patients that received venetoclax in the SACT CDF cohort. The ERG also highlighted the possibility that patients may become resistant to venetoclax therapy. However, based on clinical expert opinion in the joint patient group submission from Leukaemia Care and CLL Support, patients are "*unlikely to build up resistance to venetoclax whilst taking the [venetoclax] combinations*"; this statement was further validated by clinical expert opinion sought by AbbVie. Furthermore, the clinical expert highlighted that only a very small percentage of patients would be treated with venetoclax therapies more than twice. The ERG also investigated the evidence on the efficacy of venetoclax retreatment and concluded, along with their clinical expert, that *"venetoclax is likely to be efficacious after previous exposure to venetoclax therapy".* The statement from Leukaemia Care and CLL Support also highlighted that venetoclax monotherapy provides an extra advantageous option for patients including those "*who have previously had venetoclax combinations and relapsed subsequently"*. Finally, data from a recent publication also suggests that treatment with venetoclax monotherapy may be effective for patients who have relapsed following initial fixed duration treatment with venetoclax in combination with rituximab (VenR).[5] Based on published data available and clinical expert opinion, AbbVie agree with the conclusions from both the ERG, and Leukaemia Care and CLL Support;[6-8] AbbVie accept that there is still some uncertainty about the degree of efficacy but do not expect the acceptance and use of earlier courses of venetoclax to have a substantial impact on the efficacy of later line venetoclax monotherapy. Whilst AbbVie agree that the treatment landscape has changed since the original appraisal, this should not be considered as directly relevant to this appraisal. The CS provided by

		AbbVie aligned with the previous decision problem of TA487 as per the terms of engagement agreed with NICE. Consideration of the updated treatment pathway is therefore outside the scope of this review and should not contribute to any decision making. Finally, the ERG also noted that patients within the SACT CDF cohort were allowed to switch from venetoclax monotherapy to VenR within the five-week titration period of venetoclax. Eighty patients (19.7%) in the SACT CDF cohort received rituximab on or after the earliest venetoclax treatment start date, however only 30 of the 112 'treatment switchers' (across both the SACT CDF and EAMS cohorts) started rituximab within eight weeks; it is unclear if these patients all truly switched to VenR or instead received rituximab as a subsequent therapy. The ERG's sensitivity analysis presented in Section 3.1.2.2.3 of the ERG report and based on the combined CDF and EAMS cohort suggests rituximab may have had an effect, but the reliability of these analyses are limited considering the reason these patients received rituximab was unclear from the PHE SACT report and the limited information on the duration of rituximab treatment. Indeed, median overall survival (OS) was the same in the SACT CDF cohort for groups with and without patients treated with rituximab (full cohort = 43.1 months; sensitivity analysis cohort = 43.1 months), suggesting no impact of rituximab on OS. Whilst AbbVie acknowledge there are limitations with the SACT CDF cohort data (as discussed above), this cohort remains the most appropriate source of efficacy data for this submission, as agreed by the ERG. Importantly, use of data from the SACT CDF cohort addresses a key uncertainty raised by the committee in the original appraisal by providing a data source for venetoclax that is of direct relevance to the decision problem.
2. Uncertainty and potential for bias in data modelling of Best Supportive Care (BSC)	No	As set out in the data collection plan, PHE SACT was expected to provide BSC data. However, on 2nd March 2021, the SACT Operational Group considered that no meaningful data could be captured on BSC within SACT during the period of managed access. AbbVie therefore had a limited opportunity to identify alternative sources of BSC data. Although no formal updated searches were performed as part of this appraisal, attempts were made to explore alternative sources through clinical expert opinion; however, no further sources of

		evidence were identified. AbbVie have since followed up with an author of the 116 study to ascertain whether any further detail on post-progression treatments had been captured. However. no further data beyond what was included within the Sharman 2019 article is available.[9] AbbVie therefore utilised the rituximab arm of the 116 trial, as presented in the original submission. There remains a lack of alternate approaches available, given no BSC data could be obtained from PHE and no new evidence was identified by AbbVie. The previously suggested alternative from the original ERG to use the idelalisib arm of the 116 trial is now considered less appropriate than the rituximab arm used in the AbbVie base case due to the high post-progression survival with idelalisib of four years that did not reflect clinical practice in the UK, with broad agreement from stakeholders that survival would be considerably shorter than this.[10] This substantial limitation was also highlighted by the ERG on Page 40 of the ERG report where they concluded that the data "*had limitations and was associated with implausible extrapolations for the deletion/mutation population*". Additionally, as highlighted in the CS, the modelled patients based on the SACT CDF cohort now more closely align with the rituximab arm than previously (where the committee considered the patients in the rituximab arm to have more advanced disease than those in the venetoclax trials). Although the rituximab arm of the 116 trial has its own limitations, considering this closer alignment with the SACT CDF cohort, the face validity of the data, and the lack of appropriate alternatives, AbbVie agree with the ERG that the rituximab arm of the 116 trial continues to be the most appropriate source of BSC data for this appraisal. As discussed in further detail in Issue 7, AbbVie have accepted the ERG's updated PFS and OS values of 0.677 and 0.543, respectively as there was an error in the implementation of hazard ratios for the BSC group in the economic model for patients without del(17p)/*TP53* mutations.

3. Lack of a statistical comparison of venetoclax and BSC	No	AbbVie recognise the limitation of not being able to conduct a statistical comparison of venetoclax to BSC, however, the ERG's suggested approach to utilise data from Rigolin *et al.* and Aarup *et al.* (as detailed on Pages 35–36 of the ERG report) does not provide a robust solution.[11, 12] The ERG's estimated hazard ratio for OS of venetoclax relative to BSC has substantial limitations, as recognised by the ERG, and further outlined below. Firstly, as highlighted by the ERG, the two studies have substantial differences between their patient populations, both in terms of their baseline characteristics and the subsequent therapies they received. For example, a higher proportion of patients in the Aarup *et al.* study have a del(17p)/*TP53* mutation, and patients in the Rigolin *et al*. study had received on average a higher number of previous lines of therapy (45% with ≥3 lines of therapy, compared with 33% in Aarup *et al*.). Additionally, different measures are used across the two studies for examining disease severity (e.g. ECOG performance status is not reported in Aarup *et al*.), which makes an exact comparison of the two trials challenging. These differences mean that it is not appropriate to pool these two studies, as has been done by the ERG. Additionally, neither of these two real-world studies utilised in this analysis were conducted with any patients from the UK with Rigolin *et al*. based on data entirely from Denmark, and Aarup *et al*. entirely from Italy. Despite there being an absence of alternative approaches, this naïve, unadjusted comparison does not represent an appropriate alternative and would only serve to increase uncertainty. Due to the limitations described above and by the ERG, the scenario presented by the ERG in Section 6.1.6 of the ERG report utilising this hazard ratio is not appropriate.
4. Average age and gender of the patient population in the economic model	Yes	AbbVie agree that the ERG's approach of updating the age and gender inputs from the SACT CDF data rather than maintaining those of the pooled data from the venetoclax trials is the most appropriate approach for this appraisal. These inputs have been updated in the new base case of AbbVie, as provided in Table 2.

5. Unexpectedly high post-progression survival modelled for venetoclax, and potential inconsistency with clinical evidence	No	Based on the submitted base case modelling of venetoclax, the ERG considered that the estimates of post-progression survival (PPS) were higher than what would be experienced in clinical practice and exceeded that of an alternative source they identified, Eyre *et al*[13]. The use of data from Eyre *et al.* to estimate and validate post-progression survival introduces further uncertainty to the appraisal. Data in this study were collected from patients who had received venetoclax prior to its commissioning via the CDF; venetoclax was available to these patients initially via a named-patient scheme and subsequently through EAMS. There is a trend towards more advanced disease for the patients described in the Eyre *et al.* study compared with the SACT CDF cohort, with a higher proportion of patients with an ECOG score of 2 or above. As suggested by the ERG's clinical advisor, it is possible that patients receiving venetoclax prior to its entry to the CDF *"may have been a higher risk group with clinicians motivated to get them on venetoclax through an early access scheme*"; this assumption is likely even more relevant for patients receiving venetoclax in the UK prior to EAMS, in part explaining the difference in PPS estimates between the SACT CDF cohort and the Eyre *et al.* study. The patients in this study are, therefore, less generalisable to the patients who would receive venetoclax through routine commissioning in UK clinical practice, and therefore do not provide an appropriate comparison with the extrapolated data from the SACT CDF cohort. As described in more detail in the response to Issue 6, new survival modelling approaches have now been incorporated into the cost-effectiveness model. The revised base case includes a much lower PPS period compared to the originally submitted base case. The changes to the base case have resulted in a higher PFS curve, which subsequently reduces the area between PFS and OS in the partitioned survival model, and hence gives a lower PPS. These changes therefore support with addressing the ERG's concerns related to the post-progression modelling of venetoclax.
6. Inconsistent survival modelling	Yes	As requested by the ERG, extended survival modelling has been conducted, with details presented in Appendix A, to address potential inconsistencies in the approaches taken for modelling venetoclax and BSC. AbbVie have therefore fitted both dependent and

		independent models to the SACT CDF data for the venetoclax arms following examination of the proportional hazards assumption. The proportional hazards assumption between the two subgroups (patients with del(17p)/*TP53* mutations versus patients without del(17p)/*TP53* mutations) was tested for both OS and time on treatment (ToT) and was investigated using both qualitative assessment (with visual adequacy to parallelism of log-cumulative hazards plots and Schoenfeld residuals visualisation) and quantitative assessment (chi-square test). Based on these scenario analyses, the proportional hazards assumption was not rejected for OS and a single dependent model, including a hazard ratio for patients with del(17p)/*TP53* mutations versus patients without del(17p)/*TP53* mutations was fitted on both groups in the new base case analysis. For ToT, the proportional hazard assumption was not rejected and a single dependent model was fitted on both groups in the new base case analysis (Table 2). Furthermore, in their clarification questions, the ERG requested AbbVie fit generalised gamma and spline curves in an attempt to find more plausible extrapolations than the Weibull extrapolation used in the base case. Whilst this was not possible within the time frame of the clarification questions, AbbVie have now fitted six traditional parametric distributions, including generalised gamma and six cubic spline models, to OS and ToT of the SACT CDF cohort; these analyses are described in further detail in Appendix A. The results of these analyses demonstrate that the choice of parametric distribution has limited impact on the ICER (Table 4, Table 5), with the majority of new curves more optimistic than AbbVie's original choice of Weibull distribution. Therefore, AbbVie still consider Weibull to be the most appropriate and conservative approach for OS models. However, for ToT extrapolations, due to better performance based on AIC and BIC criteria, AbbVie have updated the base case to consider normal spline 2-knot (Table 2). These changes therefore support with addressing the ERG's concerns related to the post-progression modelling of venetoclax.
7. Use of time on treatment data to model progression-free survival	Yes	In the original appraisal (TA487), AbbVie used PFS data to fit and extrapolate PFS. However, PFS data were not available for the CDF SACT population and so AbbVie

		used ToT in the reappraisal submission to model PFS. In the clarification questions, the ERG requested that AbbVie estimates a hazard ratio of effect between the PFS and ToT from the venetoclax trials to demonstrate the similarity of the outcomes. Due to time restrictions, this was not feasible during the stage of the clarification questions. To address this issue and investigate the impact of using ToT data to model progression-free survival, longer term follow up data from the M13-982 and M14-032 trials were used to produce a hazard ratio of ToT versus PFS separately for patients with and without del(17p)/*TP53* mutations. In the CDF cohort of the SACT data, treatment duration was defined using the interval between treatment start date and final treatment date. Similarly, the first dosing date of patients in M13-982 and M14-032 was used to define the starting date of the treatment and the last dosing date was used to define the ending date of the treatment, aligning with the definition used in the PHE report. To define the difference between PFS and ToT curves, a HR was estimated via cox regression models fitted separately for patients with and without a del(17p)/*TP53* mutation. The HR of ToT versus PFS for patients with del(17p)/*TP53* mutation was estimated at 1.20 (95% CI: 1.00, 1.50) and 1.40 (95% CI: 0.89, 2.40) for patients without del(17p)/*TP53*. The model is structurally set-up to apply a ToT hazard ratio to the model's PFS curve, to generate a ToT curve (to adjust treatment costs). However, the opposite was required in this situation. That is, the PFS curve in the model is already the ToT curve (as estimated from SACT), and the PFS curve needs to be simulated using the inverse of the hazard ratio defined above. There was insufficient time to restructure the model around this nuance, and so instead, the PFS and ToT curves were switched in the model calculation sheet (T1). Mathematically, this produces the intended partitioned survival estimates and drug cost estimates, although the labelling in the backend calculation sheets is misleading (ToT and PFS are switched).

		The result is that AbbVie's previous PFS estimate is now the ToT estimate, and a new, more favourable PFS curve is represented in the model. This also acts to significantly reduce the post-progression survival period, which was one of the ERGs key issues (Issue 5). This change has been added to the companies proposed base case (Table 2).

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 1: Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Double dosing within the idelalisib arm of the 116 trial	3.2	No	As noted during the original appraisal, but not yet raised during this appraisal, 4 out of the 11 patients who had progressive disease in the idelalisib arm of the 116 trial (36%) had received double dosing of idelalisib, which may have led to increased survival outcomes in these patients. As the agreed comparator for venetoclax is best supportive care, it is not appropriate to use data including patients treated with a double dose of idelalisib. It can be expected that the survival of patients treated with idelalisib would be better than those treated with BSC, therefore over-estimating the survival of patients in the comparator arm. This was not mentioned in the ERG report but is an important factor to account for when considering the choice of data for

			BSC in the model, and further supports the conclusions made in response to issue two that the rituximab arm of the 116 trial is the most appropriate source of BSC data for this appraisal.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

In response to Key Issues 2, 4, 6 and 7 of the ERG report, AbbVie have corrected and updated the company base case. The revised economic base case addresses the ERG's concerns regarding:

- The average age and gender of the patient population in the economic model
- The implementation of hazard ratios for the BSC group in the economic model for patients without deletion/mutation
- Curve choices for survival modelling for OS and ToT
- Updated hazard ratios for PFS

This revised base case at PAS price is associated with ICERs of £44,121 for patients with a del(17p)/*TP53* mutation and £46,624 for patients without a del(17p)/*TP53* mutation, demonstrating venetoclax represents a cost-effective use of NHS resources (Table 2). Further sensitivity analyses are presented in Appendix B.

Table 2: Changes to the company's cost-effectiveness estimate (PAS price)

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Company's original base case	The company's original base case ICER was £49,213 for patients without a del(17p)/*TP53* mutation. The company's original base case ICER was £43,239 for patients with a del(17p)/*TP53* mutation	n/a	n/a
Key issue 4: Average age and gender of the patient population in the economic model	The company assumed the starting age and gender ratio of patients in the economic model from pooled data of their venetoclax trials.	The company agree that the ERG's approach of updating the age and gender inputs from the SACT CDF data rather than maintaining those of the pooled data from the venetoclax trials is the most appropriate approach for this appraisal.	Implementing this update changed the company's original base case ICER to £53,217 for patients without a del(17p)/*TP53* mutation and £46,325 for patients with a del(17p)/*TP53* mutation.
Key issue 2: Uncertainty and potential for bias in data modelling of Best Supportive Care (BSC) (section 4.1.2.1.2 and 6.1.5 in ERG report)	The company used a Weibull model to estimate PFS and OS for the deletion/mutation population for BSC. For the patient population without del(17p)/*TP53* mutations, a hazard ratio was used based on pooled data from the venetoclax trials (0.585 for PFS, 0.524 for OS) in the patient population without del(17p)/*TP53* mutations.	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) as there was an error in the implementation of hazard ratios for the BSC group in the economic model for patients without deletion/mutation.	Implementing this update changed the company's original base case ICER to £48,329 for patients without a del(17p)/*TP53* mutation. The change is not applicable to the ICER of patients with a del(17p)/*TP53* mutation.
Key Issue 6: Inconsistent survival modelling	The company's survival modelling of venetoclax data was based on independent model fits, which may be inconsistent to the survival modelling of BSC (dependent).	The company evaluated dependent models for OS and ToT from the CDF cohort. A dependent Weibull model was selected for OS and a normal spline 2-knot was selected for the new base case analysis of ToT.	Implementing this update changed the company's original base case ICER to £42,355 for patients with a del(17p)/*TP53* mutation and to £45,996 for patients without a del(17p)/*TP53* mutation.

<table>
<tr>
<td>Key Issue 7: Use of time on treatment data to model progression-free survival</td>
<td>The company used time on treatment data from the CDF cohort to represent progression-free survival in the models.</td>
<td>To define the difference between PFS and ToT curves, a HR was estimated via cox regression models fitted separately for patients with and without a del(17p)/TP53 mutation. The HR of ToT versus PFS for patients with del(17p)/TP53 mutation was estimated at 1.20 (95% CI: 1.00, 1.50) and 1.40 (95% CI: 0.89, 2.40) for patients without del(17p)/TP53. These HRs were implemented in the model to better reflect PFS estimates based on ToT survival.</td>
<td>Implementing this update changed the company’s original base case ICER to £42,062 for patients with a del(17p)/TP53 mutation and £46,562 for patients without a del(17p)/TP53 mutation.</td>
</tr>
<tr>
<td>Company’s base case following technical engagement (or revised base case)</td>
<td colspan="3">Table 3: Revised base case at PAS price
<table>
<tr><th></th><th>Incremental QALYs</th><th>Incremental Costs</th><th>ICER £/QALY</th></tr>
<tr><td>Patients with del(17p)/TP53 mutation</td><td>[redacted]</td><td>[redacted]</td><td>£44,121</td></tr>
<tr><td>Patients without del(17p)/TP53 mutation</td><td>[redacted]</td><td>[redacted]</td><td>£46,624</td></tr>
</table>
</td>
</tr>
</table>

Abbreviations: BSC: best supportive care; CDF: Cancer Drug Fund; ERG: evidence review group; ICER: incremental cost-effectiveness ratio; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year; ToT: time-on-treatment.

References

1. National Institute for Health and Care Excellence. Technology appraisal guidance: Venetoclax for treating chronic lymphocytic leukaemia [TA487]. 2017. Available at https://www.nice.org.uk/guidance/ta487. Accessed on: 12-Oct-2021
2. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax for Patients With Chronic Lymphocytic Leukemia With 17p Deletion: Results From the Full Population of a Phase II Pivotal Trial. J Clin Oncol 2018;36:1973-1980.
3. Jones JA, Mato AR, Wierda WG, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. The Lancet Oncology 2018;19:65-75.
4. Davids MS, Roberts AW, Seymour JF, et al. Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma. J Clin Oncol 2017;35:826-833.
5. John F. Seymour JQW, Relja Popovic, Barbara Eichhorst, Peter Hillmen, Thomas J. Kipps,, Anton W. Langerak, , Carolyn Owen, Julie Dubois, Clemens Mellink, Anne-Marie Van Der Kevie-Kersemaekers, Fengjiao Dunbar, Yanwen Jiang, Brenda Chyla, Michelle Boyer, Maria Thadani-Mulero, Marcus Lefebure, Rosemary Harrup and Arnon P. Kater,. 1548 Assessment of the Clonal Dynamics of Acquired Mutations in Patients (Pts) with Relapsed/Refractory Chronic Lymphocytic Leukemia (R/R CLL) Treated in the Randomized Phase 3 Murano Trial Supports Venetoclax-Rituximab (VenR) Fixed-Duration Combination Treatment (Tx). 2021.
6. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax–Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. New England Journal of Medicine 2018;378:1107-1120.
7. Thompson MC, Allan JN, Sail K, et al. Venetoclax Re-Treatment of Chronic Lymphocytic Leukemia (CLL) Patients after a Previous Venetoclax-Based Regimen. Blood 2020;136:39-41.
8. Harrup RA, Owen C, D'Rozario J, et al. Efficacy of Subsequent Novel Targeted Therapies, Including Repeated Venetoclax-Rituximab (VenR), in Patients (Pts) with Relapsed/Refractory Chronic Lymphocytic Leukemia (R/R CLL) Previously Treated with Fixed-Duration Venr in the Murano Study. Blood 2020;136:44-45.
9. Sharman JP, Coutre SE, Furman RR, et al. Final Results of a Randomized, Phase III Study of Rituximab With or Without Idelalisib Followed by Open-Label Idelalisib in Patients With Relapsed Chronic Lymphocytic Leukemia. Journal of Clinical Oncology 2019;37:1391-1402.
10. National Institute for Health and Care Excellence. Venetoclax for treating chronic lymphocytic leukaemia; Final appraisal determination. 2017 Available at https://www.nice.org.uk/guidance/ta487/documents/final-appraisal-determination-document. Accessed on: 22-Oct-2021.
11. Aarup K, Rotbain EC, Enggaard L, et al. Real-world outcomes for 205 patients with chronic lymphocytic leukemia treated with ibrutinib. European Journal of Haematology 2020;105:646-654.
12. Rigolin GM, Cavazzini F, Piciocchi A, et al. Efficacy of idelalisib and rituximab in relapsed/refractory chronic lymphocytic leukemia treated outside of clinical trials. A report of the Gimema Working Group. Hematological Oncology 2021;39:326-335.
13. Eyre TA, Kirkwood AA, Gohill S, et al. Efficacy of venetoclax monotherapy in patients with relapsed chronic lymphocytic leukaemia in the post-BCR inhibitor setting: a UK wide analysis. British Journal of Haematology 2019;185:656-669.

Appendix A: Additional information on issue 6

Proportional hazards assumption

For OS, both the log-cumulative hazard plot and the chi-square test (p-value = 0.33), suggested that the proportional hazard assumption could not be rejected (Figure 1). In addition, the assumption of a constant HR did not appear violated by the Schoenfeld residuals, as there was no clear time trend observed (Figure 2).

Figure 1: Log-cumulative hazard plot for OS

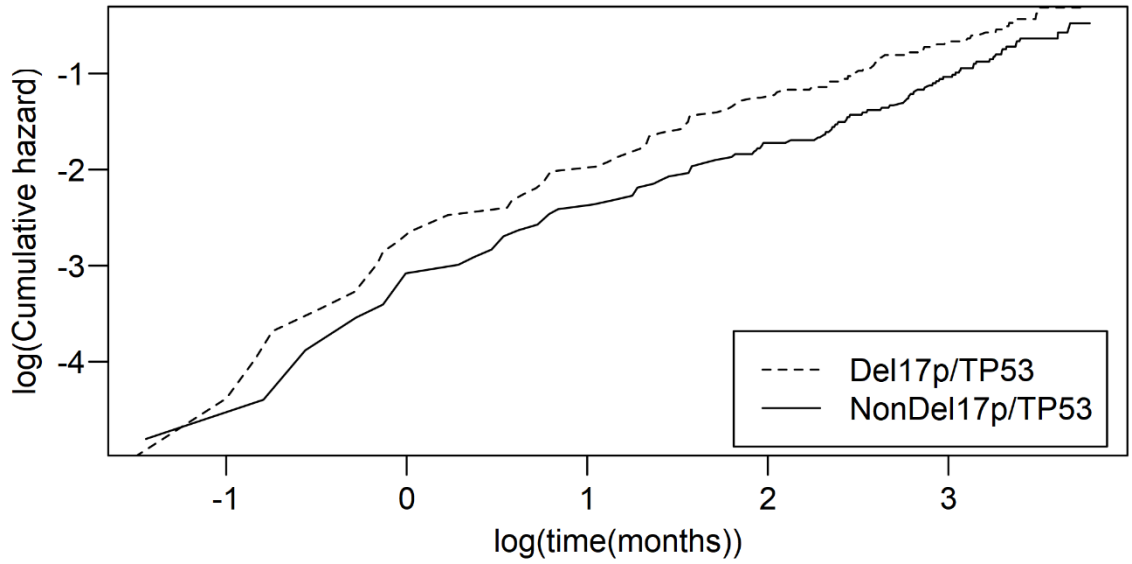
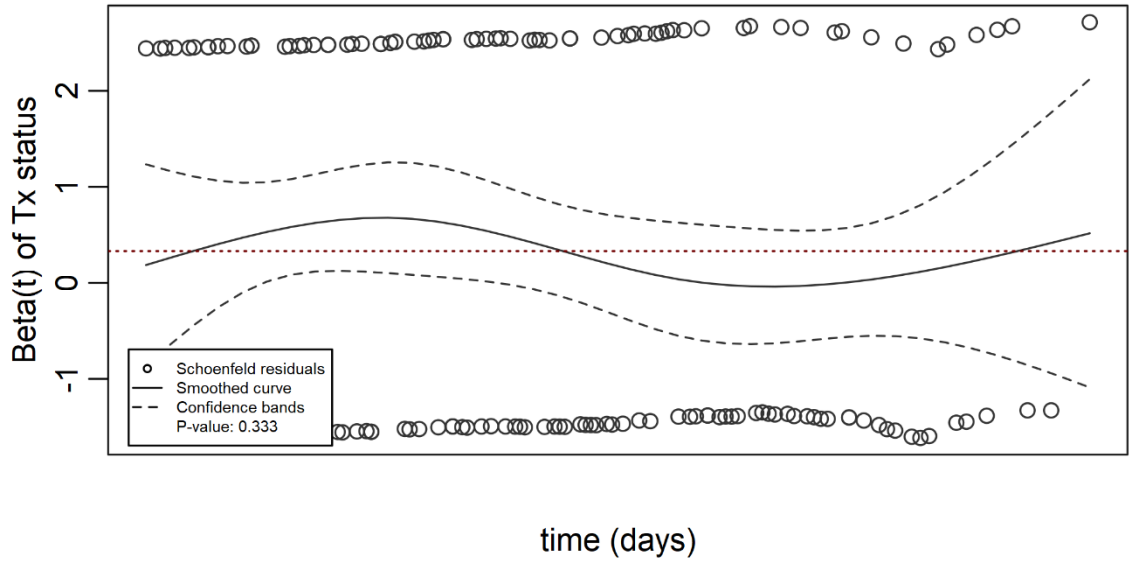


Figure 2: Schoenfeld residuals for OS



Based on these results, the proportional hazard assumption was not rejected for OS and a single dependent model, including a HR for patients with del(17p)/*TP53* mutations versus patients without del(17p)/*TP53* mutations, was fitted on both groups in the new base case analysis.

For ToT, the log-cumulative hazard plot did not suggest proportional hazards due to the crossing of the del(17p)/*TP53* and non-del(17p)/*TP53* curves (Figure 3). However, the chi-square test was not statistically significant (p-value = 0.43), indicating that the proportional hazard assumption cannot be rejected based on this test. In addition, the assumption of a constant HR did not appear violated by the Schoenfeld residuals (Figure 4). Based on these results, the proportional hazard assumption was not rejected for ToT and a single dependent model was fitted on both groups in the new base case analysis.

Figure 3: Log-cumulative hazard plot for ToT

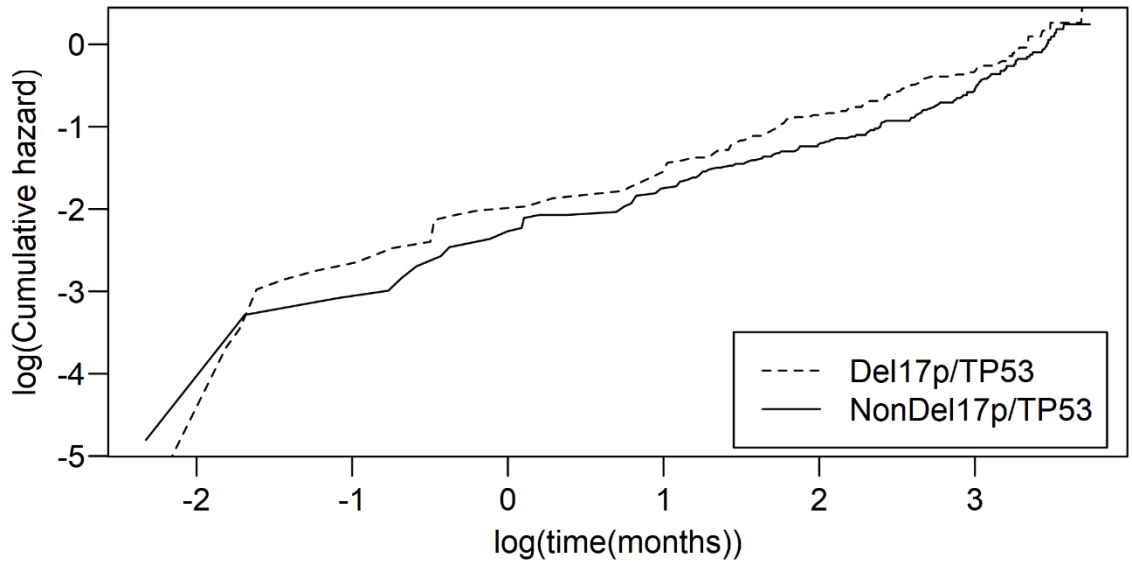
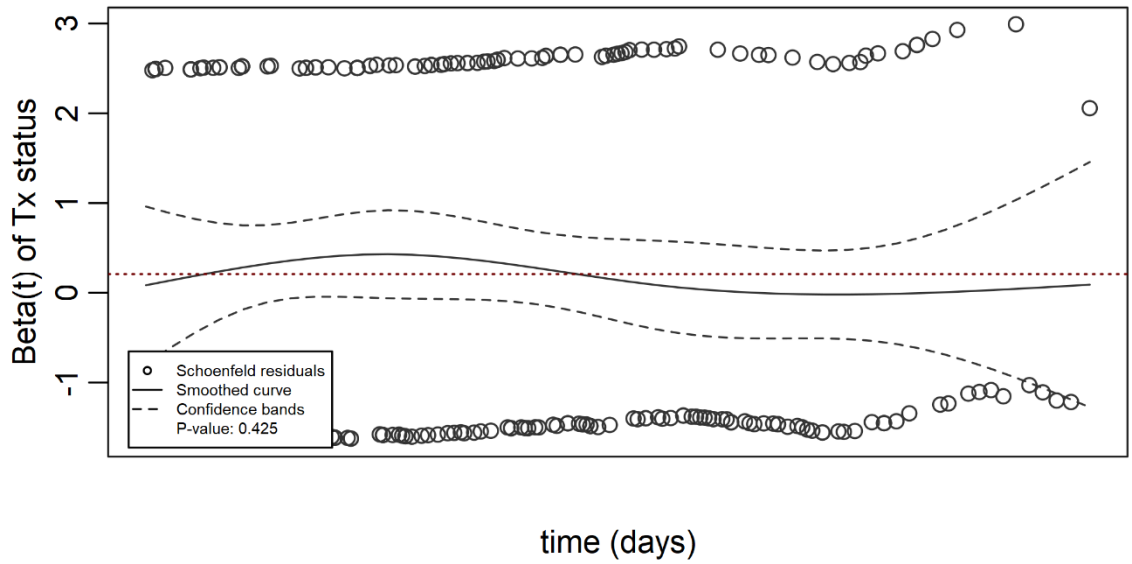


Figure 4: Schoenfeld residuals for ToT

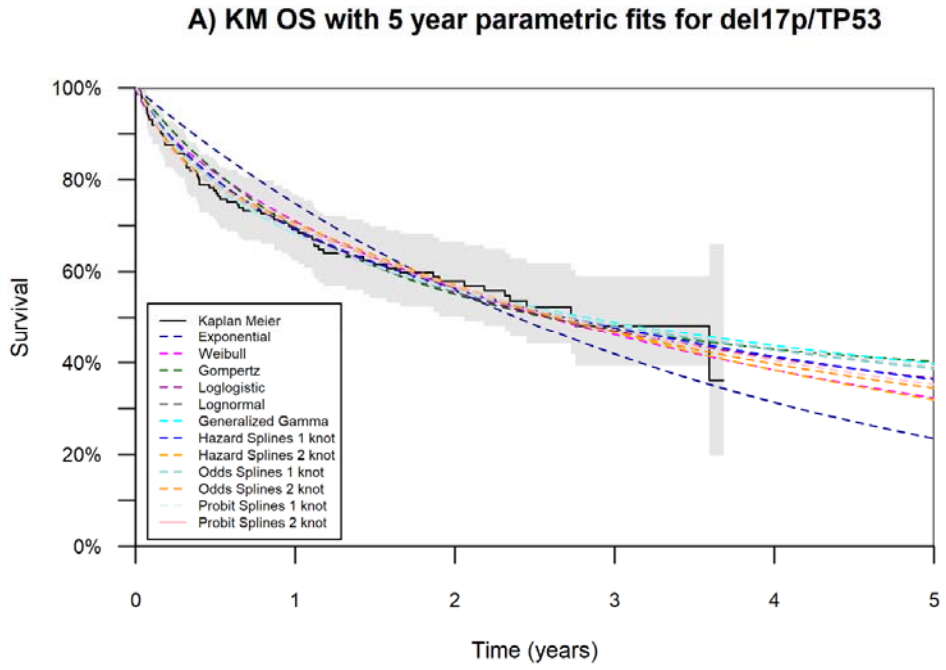


Alternative distributions: OS

Following the ERG's suggestion to explore the impact of using alternative distributions, six traditional parametric distributions, including the generalised gamma, and six cubic spline models were fitted to OS and ToT of the SACT CDF cohort. AIC and BIC were evaluated to statistically compare model fits.

Consultation with clinical experts in CLL by AbbVie during the original appraisal suggested that the 10-year OS of 12% (associated with the Weibull curve for the population with del(17p)/*TP53* mutations in the original appraisal) is a reasonable estimate of longer-term OS outcomes. Additional discussions with a clinical expert in CLL for this CDF reappraisal also supported the choice of Weibull; the clinical expert indicated that they would expect OS to be around 20% at 10 years in the population with del(17p)/*TP53* mutations, and that Weibull would be the most appropriate curves for both OS and ToT in both populations. This estimate is close to the estimates provided by the Weibull (15.12%), the hazard spline 1-knot model (21.18%), the odds spline 2-knot (20.78%) and the normal splines 2-knot (21.15%) (Figure 5). Furthermore, for the patient population without the del(17p)/*TP53* mutation the clinical expert in CLL consulted by AbbVie for the CDF reappraisal agreed that the estimate of 30% for OS, provided by the Weibull model, was appropriate. In the patient population without del(17p)/*TP53* mutations, this estimate is closer approached by the Weibull (25.98%), the hazard spline 1-knot model (32.80%), the odds spline 2-knot (28.98%) and the normal splines 2-knot (29.31%). In terms of AIC and BIC values, the normal spline 2-knot and the odds spline 2-knot distributions performed best according to the AIC criteria whereas the log-normal and log-logistic performed best in terms of BIC criteria. While most of the model fits appears to estimate higher OS than the Weibull, we consider the Weibull remains an appropriate and conservative approach for OS models. The impact of using other parametric fits in the model for OS, including the log-normal, log-logistic, odds spline 2-knot, normal spline 2-knots and hazard spline 1-knot is investigated in the scenario analyses.

Figure 5: OS parametric fits (dependent model) – patient population with a del(17p)/*TP53* mutation using A) 5 and B) 15 years' time horizon



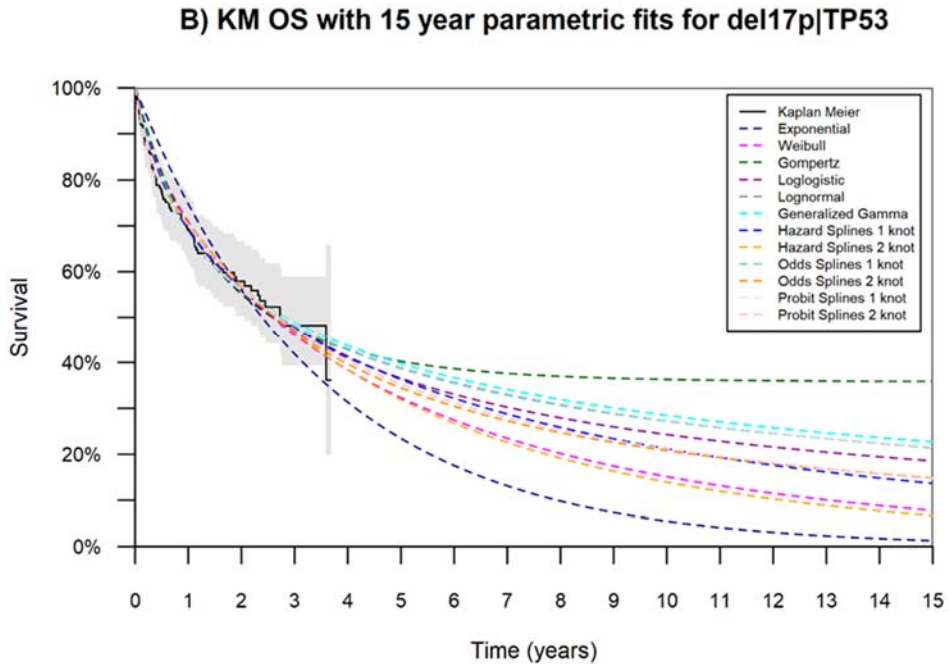
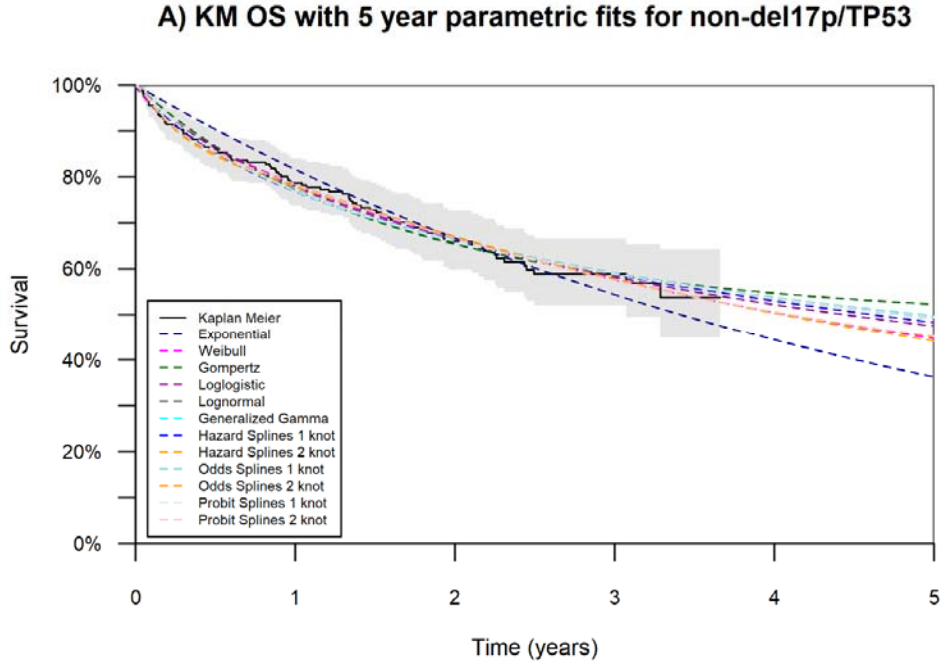
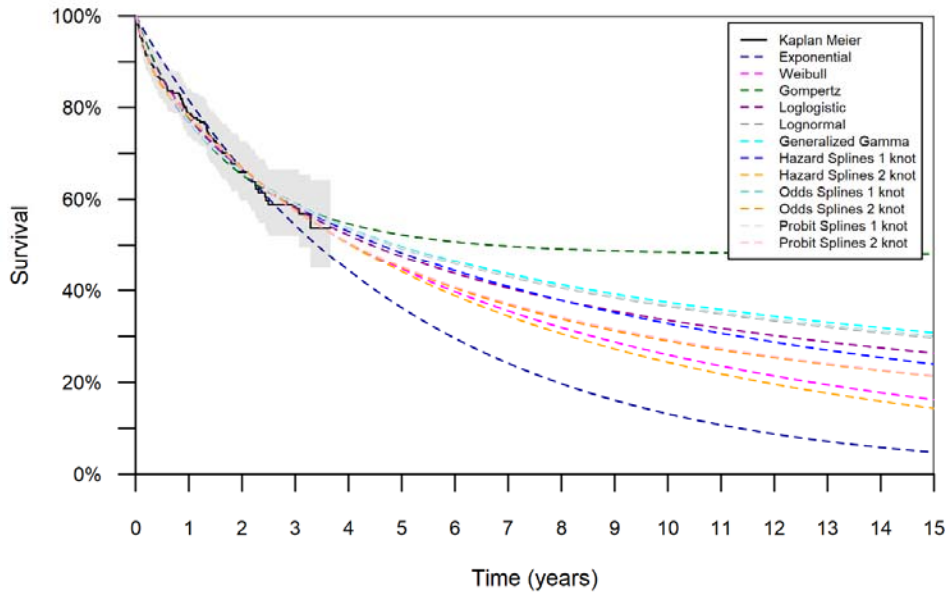


Figure 6: OS parametric fits (dependent model) – patient population without a del(17p)/*TP53* mutation using A) 5 and B) 15 years' time horizon



B) KM OS with 15 year parametric fits for non-del17p|TP53



Alternative distributions: ToT

Similarly, for ToT clinical expert consultation during the original appraisal suggested that due to the expected role for minimal residual disease (MRD) negativity in venetoclax patients, the 0% progression-free survival (PFS) associated with the Gompertz model at 10 years is perhaps an underestimation, and that the Weibull model, with an estimate of around 2%, led to more realistic longer-term outcomes for patients with a del(17p)/*TP53* mutation. This was further confirmed by discussions with a clinical expert in CLL at the time of this CDF reappraisal. For patients without a del(17p)/*TP53* mutation, long-term ToT survival estimates of 8% were considered realistic. The normal spline 2-knot with 10-year survival estimates of 4.90% for patients with del(17p)/*TP53* and 7.08% for patients without del(17p)/*TP53* (Figure 7 and Figure 8), performed best based on both the AIC and BIC criteria. Therefore, the normal spline 2-knot was selected for the new base case analysis, while the impact of using the hazard spline 2-knot, the odds-spline 2-knot and the Weibull extrapolations was investigated in the scenario analyses.

Figure 7: ToT parametric fits (dependent model) – patient population with a del(17p)/*TP53* mutation using A) 5 and B) 10 years' time horizon

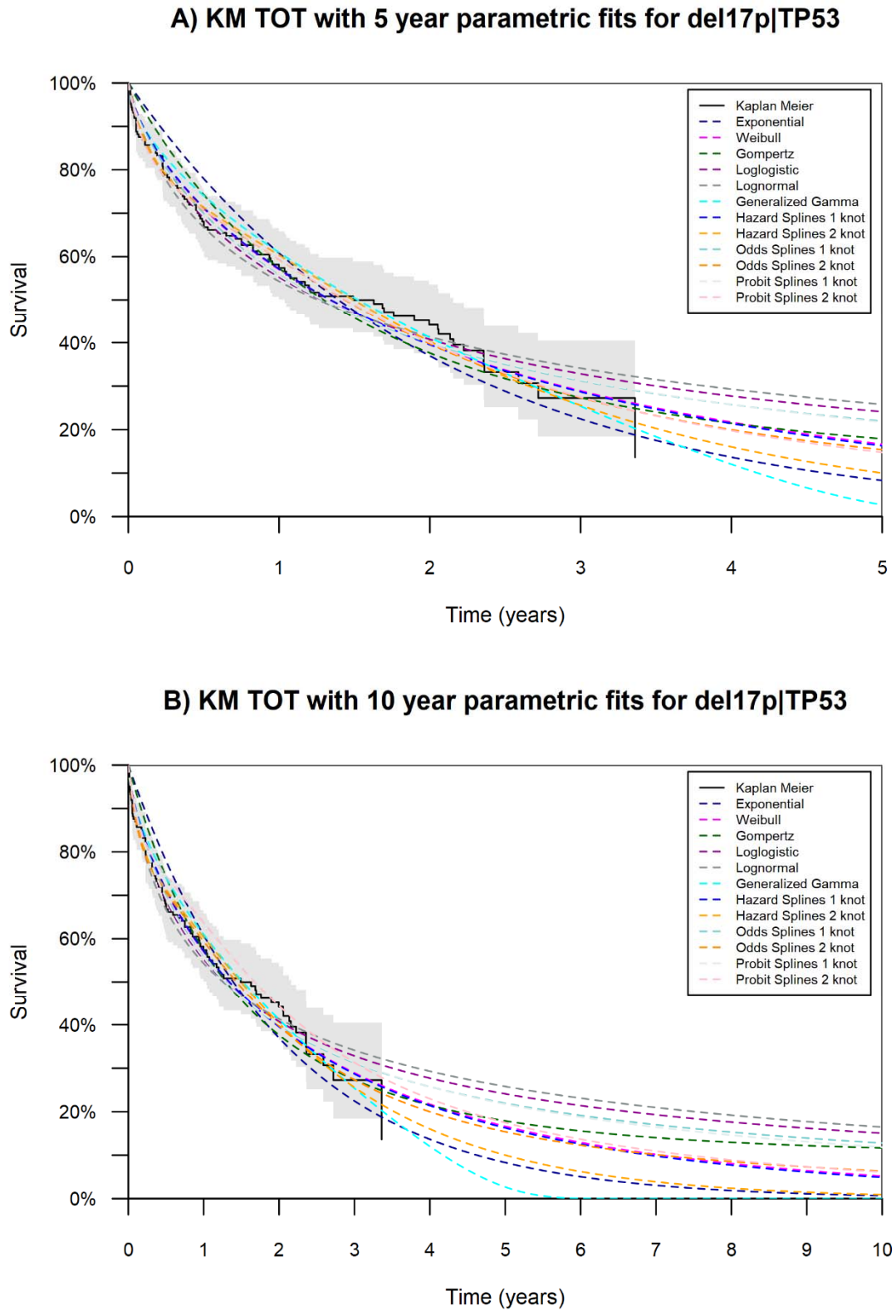
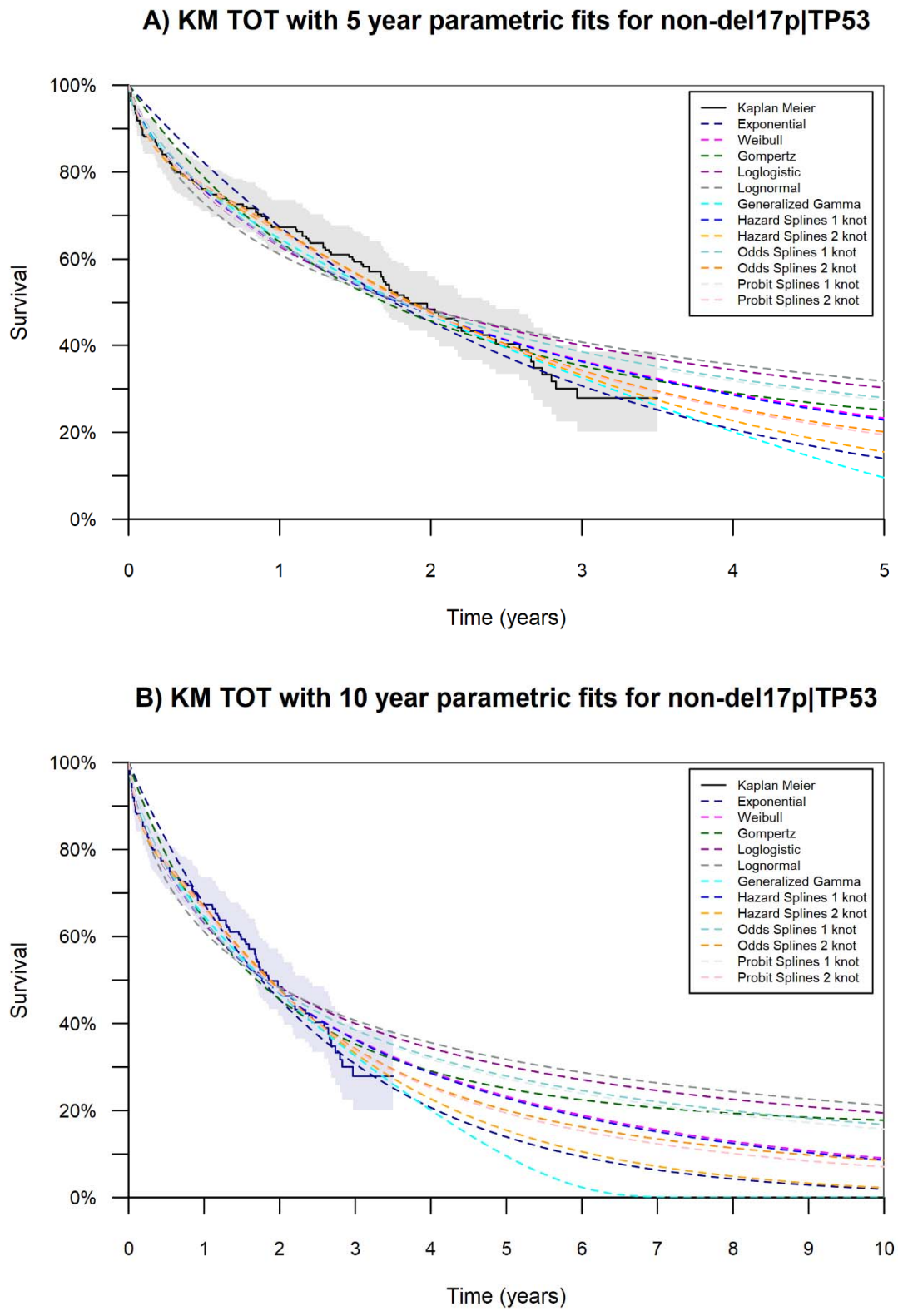


Figure 8: ToT parametric fits (dependent model) – patient population without a del(17p)/*TP53* mutation using A) 5 and B) 10 years' time horizon



The results of scenario analyses investigating the effects of different curve choices for OS and ToT on the ICER at PAS price are presented in Table 4 and Table 5 (patients with and without del(17p)/*TP53*, respectively).

Table 4: Scenario analyses undertaken for patients with del(17p)/*TP53* mutation

Scenario	Technology		Comparator		ICER £/QALY
	QALYs	Costs	QALYs	Costs	
Using normal spline 2-knots for OS (dependent fit)	[redacted]	[redacted]	0.605	[redacted]	£40,262
Using log-normal for OS (dependent fit)	[redacted]	[redacted]	0.605	[redacted]	£36,888
Using log-logistic for OS (dependent fit)	[redacted]	[redacted]	0.605	[redacted]	£38,679
Using odds spline 2-knot for OS (dependent fit)	[redacted]	[redacted]	0.605	[redacted]	£40,651
Using hazard spline 1-knot for OS (dependent fit)	[redacted]	[redacted]	0.605	[redacted]	£40,138
Using hazard spline 2-knot for ToT (dependent fit)	[redacted]	[redacted]	0.605	[redacted]	£39,202
Using Weibull for ToT (dependent fit)	[redacted]	[redacted]	0.605	[redacted]	£45,099
Using odds spline 2-knot for ToT (dependent fit)	[redacted]	[redacted]	0.605	[redacted]	£45,484

Abbreviations: ICER: incremental cost-effectiveness ratio; OS: overall survival; ToT: time-on-treatment; QALY: quality-adjusted life year.

Table 5: Scenario analyses undertaken for patients without del(17p)/*TP53* mutation

Scenario	Technology		Comparator		ICER £/QALY
	QALYs	Costs	QALYs	Costs	
Using normal spline 2-knots for OS (dependent fit)	[redacted]	[redacted]	1.068	[redacted]	£44,587
Using log-normal for OS (dependent fit)	[redacted]	[redacted]	1.068	[redacted]	£40,478
Using log-logistic for OS (dependent fit)	[redacted]	[redacted]	1.068	[redacted]	£42,043
Using odds spline 2-knot for OS (dependent fit)	[redacted]	[redacted]	1.068	[redacted]	£44,703
Using hazard spline 1-knot for OS (dependent fit)	[redacted]	[redacted]	1.068	[redacted]	£42,479
Using hazard spline 2-knot for ToT (dependent fit)	[redacted]	[redacted]	1.068	[redacted]	£42,177
Using Weibull for ToT (dependent fit)	[redacted]	[redacted]	1.068	[redacted]	£49,069
Using odds spline 2-knot for ToT (dependent fit)	[redacted]	[redacted]	1.068	[redacted]	£48,078

Abbreviations: ICER: incremental cost-effectiveness ratio; OS: overall survival; ToT: time-on-treatment; QALY: quality-adjusted life year.

Appendix B: Sensitivity analyses around revised base case

Updated probabilistic sensitivity analysis

Figure 9 and Figure 10 below present the cost-effectiveness plane plotting incremental costs at PAS price and QALYs for 1,000 probabilistic simulations for the patient populations with and without del17p/*TP53* mutations, respectively. Figure 11 and Figure 12 present the same results at venetoclax list price for the patient populations with and without del17p/*TP53* mutations, respectively. The average total costs and QALYs (including confidence intervals) for the probabilistic simulations at venetoclax PAS price and list price are presented in Table 6 and Table 7, respectively. The average ICER at venetoclax PAS price following the probabilistic simulations is £45,312/QALY gained vs BSC for the patient population with a del(17p)/*TP53* mutation and £48,290/QALY gained for the patient population without a del(17p)/*TP53* mutation. The average ICER following the probabilistic simulations is [redacted]/QALY gained vs BSC for the patient population with a del(17p)/*TP53* mutation and [redacted]/QALY gained for the patient population without a del(17p)/*TP53* mutation.

Table 6: Updated base case results at venetoclax PAS price (probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
Patient population with del(17p)/*TP53* mutation					
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	£45,312 (£34,050, £58,803)
BSC	[redacted]	0.615 (0.504, 0.771)	-	-	-
Patient population without del(17p)/*TP53* mutation					
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	£48,290 (£37,042, £64,848)
BSC	[redacted]	1.082 (0.885, 1.368)	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 7: Updated base case results at venetoclax list price (probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
Patient population with del(17p)/*TP53* mutation					
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.614 (0.500, 0.778)	-	-	-
Patient population without del(17p)/*TP53* mutation					
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	1.085 (0.888, 1.381)	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure 9: Scatterplot of probabilistic results for the patient population with a del(17p)/*TP53* mutation at venetoclax PAS price

Abbreviations: BSC: best supportive care; PAS: patient access scheme.

Figure 10: Scatterplot of probabilistic results for the patient population without a del(17p)/*TP53* mutation at venetoclax PAS price

Abbreviations: BSC: best supportive care; PAS: patient access scheme.

Figure 11: Scatterplot of probabilistic results for the patient population with a del(17p)/*TP53* mutation at venetoclax list price

Abbreviations: BSC: best supportive care.

Figure 12: Scatterplot of probabilistic results for the patient population without a del(17p)/TP53 mutation at venetoclax list price

Abbreviations: BSC: best supportive care.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Venetoclax for treating chronic lymphocytic leukaemia (CDF review of TA487) [ID3886]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Tuesday 15 February 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	Professor Adrian Bloor
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	UK CLL Forum
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Abbvie – consultancy, speaker fees, meeting attendance, advisory boards** **Janssen - speaker fees, meeting attendance, advisory boards** **Gilead - speaker fees, meeting attendance, advisory boards**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. Generalisability of venetoclax data to UK practice	Yes	The landscape for treating CLL in the UK has changed significantly over the last 5 years as a consequence of availability of increasing numbers of treatments and maturing evidence from clinical trials and real world data. The submission considered data from a number of sources: 1. Data from clinical trials (M12-175, M13-982, M14-032) are relevant to UK patients in as much as they describe the use of venetoclax in patients with relapsed/refractory disease. There is no reason to assume that the outcomes in the UK would be intrinsically different to those obtained elsewhere at the time the trials were performed. The significant limitation to current practice is however in that very few patients in these studies had received prior BTK inhibitor (BTKi) which limits their applicability to 2022 treatment pathways. A subsequent prospective trial reported overall response rate of 65% in 127 patients treated with venetoclax having failed prior BTKi (Jones JA et al Lancet Oncol 2018;19:65) and in a real world analysis, the response rate to venetoclax was 76% in 13 patients who had discontinued prior kinase inhibitor (ibrutinib or idelalisib) therapy (Mato AR et al Blood 2016;128:2199). 2. Data from the UK EAMS scheme and CDF cohort are clearly applicable to UK practice in as much as all of the patients were treated in the UK. The

		EAMS cohort is not split by TP53 status which may be required for the economic model however does not limit its relevance to UK practice. It is unclear from the report why the ERG chose not to consider Eyre et al (2019) which includes TP53 status. 3. The ERG suggests that addition of rituximab to venetoclax may have influenced outcomes. Survival curves for patients treated with and without rituximab (figures 2 and 3) in the CDF cohort appear to be superimposable suggesting that rituximab has very little impact in contrast to what is suggested in the text. A similar pattern was observed in a recently published real world UK/US cohort (Mato AR et al Blood Advances 2019;3:1568) 4. In the front line setting outside of clinical trials, venetoclax has only been available as a treatment option in the UK since December 2020 (NICE TA663) and the majority of patients treated would be expected to remain in remission with such short follow up. Published data regarding the utility of venetoclax +/- rituximab re-treatment following prior exposure are currently sparse and subject of ongoing studies however available data indicate that this is an effective therapeutic option. In the phase 1b venetoclax-rituximab trial, 3 out of 4 patients responded to further cycles of therapy having relapsed following prior fixed duration treatment (Ma S et al Blood 2021;138:836). In the MURANO trial, 32 patients in the Venetoclax-Rituximab arm received Venetoclax+/-rituximab with best overall response of 72.2% (Harrup RA et al Blood 2020;136;3139a). Lastly, a multicentre retrospective US study identified 18 patients who had received venetoclax re-treatment (monotherapy in 52%) with overall response rate of 72.2% (Thompson MC et al Blood 2020;136;642a). 5. The current treatment pathway proposed for UK patients in figure 7 is reasonable however it is unlikely that venetoclax monotherapy would be utilised in the first or second line settings with alternative options generally preferred – venetoclax+obinutuzumab or BTKi in 1L and

		venetoclax+rituximab or BTKi in 2L. Venetoclax monotherapy is currently likely to be most widely used in the 3L setting. Based on these data, the venetoclax data utilised for this analysis (particularly the EAMS and SACT data) would be expected to be broadly applicable to a UK CLL patient population. The impact of the addition of rituximab is not certain and appears to have been possibly over-interpreted. The number of patients in the UK who have been currently been re-treated with venetoclax would be expected to be extremely small and is therefore would not impact on this analysis. Importantly however emergent data indicate that venetoclax therapy is an effective therapeutic option in relapsed disease including patients who have received prior BTKi or venetoclax and we would strongly support this remaining as a treatment option in what would otherwise create an area of unmet need.
2. Uncertainty and potential for bias in data modelling of Best Supportive Care (BSC)	No	Modelling true BSC in CLL is extremely difficult for a number of reasons 1. Treatment is rapidly evolving/improving with many new therapies being introduced over the last 10 years 2. Tolerability of newer treatments has improved significantly making it applicable to a wider population of patients 3. As a consequence of 1 and 2, the concept of BSC has evolved in that best supportive care is now largely superimposable with active treatment and most patients only become eligible for purely palliative/supportive therapies in the terminal stages of their disease. The placebo arm of the Gilead 116 trial was chosen to model BSC in this analysis. The 116 trial recruited between 2012 and 2013 at which point there were few further treatment options available and had that remained the case then this would have become a BSC population as conventionally defined. However: 1. Almost 80% of the placebo arm entered into follow on studies to receive idelalisib 2. OS in the placebo arm plateaued and cross over the treatment arm with longer term follow up (Sharman JP et al J Clin Oncol 2019;37;1391)

		suggesting a significant impact of post progression therapies such as ibrutinib which became available during the follow up period. It is possible that some of these patients also received venetoclax although this is not stated in the published analysis. As the ERG notes, the use of the 116 trial data could over estimate or under-estimate any benefit. This would be the case irrespective of which arm of the trial was used for comparison. An ideal comparator population would be one in which patients had received prior BTKi and relapsed prior to availability of venetoclax. It is however challenging to identify this group on the basis that venetoclax has been available in the UK since 2016. If the 116 trial population was to be used then it would seem appropriate to use the longer term data if available as this is more representative of UK patients and current practice although the choice of treatment arm for comparison (placebo vs intervention) may not be overly important due to the significant crossover.
3. Lack of a statistical comparison of venetoclax and BSC	No	We are not aware of any data which would address this issue. This is a factor of the challenges in the identification of a BSC comparator
4. Average age and gender of the patient population in the economic model	No	The average age at diagnosis for CLL is around 72 years although patients in trials are typically younger and selected for fitness. The SACT population had an average age of 71 which is younger than would be expected for patients with relapsed CLL but probably more representative. The impact of gender distribution appears to be marginal
5. Unexpectedly high post-progression survival modelled for venetoclax, and potential inconsistency with clinical evidence	Yes	The analysis is performed on a relatively small data set and as such may not be reliable. The post progression curves look unrealistic as presented although the outcome of patients following venetoclax is variable and depends on a number of factors including the reason for discontinuation (failure vs toxicity) and prior exposure to other treatments (notably BTK inhibitors) – see for example Mato AR et al Clin Cancer Res 2020;26:3589
6. Inconsistent survival modelling	No	A single model not split by TP53 status would likely be more informative especially given the constraints imposed by sample size. This could however introduce bias if the size of the TP53 mutated/deleted population was significantly different to the comparator.

7. Use of time on treatment data to model progression-free survival	Yes	The ERG uses time on treatment (TOT) as a surrogate for PFS which is a flawed assumption. TOT may be influenced by a number of factors including patient choice, treatment toxicity and disease progression. In addition CLL patients may show early disease progression whilst still benefiting from treatment and remain on therapy (Pazdur R Oncologist 2008;13(s2):19-21)

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Venetoclax for treating chronic lymphocytic leukaemia (CDF review of TA487) [ID3886]

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (sections 1.1, 1.3 and 1.4). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Clinical expert statement

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments is by **5pm** on **15 February 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Clinical expert statement

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating chronic lymphocytic leukaemia and current treatment options

Table 1 About you, aim of treatment, place and use of the technology, sources of evidence and equality

1. Your name	Peter Hillmen
2. Name of organisation	University of Leeds
3. Job title or position	Professor of Experimental Haematology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with chronic lymphocytic leukaemia? ☐ A specialist in the clinical evidence base for chronic lymphocytic leukaemia or venetoclax? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for chronic lymphocytic leukaemia?	To provide the most effective treatment for patients. This varies according to the patient's disease (i.e. relapsed/frontline, good/poor risk), age/fitness (elderly with

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	comorbidities or younger and otherwise well) and wishes. Improve quality and length of life. In some patients the aim is to achieve a deep remission and stopping therapy. In others controlling disease with continuous therapy is more appropriate.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Control of disease in terms of significant improvement in nodal disease, normalisation of blood counts and resolution of symptoms.
10. In your view, is there an unmet need for patients and healthcare professionals in chronic lymphocytic leukaemia?	Yes. Patients who have failed conventional therapies such as BTK inhibitors, venetoclax in combination with monoclonal antibodies and in some chemoimmunotherapy (although not always appropriate).
11. How is chronic lymphocytic leukaemia currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would venetoclax have on the current pathway of care?	BCSH CLL guidelines and ESMO Guidelines I believe that the pathway of care is well defined. It has changed dramatically over the last few years and is determined by disease characteristics. Venetoclax targets one of the two key pathways in CLL – the apoptotic pathway. It is the only drug effectively targeting apoptosis and is therefore a key drug in the treatment of CLL. In patients who have failed all other options venetoclax monotherapy can improve the quality and duration of life. In some patients it can act as a bridge to transplant.
12. Will venetoclax be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between venetoclax and current care? • In what clinical setting should venetoclax be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce venetoclax? (for example, for facilities, equipment, or training)	Yes. Venetoclax will only be used by haematologists or oncologists Venetoclax will need to be given by a specialist haematology team but no specific facilities are required.

13. Do you expect venetoclax to provide clinically meaningful benefits compared with current care? • Do you expect venetoclax to increase length of life more than current care? • Do you expect venetoclax to increase health-related quality of life more than current care?	Yes venetoclax provides clinically meaningful benefits. Venetoclax monotherapy will prolong life for patients who have failed conventional therapies and will improve QoL.
14. Are there any groups of people for whom venetoclax would be more or less effective (or appropriate) than the general population?	Venetoclax monotherapy should be available for all patients with relapsed CLL. It is not appropriate for patients with severe renal dysfunction.
15. Will venetoclax be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Venetoclax is already part of current care. Care needs to be taken when initiating therapy including regular biochemistry monitoring and, in some patients, rasburicase. A small number of patients require intravenous hydration and hospital admission at the initiation of therapy although this is only occasionally and only in the first few weeks of treatment. Occasional patients require G-CSF for neutropenia.
16. Will any rules (informal or formal) be used to start or stop treatment with venetoclax? Do these include any additional testing?	Tumour lysis monitoring in the first 5 weeks of therapy.
17. Do you consider that the use of venetoclax will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of venetoclax or have some been missed? For example, the treatment regimen	Yes I believe that venetoclax monotherapy will result in substantial health-related benefits.

may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider venetoclax to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is venetoclax a 'step-change' in the management of the condition? • Does the use of venetoclax address any particular unmet need of the patient population?	Venetoclax was definitely innovative when first introduced and no alternative has been approved since then. It is the most effective single drug in CLL. Venetoclax monotherapy addresses the unmet need of patients who have failed all other conventional therapies.
19. How do any side effects or adverse effects of venetoclax affect the management of the condition and the patient's quality of life?	Venetoclax is well tolerated. The main side effects are the risk of tumour lysis syndrome in the first few weeks (due to it's high efficacy) and neutropenia. These are easily managed and have no effect on the patient's QoL.
20. Do the clinical trials on venetoclax reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The clinical trials of venetoclax monotherapy are from several years ago and since then a number of therapies have been NICE-approved. However the results can be extrapolated to the current UK setting. The most important outcomes are deep remissions and improved symptoms. It can lead to a reduction in blood product use. Surrigate outcomes that predict long-term clinical outcomes are response (CR and PR) as defined by the IWCLL. No other adverse effects.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Real world evidence, including from the UK, compare well to the clinical trial data. They also allow us to interpret the use of venetoclax in patients who have

	previously been treated with B-cell receptor antagonists (ibrutinib, acalabrutinb and idelalisib) which are now NICE-approved.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme.	CLL is generally a disease of the elderly. If venetoclax is withdrawn this will therefore have a disproportionate effect for older people.

Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue 1: Generalisability of venetoclax data to UK practice • ***How is the potential for prior use of venetoclax and/or subsequent use of rituximab in the treatment pathway likely to affect the generalisability of the SACT data?***	Venetoclax combined with anti-CD20 antibodies (either obinutuzumab or rituximab) is NICE approved. When used the therapy is time-limited (either 12 or 24 months). When patients relapse after stopping therapy they have a high probability of responding to venetoclax monotherapy - they have already demonstrated their CLL is sensitive. I don't believe the the prior use of venetoclax will impact the generalisability of the SACT data.

Clinical expert statement

Key issue 2: Uncertainty and potential for bias in data modelling of Best Supportive Care (BSC) • ***Do you know of any available data that may better represent BSC than the 116 trial?***	No. There is no data that directly relates to this population except of the 116 trial. We can extrapolate from the RESONATE trial (ibrutinib versus ofatumumab) in that patients who relapse after ibrutinib have a short survival (i.e. the difference between PFS and OS).
Key issue 3: Lack of a statistical comparison of venetoclax and BSC	The outcome with BSC in this patient group is extremely poor. It would be unethical to use BSC as the control arm in a trial of CLL.
Key issue 4: Average age and gender of the patient population in the economic model • ***Should baseline characteristics in the economic model be taken from the venetoclax trials or from SACT data?***	The average and gender should be taken from the SACT data,
Key issue 5: Unexpectedly high post-progression survival modelled for	The most plausible estimate of mean survival after progression for people having venetoclax is: • *Deletion/mutation population: 0.4 years*

venetoclax, and potential inconsistency with clinical evidence • ***Which is the most plausible estimate of mean survival after progression for people having venetoclax?*** o ***Deletion/mutation population: 1.8 or 0.4 years?*** o ***Non-deletion/mutation population: 2.4 or 1.0 years?***	• *Non-deletion/mutation population: 1.0 years*
Key issue 6: Inconsistent survival modelling	Survival modelling is difficult as patients who relapse on BCRi and those who are considered unsuitable are two different populations with different expected survival. In addition, patients who are refractory to chemotherapy and very different to those who responded and then relapsed sometime later. Venetoclax monotherapy will be used in my opinion for multiply treated, refractory patients and post-progression survival will be short.
Key issue 7: Use of time on treatment data to model progression-free survival • ***How plausible is it that time on***	This is plausible as with venetoclax monotherapy patients will remain on therapy until they progress. Therefore time on treatment largely equates to PFS.

treatment represents progression-free survival?	
Are there any important issues that have been missed in the EAR?	No

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Venetoclax is a unique drug in CLL with clear benefits for patients with the disease
Venetoclax monotherapy is important for patients with an unmet need
Venetoclax can be used to bridge to more definitive therapy and for some patients will be the only option
The Real World Evidence supports the use of venetoclax in CLL after failure of B-cell receptor inhibitors
International and national guidelines recommend the use of venetoclax monotherapy as an option in CLL

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Venetoclax for treating chronic lymphocytic leukaemia (CDF review of TA487) [ID3886]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Tuesday 15 February 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Leukaemia Care and CLL Support
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. Generalisability of venetoclax data to UK practice	**Yes**/No	We are disappointed to learn that the data for use of venetoclax as monotherapy is not able to be separated from the data on those who are receiving venetoclax with rituximab. A report by the Blood Cancer Alliance entitled Access to Medicines highlights evidence that the data collected in the CDF is not always adequate to address the uncertainty that led to the treatment entering the CDF. We hope this does not disadvantage this treatment.
2. Uncertainty and potential for bias in data modelling of Best Supportive Care (BSC)	Yes/**No**	No comments
3. Lack of a statistical comparison of venetoclax and BSC	Yes/**No**	No comments
4. Average age and gender of the patient population in the economic model	Yes/**No**	No comments
5. Unexpectedly high post-progression survival modelled for	Yes/**No**	No comments

venetoclax, and potential inconsistency with clinical evidence		
6. Inconsistent survival modelling	Yes/**No**	No comments
7. Use of time on treatment data to model progression-free survival	Yes/**No**	No comments

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

NICE National Institute for Health and Care Excellence

Technical engagement response form

Venetoclax for treating chronic lymphocytic leukaemia (CDF review of TA487) [ID3886]

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Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Tuesday 15 February 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	UK CLL Forum
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None.**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. Generalisability of venetoclax data to UK practice	Yes	The landscape for treating CLL in the UK has changed significantly over the last 5 years as a consequence of availability of increasing numbers of treatments and maturing evidence from clinical trials and real world data. The submission considered data from a number of sources: 1. Data from clinical trials (M12-175, M13-982, M14-032) are relevant to UK patients in as much as they describe the use of venetoclax in patients with relapsed/refractory disease. There is no reason to assume that the outcomes in the UK would be intrinsically different to those obtained elsewhere at the time the trials were performed. The significant limitation to current practice is however in that very few patients in these studies had received prior BTK inhibitor (BTKi) which limits their applicability to 2022 treatment pathways. A subsequent prospective trial reported overall response rate of 65% in 127 patients treated with venetoclax having failed prior BTKi (Jones JA et al Lancet Oncol 2018;19:65) and in a real world analysis, the response rate to venetoclax was 76% in 13 patients who had discontinued prior kinase inhibitor (ibrutinib or idelalisib) therapy (Mato AR et al Blood 2016;128:2199). 2. Data from the UK EAMS scheme and CDF cohort are clearly applicable to UK practice in as much as all of the patients were treated in the UK. The

		EAMS cohort is not split by TP53 status which may be required for the economic model however does not limit its relevance to UK practice. It is unclear from the report why the ERG chose not to consider Eyre et al (2019) which includes TP53 status. 3. The ERG suggests that addition of rituximab to venetoclax may have influenced outcomes. Survival curves for patients treated with and without rituximab (figures 2 and 3) in the CDF cohort appear to be superimposable suggesting that rituximab has very little impact in contrast to what is suggested in the text. A similar pattern was observed in a recently published real world UK/US cohort (Mato AR et al Blood Advances 2019;3:1568) 4. In the front line setting outside of clinical trials, venetoclax has only been available as a treatment option in the UK since December 2020 (NICE TA663) and the majority of patients treated would be expected to remain in remission with such short follow up. Published data regarding the utility of venetoclax +/- rituximab re-treatment following prior exposure are currently sparse and subject of ongoing studies however available data indicate that this is an effective therapeutic option. In the phase 1b venetoclax-rituximab trial, 3 out of 4 patients responded to further cycles of therapy having relapsed following prior fixed duration treatment (Ma S et al Blood 2021;138:836). In the MURANO trial, 32 patients in the Venetoclax-Rituximab arm received Venetoclax+/-rituximab with best overall response of 72.2% (Harrup RA et al Blood 2020;136;3139a). Lastly, a multicentre retrospective US study identified 18 patients who had received venetoclax re-treatment (monotherapy in 52%) with overall response rate of 72.2% (Thompson MC et al Blood 2020;136;642a). 5. The current treatment pathway proposed for UK patients in figure 7 is reasonable however it is unlikely that venetoclax monotherapy would be utilised in the first or second line settings with alternative options generally preferred – venetoclax+obinutuzumab or BTKi in 1L and

		venetoclax+rituximab or BTKi in 2L. Venetoclax monotherapy is currently likely to be most widely used in the 3L setting. Based on these data, the venetoclax data utilised for this analysis (particularly the EAMS and SACT data) would be expected to be broadly applicable to a UK CLL patient population. The impact of the addition of rituximab is not certain and appears to have been possibly over-interpreted. The number of patients in the UK who have been currently been re-treated with venetoclax would be expected to be extremely small and is therefore would not impact on this analysis. Importantly however emergent data indicate that venetoclax therapy is an effective therapeutic option in relapsed disease including patients who have received prior BTKi or venetoclax and we would strongly support this remaining as a treatment option in what would otherwise create an area of unmet need.
2. Uncertainty and potential for bias in data modelling of Best Supportive Care (BSC)	No	Modelling true BSC in CLL is extremely difficult for a number of reasons 1. Treatment is rapidly evolving/improving with many new therapies being introduced over the last 10 years 2. Tolerability of newer treatments has improved significantly making it applicable to a wider population of patients 3. As a consequence of 1 and 2, the concept of BSC has evolved in that best supportive care is now largely superimposable with active treatment and most patients only become eligible for purely palliative/supportive therapies in the terminal stages of their disease. The placebo arm of the Gilead 116 trial was chosen to model BSC in this analysis. The 116 trial recruited between 2012 and 2013 at which point there were few further treatment options available and had that remained the case then this would have become a BSC population as conventionally defined. However: 1. Almost 80% of the placebo arm entered into follow on studies to receive idelalisib 2. OS in the placebo arm plateaued and cross over the treatment arm with longer term follow up (Sharman JP et al J Clin Oncol 2019;37;1391)

		suggesting a significant impact of post progression therapies such as ibrutinib which became available during the follow up period. It is possible that some of these patients also received venetoclax although this is not stated in the published analysis. As the ERG notes, the use of the 116 trial data could over estimate or under-estimate any benefit. This would be the case irrespective of which arm of the trial was used for comparison. An ideal comparator population would be one in which patients had received prior BTKi and relapsed prior to availability of venetoclax. It is however challenging to identify this group on the basis that venetoclax has been available in the UK since 2016. If the 116 trial population was to be used then it would seem appropriate to use the longer term data if available as this is more representative of UK patients and current practice although the choice of treatment arm for comparison (placebo vs intervention) may not be overly important due to the significant crossover.
3. Lack of a statistical comparison of venetoclax and BSC	No	We are not aware of any data which would address this issue. This is a factor of the challenges in the identification of a BSC comparator
4. Average age and gender of the patient population in the economic model	No	The average age at diagnosis for CLL is around 72 years although patients in trials are typically younger and selected for fitness. The SACT population had an average age of 71 which is younger than would be expected for patients with relapsed CLL but probably more representative. The impact of gender distribution appears to be marginal
5. Unexpectedly high post-progression survival modelled for venetoclax, and potential inconsistency with clinical evidence	Yes	The analysis is performed on a relatively small data set and as such may not be reliable. The post progression curves look unrealistic as presented although the outcome of patients following venetoclax is variable and depends on a number of factors including the reason for discontinuation (failure vs toxicity) and prior exposure to other treatments (notably BTK inhibitors) – see for example Mato AR et al Clin Cancer Res 2020;26:3589
6. Inconsistent survival modelling	No	A single model not split by TP53 status would likely be more informative especially given the constraints imposed by sample size. This could however introduce bias if the size of the TP53 mutated/deleted population was significantly different to the comparator.

7. Use of time on treatment data to model progression-free survival	Yes	The ERG uses time on treatment (TOT) as a surrogate for PFS which is a flawed assumption. TOT may be influenced by a number of factors including patient choice, treatment toxicity and disease progression. In addition CLL patients may show early disease progression whilst still benefiting from treatment and remain on therapy (Pazdur R Oncologist 2008;13(s2):19-21)

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

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Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

NICE National Institute for Health and Care Excellence

Technical engagement response form

Venetoclax for treating chronic lymphocytic leukaemia (CDF review of TA487) [ID3886]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

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NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	NCRI-ACP-RCP-RCR
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No
General	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to comment as follows.

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. Generalisability of venetoclax data to UK practice	Yes	Our experts applaud Abbvie for engaging with NICE's demands and trying to analyse SACT data. Clinicians are acutely aware and even more frustrated by the lack of good real-world data collections. Clinicians have also asked for external audits of the SACT data to be performed on a regular basis and to hold NHS trusts to account on quality. Finally, none of the multiple papers published on real-world evidence by our group of CLL specialists used NHS digital or SACT or cancer registry data because in the past, there was scepticism of the granularity of the data and its quality. Considering all of this, our experts were positively surprised that the company managed to derive very useful information supporting that the UK population is indeed comparable to the clinical trial populations which is all the company was asked to do initially. The ERG's critique of the data is therefore understandable, but the data quality is completely outside of the company's control. Our experts would encourage NICE to feed this appraisal back to NHS digital. Specifically:

		The response includes SACT data which is real world UK data. The quality of SACT data collection from NHS trusts is now audited on a regular basis. Despite this, the data quality is not as granular and robust as that obtained from clinical studies, but the ERG has to be fair and realistic: this is the best UK data they will ever get on Venetoclax monotherapy and the largest cohort of patients treated with this regimen during a period of time of evolving therapy in CLL. The fact that some patients received rituximab does not change the message. From a clinical perspective, we can assume that the majority of patients with multiply relapsed refractory CLL are rituximab refractory. This is supported by the KM curves showing no difference in outcome between Ven-R and Ven-mono treated patients.
2. Uncertainty and potential for bias in data modelling of Best Supportive Care (BSC)	Yes	Our experts agree with the updated treatment algorithm. Treatment of CLL has evolved a lot over the past few years. However, as Ven-mono is considered the last treatment option and/or as a bridge to transplant, BSC in this group a not changed and remains Methyl-Pred, palliative care or possibly PI3Ki for some patients fit enough to tolerate potential side-effects.
3. Lack of a statistical comparison of venetoclax and BSC	No	See above
4. Average age and gender of the patient population in the economic model	Yes	The SACT population compares to the study populations and looks representative of the UK patients receiving Ven-mono in my practice with a median age of 72 and two-thirds being male (CLL is more frequent in male).
5. Unexpectedly high post-progression survival modelled for venetoclax, and potential inconsistency with clinical evidence	Yes	Our experts have observed this improvement in OS in recent years. It might be related to changes in the frontline and early relapse setting, esp. the reduced use of chemotherapy for frail patients and those with del17p/TP53mut observed from 2015 when Ibrutinib received NICE approval. The initial early access data of Ven-mono (Eyre T et al) suggested a poor OS after failure, but these patients had received multiple rounds of CIT and then Ibrutinib as a last option before accessing

		Ven-mono. More recently treated patient populations have been less exposed to chemotherapy.
6. Inconsistent survival modelling	Yes	See above.
7. Use of time on treatment data to model progression-free survival	Yes	This is an acceptable endpoint when dealing with real-world data and has been used in all of the peer reviewed real world data publications. It is due to the fact that in the real world, we will not perform whole body CT scans and repeat BM examinations to test for relapse defined by iwCLL international criteria. This would significantly increase the cost of routine CLL management and lead to unnecessary radiation exposure. Our experts note that they do not perform MRD measurements as these are also not accepted as endpoints by the regulator. So, the only way to measure progression in the clinical routine is by time on treatment.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
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Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

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Table 4 Changes to the company's cost-effectiveness estimate

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Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

Title Venetoclax for treating chronic lymphocytic leukaemia (CDF review of TA487) [ID3886] - ERG comments on TE responses

Produced by	*Warwick Evidence*
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Date completed	*Date completed (23/02/2022)*

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Declared competing interests of the authors

None.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Lamina T, Maredza M, Evans K, Achana F, Court R, Marshall S, Gallacher D Venetoclax for treating chronic lymphocytic leukaemia (CDF review of TA487) [ID3886] – ERG comments on TE responses. Warwick Evidence, 2022.

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List of Tables

1.1. ERG responses to the technical engagement response form

The ERG's comments have been added to the company's TE responses in Table 1 and

Table 2.

Table 1: ERG comments on technical engagement response form

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
1. Generalisability of venetoclax data to UK practice	No	The generalisability of the venetoclax trial data was a key uncertainty of the original appraisal; in TA487, the committee considered that the patients included in the venetoclax trials may be younger and have a lower burden of disease compared with patients who would be expected to receive venetoclax in clinical practice.[1] To address this uncertainty, data collected from SACT rather than updated data from the venetoclax trials have been used to inform the model for this appraisal. Although SACT data were provided separately for the Cancer Drug Fund (CDF) and Early Access to Medicine Scheme (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 were presented within the submission. As noted on Page 26 of the ERG report, the *"ERG agrees with this statement"*. A clinical expert in CLL consulted by AbbVie further agreed with this approach. Additionally, as presented in the company submission (CS), patients in the SACT CDF cohort are closer in age to the mean age of patients with CLL at diagnosis in England (71 years), compared with a mean	The company's response does not alleviate the ERG's concerns regarding the generalisability of the SACT CDF venetoclax data to routine venetoclax therapy moving forward. The ERG reiterates that there remains some not-insignificant uncertainty surrounding this issue, which should be carefully considered by the committee. The ERG welcomes the company's acknowledgement of the uncertainty around the long-term efficacy of venetoclax. The reference provided by the company[5] reports 11/19 (58%) patients retreated with venetoclax responded to the therapy, compared to an initial response rate of independently assessed overall responses rate of 92% to venetoclax-rituximab in the MURANO trial. This is additional support of the ERG's concerns of the potential reduced efficacy of later lines of venetoclax therapy. The company suggest the possibility of differences between patients who received rituximab and those who did not. The ERG agrees that this is a possibility and suggests this emphasises the lack of

		age of 65 years in the venetoclax trials.[2-4] When excluding patients with missing Eastern Cooperative Oncology Group (ECOG) scores in the SACT CDF cohort, there is a trend towards more advanced disease compared with the patients in the venetoclax trials, with a higher proportion of patients with a ECOG score of 2 or above.[1] Additionally, AbbVie's clinical expert highlighted that the EAMS cohort was a more heavily pre-treated cohort when compared with patients in the CDF cohort. Therefore, considering both the improved generalisability of the SACT CDF data to UK clinical practice, and the relevance of the cohort to the economic model by providing separate data split by del(17p)/*TP53* mutation status, the SACT CDF cohort is considered the most appropriate source of efficacy data for this submission. The ERG noted that since the original appraisal, venetoclax combinations have been made available to patients as both front line and relapsed/refractory options; this means that the patients within this indication today will have followed a different treatment pathway to patients that received venetoclax in the SACT CDF cohort. The ERG also highlighted the possibility that patients may become resistant to venetoclax therapy. However, based on clinical expert opinion in the joint patient group submission from Leukaemia Care and CLL Support, patients are "*unlikely to build up resistance to venetoclax whilst taking the [venetoclax] combinations*"; this statement was further validated by clinical expert opinion sought	generalisability of the SACT CDF data. Some patients in the SACT CDF data may not receive venetoclax under this indication if the CDF data collection was instigated now, but instead venetoclax rituximab, suggesting the estimates and extrapolations coming from the SACT CDF data may be unreliable. The effects of rituximab and prior venetoclax therapy may have much larger influences on the extrapolations and cost-effectiveness analyses than on the observed period. Whilst there remains uncertainty over the influence of these two factors, the ERG is of the view that if it were possible to remove the effect of rituximab and factor in the effects of prior therapy it is likely the efficacy of venetoclax would decrease. Furthermore, had the SACT EAMS data been broken down by deletion/mutation status and included in the economic modelling, then the venetoclax data and extrapolations would likely reduce the benefits of venetoclax therapy compared to the company's base case. The company's exploration of the effect of including and excluding patients who received rituximab by comparing only the median survival times is potentially misleading, and the ERG recommends a more detailed comparison provided in the ERG report section 3.1.2.2.3.

		by AbbVie. Furthermore, the clinical expert highlighted that only a very small percentage of patients would be treated with venetoclax therapies more than twice. The ERG also investigated the evidence on the efficacy of venetoclax retreatment and concluded, along with their clinical expert, that *"venetoclax is likely to be efficacious after previous exposure to venetoclax therapy".* The statement from Leukaemia Care and CLL Support also highlighted that venetoclax monotherapy provides an extra advantageous option for patients including those "*who have previously had venetoclax combinations and relapsed subsequently"*. Finally, data from a recent publication also suggests that treatment with venetoclax monotherapy may be effective for patients who have relapsed following initial fixed duration treatment with venetoclax in combination with rituximab (VenR).[5] Based on published data available and clinical expert opinion, AbbVie agree with the conclusions from both the ERG, and Leukaemia Care and CLL Support;[6-8] AbbVie accept that there is still some uncertainty about the degree of efficacy but do not expect the acceptance and use of earlier courses of venetoclax to have a substantial impact on the efficacy of later line venetoclax monotherapy. Whilst AbbVie agree that the treatment landscape has changed since the original appraisal, this should not be considered as directly relevant to this appraisal. The CS provided by AbbVie aligned with the previous decision problem of TA487 as per the terms of engagement agreed with NICE. Consideration of the updated	

		treatment pathway is therefore outside the scope of this review and should not contribute to any decision making. Finally, the ERG also noted that patients within the SACT CDF cohort were allowed to switch from venetoclax monotherapy to VenR within the five-week titration period of venetoclax. Eighty patients (19.7%) in the SACT CDF cohort received rituximab on or after the earliest venetoclax treatment start date, however only 30 of the 112 'treatment switchers' (across both the SACT CDF and EAMS cohorts) started rituximab within eight weeks; it is unclear if these patients all truly switched to VenR or instead received rituximab as a subsequent therapy. The ERG's sensitivity analysis presented in Section 3.1.2.2.3 of the ERG report and based on the combined CDF and EAMS cohort suggests rituximab may have had an effect, but the reliability of these analyses are limited considering the reason these patients received rituximab was unclear from the PHE SACT report and the limited information on the duration of rituximab treatment. Indeed, median overall survival (OS) was the same in the SACT CDF cohort for groups with and without patients treated with rituximab (full cohort = 43.1 months; sensitivity analysis cohort = 43.1 months), suggesting no impact of rituximab on OS. Whilst AbbVie acknowledge there are limitations with the SACT CDF cohort data (as discussed above), this cohort remains the most appropriate source of efficacy	

		data for this submission, as agreed by the ERG. Importantly, use of data from the SACT CDF cohort addresses a key uncertainty raised by the committee in the original appraisal by providing a data source for venetoclax that is of direct relevance to the decision problem.	
2. Uncertainty and potential for bias in data modelling of Best Supportive Care (BSC)	No	As set out in the data collection plan, PHE SACT was expected to provide BSC data. However, on 2nd March 2021, the SACT Operational Group considered that no meaningful data could be captured on BSC within SACT during the period of managed access. AbbVie therefore had a limited opportunity to identify alternative sources of BSC data. Although no formal updated searches were performed as part of this appraisal, attempts were made to explore alternative sources through clinical expert opinion; however, no further sources of evidence were identified. AbbVie have since followed up with an author of the 116 study to ascertain whether any further detail on post-progression treatments had been captured. However. no further data beyond what was included within the Sharman 2019 article is available.[9] AbbVie therefore utilised the rituximab arm of the 116 trial, as presented in the original submission. There remains a lack of alternate approaches available, given no BSC data could be obtained from PHE and no new evidence was identified by AbbVie. The previously suggested alternative from the original ERG to use the idelalisib arm of the 116 trial is now considered less	The company's approach to modelling the deletion/mutation populations separately means that the only identified source of information for BSC remains the Weibull model as reported in the appraisal of idelalisib (TA359). Had a pooled approach been considered as a scenario analysis, this could have allowed comparison to other sources such as Rigolin *et al*. or Aarup *et al*. This would also have allowed inclusion of the SACT EAMS data, which was not broken down into the deletion/mutation subgroups. As it stands, the ERG has been unable to identify an alternative source of data that could be utilised to assess the clinical or cost-effectiveness of BSC. Uncertainty remains over the suitability of the study 116 data, as outlined in the ERG report.

		appropriate than the rituximab arm used in the AbbVie base case due to the high post-progression survival with idelalisib of four years that did not reflect clinical practice in the UK, with broad agreement from stakeholders that survival would be considerably shorter than this.[10] This substantial limitation was also highlighted by the ERG on Page 40 of the ERG report where they concluded that the data "*had limitations and was associated with implausible extrapolations for the deletion/mutation population*". Additionally, as highlighted in the CS, the modelled patients based on the SACT CDF cohort now more closely align with the rituximab arm than previously (where the committee considered the patients in the rituximab arm to have more advanced disease than those in the venetoclax trials). Although the rituximab arm of the 116 trial has its own limitations, considering this closer alignment with the SACT CDF cohort, the face validity of the data, and the lack of appropriate alternatives, AbbVie agree with the ERG that the rituximab arm of the 116 trial continues to be the most appropriate source of BSC data for this appraisal. As discussed in further detail in Issue 7, AbbVie have accepted the ERG's updated PFS and OS values of 0.677 and 0.543, respectively as there was an error in the implementation of hazard ratios for the BSC group in the economic model for patients without del(17p)/*TP53* mutations.	

3. Lack of a statistical comparison of venetoclax and BSC	No	AbbVie recognise the limitation of not being able to conduct a statistical comparison of venetoclax to BSC, however, the ERG's suggested approach to utilise data from Rigolin *et al.* and Aarup *et al.* (as detailed on Pages 35–36 of the ERG report) does not provide a robust solution.[11, 12] The ERG's estimated hazard ratio for OS of venetoclax relative to BSC has substantial limitations, as recognised by the ERG, and further outlined below. Firstly, as highlighted by the ERG, the two studies have substantial differences between their patient populations, both in terms of their baseline characteristics and the subsequent therapies they received. For example, a higher proportion of patients in the Aarup *et al.* study have a del(17p)/*TP53* mutation, and patients in the Rigolin *et al*. study had received on average a higher number of previous lines of therapy (45% with ≥3 lines of therapy, compared with 33% in Aarup *et al*.). Additionally, different measures are used across the two studies for examining disease severity (e.g. ECOG performance status is not reported in Aarup *et al*.), which makes an exact comparison of the two trials challenging. These differences mean that it is not appropriate to pool these two studies, as has been done by the ERG. Additionally, neither of these two real-world studies utilised in this analysis were conducted with any patients from the UK with Rigolin *et al*. based on data entirely from Denmark, and Aarup *et al*. entirely from Italy.	The ERG does not suggest the populations of Rigolin *et al*. and Aarup *et al*. publications are homogeneous, but that when combined that they may serve as a reasonable comparator group to the SACT CDF population, in the absence of any clearly stronger comparisons. Whilst the lack of overlapping reported characteristics for the populations makes it difficult to show similarity, it also does not show clear differences between them. Given there are similar concerns over the comparison between the SACT CDF and study 116 population, the ERG maintains that the comparison to Aarup *et al.* and Rigolin *et al.* provides a valuable reference point and should be given consideration.

		Despite there being an absence of alternative approaches, this naïve, unadjusted comparison does not represent an appropriate alternative and would only serve to increase uncertainty. Due to the limitations described above and by the ERG, the scenario presented by the ERG in Section 6.1.6 of the ERG report utilising this hazard ratio is not appropriate.	
4. Average age and gender of the patient population in the economic model	Yes	AbbVie agree that the ERG's approach of updating the age and gender inputs from the SACT CDF data rather than maintaining those of the pooled data from the venetoclax trials is the most appropriate approach for this appraisal. These inputs have been updated in the new base case of AbbVie, as provided in **Error! Reference source not found.**.	The ERG welcomes the company's decision to update the baseline characteristics and to use inputs from the SACT CDF data.
5. Unexpectedly high post-progression survival modelled for venetoclax, and potential inconsistency with clinical evidence	No	Based on the submitted base case modelling of venetoclax, the ERG considered that the estimates of post-progression survival (PPS) were higher than what would be experienced in clinical practice and exceeded that of an alternative source they identified, Eyre *et al*[13]. The use of data from Eyre *et al.* to estimate and validate post-progression survival introduces further uncertainty to the appraisal. Data in this study were collected from patients who had received venetoclax prior to its commissioning via the CDF; venetoclax was available to these patients initially via a named-patient scheme and subsequently through EAMS. There is a	In the absence of any other data, the ERG maintains that the Eyre paper is a valuable reference point to compare post-progression survival. The ERG requested that the company explore fitting other parametric models specifically because the OS and ToT data showed an increasing hazard rate towards the end of the follow-up, which was not captured in the parametric modelling. However, instead of fitting an OS extrapolation which modelled an increasing hazard rate, and therefore reduced the post-progression survival, the company

		trend towards more advanced disease for the patients described in the Eyre *et al.* study compared with the SACT CDF cohort, with a higher proportion of patients with an ECOG score of 2 or above. As suggested by the ERG's clinical advisor, it is possible that patients receiving venetoclax prior to its entry to the CDF *"may have been a higher risk group with clinicians motivated to get them on venetoclax through an early access scheme*"; this assumption is likely even more relevant for patients receiving venetoclax in the UK prior to EAMS, in part explaining the difference in PPS estimates between the SACT CDF cohort and the Eyre *et al.* study. The patients in this study are, therefore, less generalisable to the patients who would receive venetoclax through routine commissioning in UK clinical practice, and therefore do not provide an appropriate comparison with the extrapolated data from the SACT CDF cohort. As described in more detail in the response to Issue 6, new survival modelling approaches have now been incorporated into the cost-effectiveness model. The revised base case includes a much lower PPS period compared to the originally submitted base case. The changes to the base case have resulted in a higher PFS curve, which subsequently reduces the area between PFS and OS in the partitioned survival model, and hence gives a lower PPS. These changes therefore support with addressing the ERG's concerns related to the post-progression modelling of venetoclax.	have instead remodelled PFS, increasing the progression-free period and decreasing post-progression survival. This has not alleviated the problem identified by the ERG, but just alleviated one of the indicators of the problem. The ERG presents two scenarios exploring the application of an increasing hazard rate to venetoclax, which were presented in the ERG report, but have been updated for the company's new model.

6. Inconsistent survival modelling	Yes	As requested by the ERG, extended survival modelling has been conducted, with details presented in Appendix A, to address potential inconsistencies in the approaches taken for modelling venetoclax and BSC. AbbVie have therefore fitted both dependent and independent models to the SACT CDF data for the venetoclax arms following examination of the proportional hazards assumption. The proportional hazards assumption between the two subgroups (patients with del(17p)/*TP53* mutations versus patients without del(17p)/*TP53* mutations) was tested for both OS and time on treatment (ToT) and was investigated using both qualitative assessment (with visual adequacy to parallelism of log-cumulative hazards plots and Schoenfeld residuals visualisation) and quantitative assessment (chi-square test). Based on these scenario analyses, the proportional hazards assumption was not rejected for OS and a single dependent model, including a hazard ratio for patients with del(17p)/*TP53* mutations versus patients without del(17p)/*TP53* mutations was fitted on both groups in the new base case analysis. For ToT, the proportional hazard assumption was not rejected and a single dependent model was fitted on both groups in the new base case analysis (**Error! Reference source not found.**). Furthermore, in their clarification questions, the ERG requested AbbVie fit generalised gamma and spline curves in an attempt to find more plausible extrapolations than the Weibull extrapolation used in the base case. Whilst this was not possible within the	The company have now modelled the time-to-event outcomes for venetoclax in a more consistent manner to the modelling of the BSC. Data for both deletion/mutation subgroups have been modelled simultaneously, assuming proportionality of their hazard rates. The hazard ratios for the effect of deletion/mutation status as estimated from the SACT CDF data were 0.59 and 0.52 for ToT and OS respectively. This compares with respective hazard ratios of 0.68 and 0.54 that were used in the BSC modelling for PFS and OS. No confidence intervals were reported for these estimates. As the company state, the ERG suggested that the company also consider alternative parametric fits for the venetoclax ToT and OS data. The justification for this was due to the data showing an increased hazard rate, which occurred from 15 and 24 months in ToT and OS respectively for the deletion/mutation population. This increase was not captured in any of the parametric models previously used, and unfortunately is not captured in any of the new models fitted by the company. The ERG is unable to comprehensively critique the company's decision to switch to the 2-knot normal spline model for ToT, as the company has not provided

		time frame of the clarification questions, AbbVie have now fitted six traditional parametric distributions, including generalised gamma and six cubic spline models, to OS and ToT of the SACT CDF cohort; these analyses are described in further detail in Appendix A. The results of these analyses demonstrate that the choice of parametric distribution has limited impact on the ICER (**Error! Reference source not found.**, **Error! Reference source not found.**), with the majority of new curves more optimistic than AbbVie's original choice of Weibull distribution. Therefore, AbbVie still consider Weibull to be the most appropriate and conservative approach for OS models. However, for ToT extrapolations, due to better performance based on AIC and BIC criteria, AbbVie have updated the base case to consider normal spline 2-knot (**Error! Reference source not found.**). These changes therefore support with addressing the ERG's concerns related to the post-progression modelling of venetoclax.	detailed information on AIC/BIC or hazard/cumulative hazard plots. Hence the ERG maintains the company's choice of models but reiterate that a decreasing hazard over time is being modelled, which is inconsistent with the data and likely overestimating the benefit of venetoclax, particularly for the deletion/mutation population.
7. Use of time on treatment data to model progression-free survival	Yes	In the original appraisal (TA487), AbbVie used PFS data to fit and extrapolate PFS. However, PFS data were not available for the CDF SACT population and so AbbVie used ToT in the reappraisal submission to model PFS. In the clarification questions, the ERG requested that AbbVie estimates a hazard ratio of effect between the PFS and ToT from the venetoclax trials to demonstrate the similarity of the outcomes. Due to time restrictions, this was not feasible during the stage of the clarification questions. To address this issue and investigate the impact of using ToT data to model	The ERG originally requested that the company verify that the assumption of equivalence of PFS and ToT was valid originally made within the economic model. After investigating this, the company have changed their approach to modelling PFS and ToT. The company now distinguish between the outcomes of PFS and ToT within their economic model. The ERG has some concerns about the company's new approach.

		progression-free survival, longer term follow up data from the M13-982 and M14-032 trials were used to produce a hazard ratio of ToT versus PFS separately for patients with and without del(17p)/*TP53* mutations. In the CDF cohort of the SACT data, treatment duration was defined using the interval between treatment start date and final treatment date. Similarly, the first dosing date of patients in M13-982 and M14-032 was used to define the starting date of the treatment and the last dosing date was used to define the ending date of the treatment, aligning with the definition used in the PHE report. To define the difference between PFS and ToT curves, a HR was estimated via cox regression models fitted separately for patients with and without a del(17p)/*TP53* mutation. The HR of ToT versus PFS for patients with del(17p)/*TP53* mutation was estimated at 1.20 (95% CI: 1.00, 1.50) and 1.40 (95% CI: 0.89, 2.40) for patients without del(17p)/*TP53*. The model is structurally set-up to apply a ToT hazard ratio to the model's PFS curve, to generate a ToT curve (to adjust treatment costs). However, the opposite was required in this situation. That is, the PFS curve in the model is already the ToT curve (as estimated from SACT), and the PFS curve needs to be simulated using the inverse of the hazard ratio defined above. There was insufficient time to restructure the model around this nuance, and so instead, the PFS and ToT curves were switched in the model calculation sheet (T1). Mathematically, this produces the intended partitioned	Firstly, it is inconsistent with the modelling of BSC, which does not distinguish between these two outcomes. The model does not allow for the ERG to model ToT separately to PFS for BSC, but doing so would likely reduce the treatment costs for BSC (see Figure 26 of Company Submission, TA359). Secondly, it is unclear why the company have chosen to only use data from two of their three venetoclax trials to calculate the hazard ratios between PFS and ToT for both deletion/mutation populations, excluding M12-175. Thirdly, it is also unclear why the company has estimated the hazard ratio separately for each deletion/mutation subgroup. Doing so would reduce PFS in the non-deletion/mutation population, decreasing the efficacy of venetoclax. Fourthly, the suitability and representativeness of the hazard ratio applied comes into question. There is no evidence presented to support that a single hazard ratio captures the relationship between PFS and ToT observed in the two trials. For example, the hazard ratio may vary over time. Furthermore, this estimate has come from the trials, but is applied to the SACT CDF dataset, where the relationship may be very different.

		survival estimates and drug cost estimates, although the labelling in the backend calculation sheets is misleading (ToT and PFS are switched). The result is that AbbVie's previous PFS estimate is now the ToT estimate, and a new, more favourable PFS curve is represented in the model. This also acts to significantly reduce the post-progression survival period, which was one of the ERGs key issues (Issue 5). This change has been added to the companies proposed base case (**Error! Reference source not found.**).	Finally, the company have incorrectly applied the hazard ratio calculated as the difference between ToT and PFS. The company have applied it as a risk ratio, however the ERG has been able to apply it as a hazard ratio by amending the formula of the spline model fitted to the ToT data, rectifying the error. The effect of this correction on the ICER is small.

Table 2: ERG comment on additional issues raised by the company

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response	ERG Comment
Additional issue 1: Double dosing within the idelalisib arm of the 116 trial	3.2	No	As noted during the original appraisal, but not yet raised during this appraisal, 4 out of the 11 patients who had progressive disease in the idelalisib arm of the 116 trial (36%) had received double dosing of idelalisib, which may have led to increased survival outcomes in these patients. As the agreed comparator for venetoclax is best supportive care, it is not appropriate to use data including patients treated with a double dose of idelalisib. It can be expected that the survival of patients treated with idelalisib would be better than those treated with BSC, therefore over-estimating the survival of patients in the comparator arm. This was not mentioned in the ERG report but is an important factor to account for when considering the choice of data for BSC in the model, and further supports the conclusions made in response to issue two that the rituximab arm of the 116 trial is the most appropriate source of BSC data for this appraisal.	The ERG accepts this potential limitation, however it relies upon these four patients receiving benefit from their second course of idelalisib within the observed period, which is not guaranteed. These patients may have experienced the same event or censoring times regardless of whether they received additional idelalisib therapy. As this point does not influence the base-case analyses, the ERG considers that it is of low relevance.

1.2. Validation of company's cost-effectiveness analysis using updated model

Using the company's updated model, the ERG was able to reproduce the company's base case analysis for both subgroup populations (Table 3 and 4).

Table 3: Revised company deterministic base case for patients with deletion/mutation at PAS price

Technology	Total		Incremental: venetoclax vs BSC		ICER / QALYs, £
	Costs, £	QALYs	Costs, £	QALYs	
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	£44,121
BSC	[redacted]	0.605			

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

Table 4: Revised company deterministic base case for patients without deletion/mutation at PAS price

Technology	Total		Incremental: venetoclax vs BSC		ICER / QALYs, £
	Costs, £	QALYs	Costs, £	QALYs	
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	£46,624
BSC	[redacted]	1.068			

The ERG was able to correct the company's error of applying the hazard ratio for the difference between ToT and PFS as a risk ratio. The ERG presents corrected company base-case analyses in Table 5 and 6.

Table 5: Corrected modelling of ToT to PFS for patients with deletion/mutation (ERG's corrected company base case)

Technology	Total		Incremental: venetoclax vs BSC		ICER / QALYs, £
	Costs, £	QALYs	Costs, £	QALYs	
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	£44,237
BSC	[redacted]	0.605			

Table 6: Correcting modelling of ToT to PFS for patients without deletion/mutation (ERG's corrected company base case)

Technology	Total		Incremental: venetoclax vs BSC		ICER / QALYs, £
	Costs, £	QALYs	Costs, £	QALYs	
Venetoclax	[redacted]	[redacted]	[redacted]	[redacted]	£46,776
BSC	[redacted]	1.068			

1.3. ERG base-case and scenario analyses

The ERG did not deviate from the company's base case as it is not able to robustly improve on the company's assumptions. There remains substantial uncertainty over the cost-effectiveness of venetoclax as a result of an accumulated uncertainty around key factors of this appraisal. The lack of any statistical comparison of venetoclax to BSC is a major concern and prevents validation of the modelled benefit. The ERG interprets that the venetoclax extrapolation may be over-optimistic relative to the observed data due to the modelled decreasing hazard rate. Furthermore, the venetoclax data may over-estimate the efficacy of newly administered venetoclax therapy due to the issues around the generalisability of the data.

Four scenarios presented in the ERG report are still relevant and have not been presented by the company. The ERG presents three of these now, updated for the

company's new approach to modelling for venetoclax PFS, ToT and OS. The fourth scenario of using the old ERG modelling for BSC could not be performed as it was not implemented by the company in the models submitted for the TE, despite being added in the earlier response to clarifications.

Table 7 contains results for patients with deletion/mutation and

Table 8 for those without deletion/mutation. The ERG presents an additional scenario, removing the applied hazard ratio for a difference between PFS and ToT, to demonstrate the influence of this change.

Table 7: ERG scenario analyses for patients with deletion/mutation

Scenario	Incremental Costs	Incremental QALYs	ICER	Change (from base case)
Base case	[redacted]	[redacted]	£44,237	+ £0
Including costs of rituximab therapy to the venetoclax arm	[redacted]	[redacted]	£45,098	+ £977
Combining OS transition probabilities to estimate long term OS for venetoclax	[redacted]	[redacted]	£59,439	+ £15,202
Applying HR of benefit to BSC OS extrapolation for venetoclax	[redacted]	[redacted]	£72,038	+ £27,801
ERG preferred modelling for BSC in TA487	NA	NA	NA	NA
Setting PFS = ToT for venetoclax	[redacted]	[redacted]	£45,300	+ £1,063

Table 8: ERG scenario analyses for patients without deletion/mutation

Scenario	Incremental Costs	Incremental QALYs	ICER	Change (from base case)
Base case	[redacted]	[redacted]	£46,776	+ £0
Including costs of rituximab therapy to the venetoclax arm	[redacted]	[redacted]	£47,527	+ £903
Combining OS transition probabilities to estimate long term OS for venetoclax	[redacted]	[redacted]	£62,862	+ £16,086
Applying HR of benefit to BSC OS extrapolation for venetoclax	[redacted]	[redacted]	£74,056	+ £27,280
ERG preferred modelling for BSC in TA487	NA	NA	NA	NA
Setting PFS = ToT for venetoclax	[redacted]	[redacted]	£49,024	+ £2,248

Company References

1. National Institute for Health and Care Excellence. Technology appraisal guidance: Venetoclax for treating chronic lymphocytic leukaemia [TA487]. 2017. Available at https://www.nice.org.uk/guidance/ta487. Accessed on: 12-Oct-2021
2. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax for Patients With Chronic Lymphocytic Leukemia With 17p Deletion: Results From the Full Population of a Phase II Pivotal Trial. J Clin Oncol 2018;36:1973-1980.
3. Jones JA, Mato AR, Wierda WG, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. The Lancet Oncology 2018;19:65-75.
4. Davids MS, Roberts AW, Seymour JF, et al. Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma. J Clin Oncol 2017;35:826-833.
5. John F. Seymour JQW, Relja Popovic, Barbara Eichhorst, Peter Hillmen, Thomas J. Kipps,, Anton W. Langerak, , Carolyn Owen, Julie Dubois, Clemens Mellink, Anne-Marie Van Der Kevie-Kersemaekers, Fengjiao Dunbar, Yanwen Jiang, Brenda Chyla, Michelle Boyer, Maria Thadani-Mulero, Marcus Lefebure, Rosemary Harrup and Arnon P. Kater,. 1548 Assessment of the Clonal Dynamics of Acquired Mutations in Patients (Pts) with Relapsed/Refractory Chronic Lymphocytic Leukemia (R/R CLL) Treated in the Randomized Phase 3 Murano Trial Supports Venetoclax-Rituximab (VenR) Fixed-Duration Combination Treatment (Tx). 2021.
6. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax–Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. New England Journal of Medicine 2018;378:1107-1120.
7. Thompson MC, Allan JN, Sail K, et al. Venetoclax Re-Treatment of Chronic Lymphocytic Leukemia (CLL) Patients after a Previous Venetoclax-Based Regimen. Blood 2020;136:39-41.
8. Harrup RA, Owen C, D'Rozario J, et al. Efficacy of Subsequent Novel Targeted Therapies, Including Repeated Venetoclax-Rituximab (VenR), in Patients (Pts) with Relapsed/Refractory Chronic Lymphocytic Leukemia (R/R CLL) Previously Treated with Fixed-Duration Venr in the Murano Study. Blood 2020;136:44-45.
9. Sharman JP, Coutre SE, Furman RR, et al. Final Results of a Randomized, Phase III Study of Rituximab With or Without Idelalisib Followed by Open-Label Idelalisib in Patients With Relapsed Chronic Lymphocytic Leukemia. Journal of Clinical Oncology 2019;37:1391-1402.
10. National Institute for Health and Care Excellence. Venetoclax for treating chronic lymphocytic leukaemia; Final appraisal determination. 2017 Available at https://www.nice.org.uk/guidance/ta487/documents/final-appraisal-determination-document. Accessed on: 22-Oct-2021.
11. Aarup K, Rotbain EC, Enggaard L, et al. Real-world outcomes for 205 patients with chronic lymphocytic leukemia treated with ibrutinib. European Journal of Haematology 2020;105:646-654.
12. Rigolin GM, Cavazzini F, Piciocchi A, et al. Efficacy of idelalisib and rituximab in relapsed/refractory chronic lymphocytic leukemia treated outside of clinical trials. A report of the Gimema Working Group. Hematological Oncology 2021;39:326-335.
13. Eyre TA, Kirkwood AA, Gohill S, et al. Efficacy of venetoclax monotherapy in patients with relapsed chronic lymphocytic leukaemia in the post-BCR inhibitor setting: a UK wide analysis. British Journal of Haematology 2019;185:656-669.

It was noted that results for one of the scenarios presented by the ERG was based on the uncorrected TE economic model. The ERG now present results for the corrected model below.

This replaces the relevant scenario in the main ERG report. It does not include CMU pricing, and so may be shared with the company.

Parameter	**Results** **(Impact to base-case ICER): del(17p)/TP53 mutation**	**Results** **(Impact to base-case ICER): non-del(17p)/TP53 mutation**
Incremental costs of including costs of rituximab therapy to the venetoclax arm	[redacted]	[redacted]
Incremental QALYs of including costs of rituximab therapy to the venetoclax arm	[redacted]	[redacted]
ICER for Including costs of rituximab therapy to the venetoclax arm	£45,220 / QALY	£47,685 / QALY