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

For public observers – redacted

Technology appraisal committee C [8 March 2022]

Chair: Richard Nicholas

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Evidence review group: Warwick Evidence

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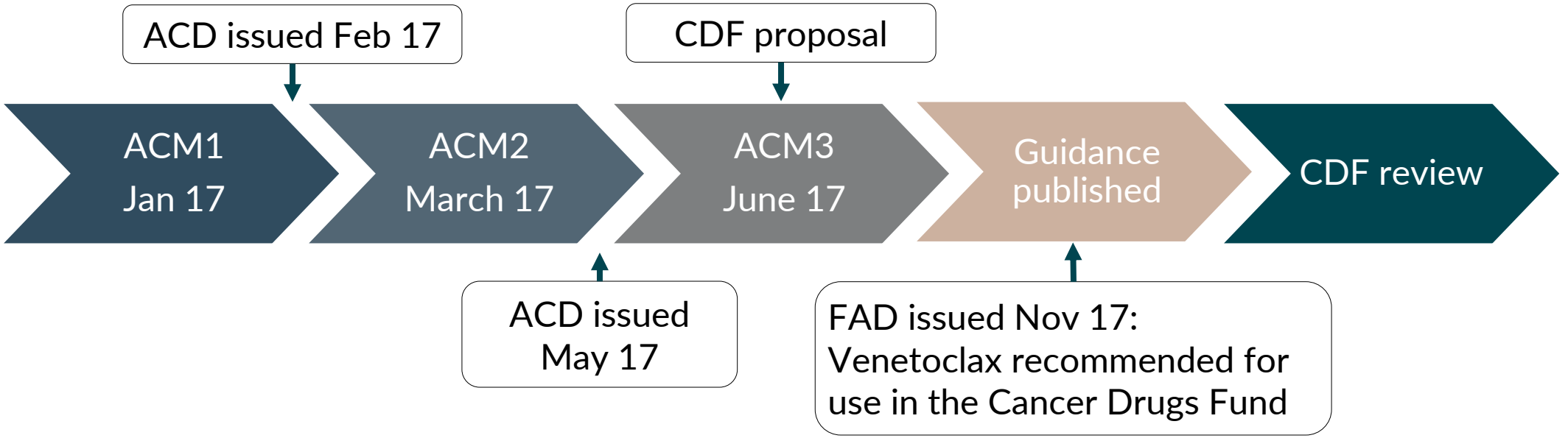
Company: AbbVie

NICE

Summary of original appraisal TA487 (2017)



TA487 recommendation: 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

Abbreviations: ACD, appraisal consultation document; FAD, final appraisal document

Cancer Drugs Fund (CDF) review process

A CDF review, following a period of data collection in managed access, is slightly different to a standard NICE guidance review

- The comparators are **the same as those in the original scope**
- The managed access agreement listed key uncertainties for which data have been collected. Key assumptions related to these should be revisited
- Other key assumptions not addressed during the period of managed access remain unchanged

Note: The guidance update process following a period of managed access will be changing when the new NICE manual is launched in 2022, the process will include a re-scoping exercise to take account of changes to the treatment pathway that have occurred since the original recommendation.

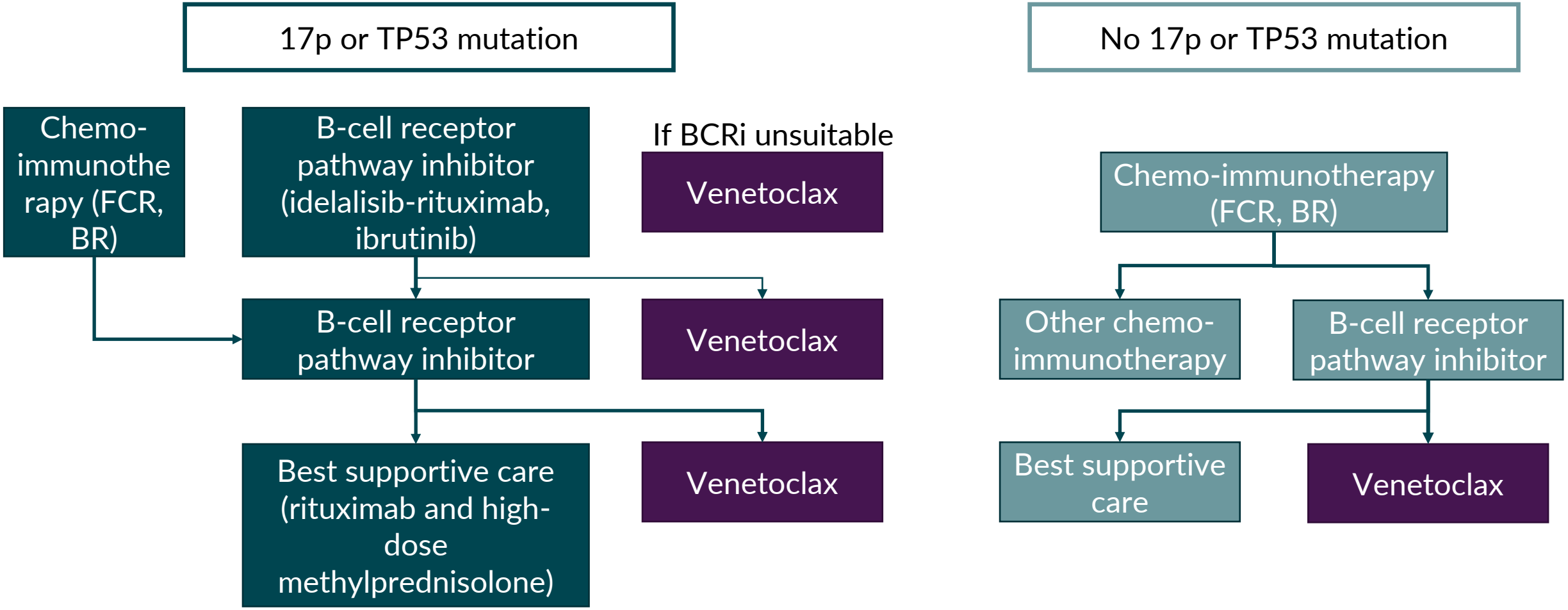
Venetoclax (Venclyxto, AbbVie)

Table 1 Technology details

Marketing authorisation	Venetoclax monotherapy is indicated for the treatment of CLL: • in the presence of 17p deletion or *TP53* mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or • in the absence of 17p deletion or *TP53* mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.
Mechanism of action	Selective small molecule inhibitor of B-cell lymphoma-2. Overexpression of Bcl-2 can cause cells to resist apoptosis and therefore continue to survive
Administration	Oral tablet
Price	• 112 tablet pack (100 mg) = £4,789 (Week 5 onwards, 400 mg per day) • Average cost for year 1 is £58,752 and for year 2 onwards is £41,127 • There is a patient access scheme in place for venetoclax

Treatment pathway (TA487)

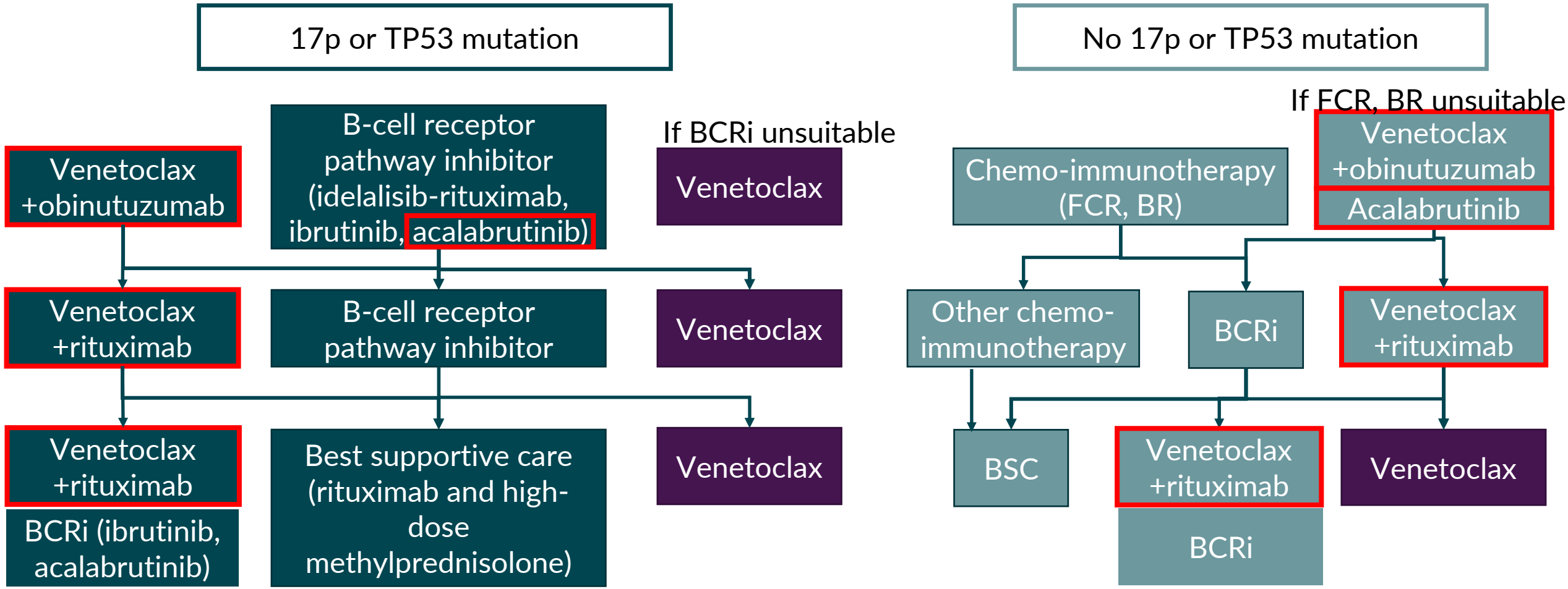
CDF review cannot account for changes to treatment pathway since original appraisal



Abbreviations: FCR, fludarabine, cyclophosphamide+rituximab; BR, bendamustine+rituximab

Treatment pathway (current)

Pathway has evolved, which may impact data generalisability



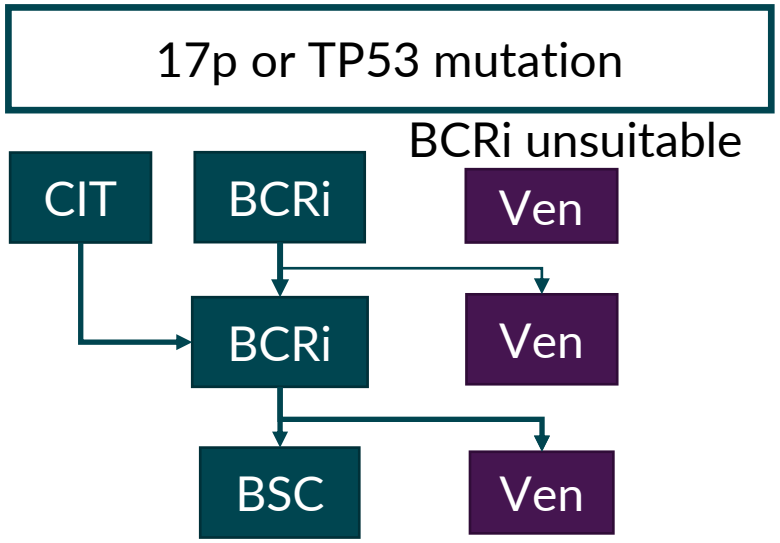
NICE recommended treatments since original appraisal

Abbreviations: FCR, fludarabine, cyclophosphamide+ rituximab; BR, bendamustine+rituximab

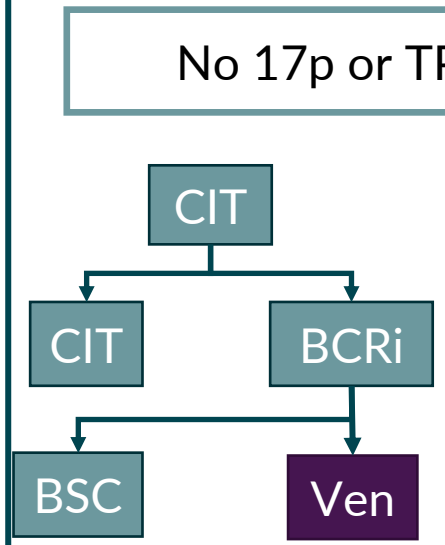
Recap TA487: Summary of trial evidence and populations

How the venetoclax trials relate to position in treatment pathway

- Evidence for venetoclax came from 3 single-arm trials:
  - **M13-982:** Multicentre (11 UK), open-label, phase II
  - **M12-175:** Phase I dose escalation and safety (US & Australia)
  - **M14-032:** Multicentre (US), open-label, phase II



M13-982 (N=158)	M12-175 (N=67)	M14-032 (N=105)
N=5	N=0	N=0
N=18	Progress-ion after BCRi not reported	N=44

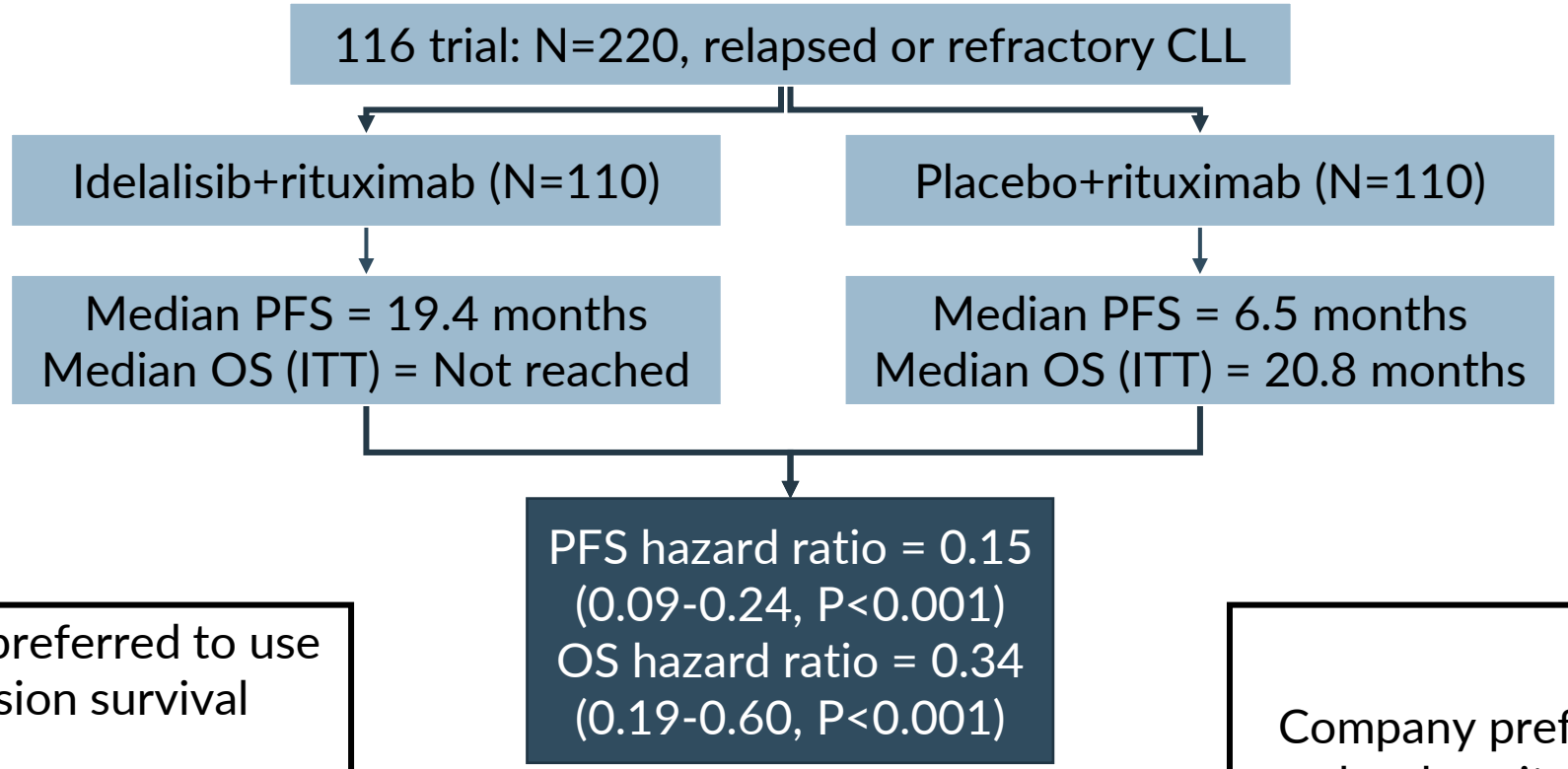


M13-982	M12-175	M14-032
N=0	N=3	N=37

BCRi suitability was not defined in any of the 3 trials

Abbreviations: CIT, chemoimmunotherapy, BCRi, B-cell receptor pathway inhibitor; BSC, best supportive care; Ven, venetoclax

Recap TA487: 116 trial for BSC comparator arm



TA487 ERG preferred to use post-progression survival data from idelalisib+rituximab arm, because patients in placebo+rituximab arm did not have relapsed or refractory disease after BCRi

Company preferred to use placebo+rituximab arm **- Retained as best supportive care data source in current appraisal**

Abbreviations: BSC, best supportive care; OS, overall survival; PFS, progression-free survival; ITT, intention to treat; BCRi, B-cell receptor pathway inhibitor

Recap TA487: Clinical effectiveness

- Company pooled venetoclax data from 3 trials and compared with placebo+rituximab arm of 116 trial
    - Committee concluded that although imperfect, the company's pooling of the data was acceptable
- Showed overall survival was much higher with venetoclax

Issues with venetoclax trials	Issues with indirect comparison
• Few UK patients • People in trials likely younger and had a lower burden of disease than people likely to have venetoclax in clinical practice	• 116 trial: not people with relapsed or refractory disease after B-cell receptor inhibitors – earlier position in pathway • No matching on baseline characteristics • People in 116 trial likely had more advanced disease than venetoclax trials

Original SACT data collection plan

- Support generalisability of venetoclax trial data (baseline characteristics, treatment duration and overall survival)
- Provide an approximation of outcomes of BSC in a population relevant to clinical practice in England (retrospective analyses on ibrutinib and idelalisib with rituximab – treatment duration and overall survival)

Recap TA487: Cost effectiveness

- Company extrapolated venetoclax progression-free survival and overall survival using Weibull distribution
  - Committee agreed Weibull distribution was justifiable, despite the uncertainty
- Company used placebo+rituximab arm of 116 trial for best supportive care data
  - Committee preferred ERG approach of using post-progression survival data from idelalisib+rituximab arm of 116 trial
  - Committee considered that post-progression population of idelalisib arm more closely matched population who would be offered venetoclax

Uncertainty with Weibull distribution
When looking at alternative distributions, curves diverged greatly after 4 years of observed data

Uncertainty with ERG's approach to BSC data source
• Only 17 patients • Some patients had second dose of idelalisib (company state 4/11) • OS for non-del/mut group estimated at around 4 years – higher than clinical expert opinion expected • ERG modelling suggested for non-deletion/mutation population, post-progression survival was longer than PFS – inconsistent with expert opinion • Other data sources available, e.g., RESONATE trial

Abbreviations: OS, overall survival; PFS, progression-free survival

Terms of engagement for CDF review

Table 2 Summary of terms of engagement for the CDF review

	Terms of engagement	Addressed in submission? (ERG opinion)
Comparators	Company should present clinical and cost-effective evidence for venetoclax compared with best supportive care (BSC)	Yes
Generalisability of the trial data	SACT data should inform the generalisability of the trial data	Yes
Survival data	Company should explore the most appropriate extrapolation method given more mature trial data and SACT data collected during managed access period	Partially
Source of BSC data	Company should fully explore the most appropriate source of BSC based on data collected during managed access period	No
Indirect comparison	Company should fully explore the most appropriate comparison based on data collected during managed access period, with particular focus on SACT data to establish relative effectiveness of venetoclax compared with BSC	N/A
Utility values	Company should use a utility value of 0.748 for the progression-free health state, unless SACT data provides a strong justification to deviate from this	Yes
End of life	Venetoclax meets the end of life criteria	N/A

Abbreviations: BSC, best supportive care; SACT, Systemic Anti-Cancer Therapy

Data collected during managed access period

Original data collection plan	Data collected?
SACT data on baseline characteristics, treatment duration and overall survival for people having venetoclax	Yes
Retrospective analyses on ibrutinib and idelalisib with rituximab from SACT, to capture BSC in practice (treatment duration and overall survival)	**Not collected** due to underreporting of haematological malignancies in SACT dataset, differences in patient eligibility, lack of baseline co-variate information and approaches to adjust for treatment switching
Additional data	Updated data for M13-982 (April 2017) and M14-032 (June 2017) – company stated no further follow-up available beyond this

Abbreviations: Systemic Anti-Cancer Therapy, SACT; BSC, best supportive care

Updated treatment outcomes after CDF

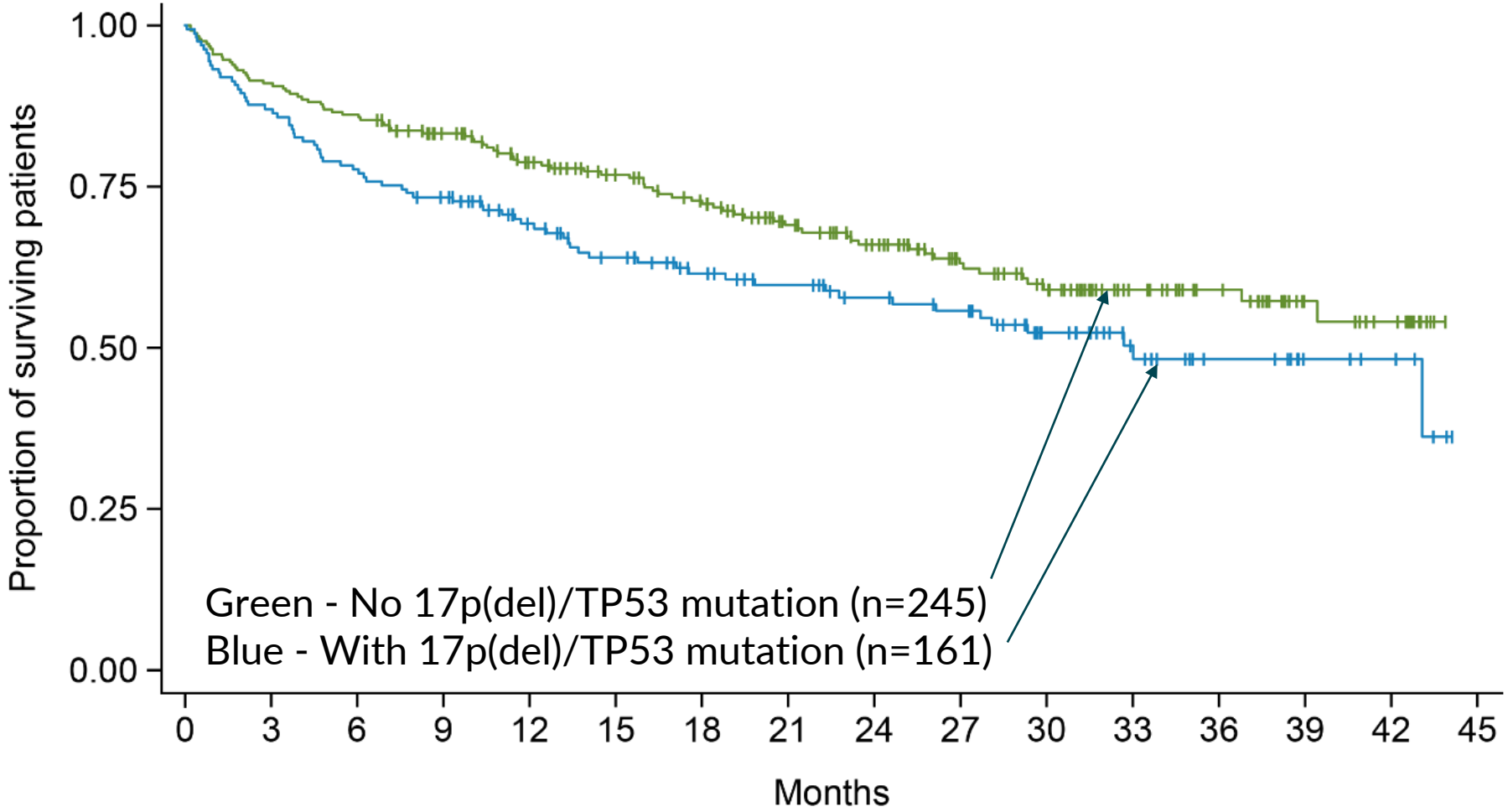
Table 3 Results after period of CDF data collection

Trial	M13-982 2017	M12-175*	M14-032 2017	SACT Data CDF Cohort			SACT Data EAMS Cohort	Trial 116 (rituximab arm)*		
				With del/mut	Without del/mut	Total		No del/mut	With del/mut	Total
Median time on treatment (months)	23.1	Not reported	Not reported	17.9	22.3	21.2	19.1	Not reported	Not reported	19.4
Median PFS (months)	27.2	41.4	24.7	Not reported				8.1	4.0	6.5
Median OS (months)	Not reached	[redacted]	Not reached	33	Not reached	43.1	32.5	20.8	14.8	20.8
Median OS Follow-up (months)	Not reported	Not reported	Not reported	15.5	20.6	18.9	33.1	Not reported	Not reported	Not reported

*Not updated since original appraisal (TA487)

Abbreviations: Systemic Anti-Cancer Therapy, SACT; PFS, progression-free survival; OS, overall survival; EAMS, Early Access to Medicines Scheme

SACT CDF data
Kaplan-Meier curve: venetoclax overall survival



Patient perspectives

Venetoclax monotherapy would be valued by patients

Submissions from Lymphoma Action, Leukaemia Care and CLL Support

- CLL has high relapse rates and need for more treatment options is high because of range of comorbidities in population
- Many people having venetoclax monotherapy can now receive dose escalation as outpatients, reducing time spent in hospital
- Some people (particularly those that are older) prefer continuous rather than fixed-term treatment
- Side effects considered tolerable
- While treatment options have increased since the original appraisal, venetoclax monotherapy is still an important option

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

Clinical perspectives

There remains an unmet need for patients with relapsed CLL

Submission from UK CLL Forum

- Most people with CLL now have B-cell receptor pathway inhibitors (usually ibrutinib or acalabrutinib), or venetoclax plus obinutuzumab in first line, and venetoclax plus rituximab in second line
- Chemoimmunotherapy is now rarely used
- Venetoclax has made a big difference to progression-free survival, quality and quantity of life in CLL
- Unmet need for patients with relapsed CLL, particularly those who cannot tolerate monoclonal antibodies
- Venetoclax monotherapy may be used after venetoclax combination therapies that have been recommended since the original appraisal
- One study suggests equivalence of venetoclax monotherapy to venetoclax plus rituximab
- The efficacy of venetoclax after Bruton's tyrosine kinase (BTK) inhibitors (e.g., ibrutinib) is well documented

Key issues

Key: Large impact  Small/moderate impact  Unknown impact 

Table 4 Key issues

Issue	Resolved?	ICER impact
Generalisability of venetoclax SACT CDF data to UK practice	No – for discussion	
Uncertainty around best supportive care data	No – for discussion	
Lack of matching-adjusted or naïve statistical comparison of venetoclax and best supportive care	No – for discussion	
Source of baseline characteristics inputs	Yes	
Venetoclax post-progression survival modelling	No – for discussion	
Inconsistent modelling of survival data between venetoclax and best supportive care	Partially – for discussion	
Use of time on treatment data to model progression-free survival for venetoclax	Partially – for discussion	

Clinical effectiveness

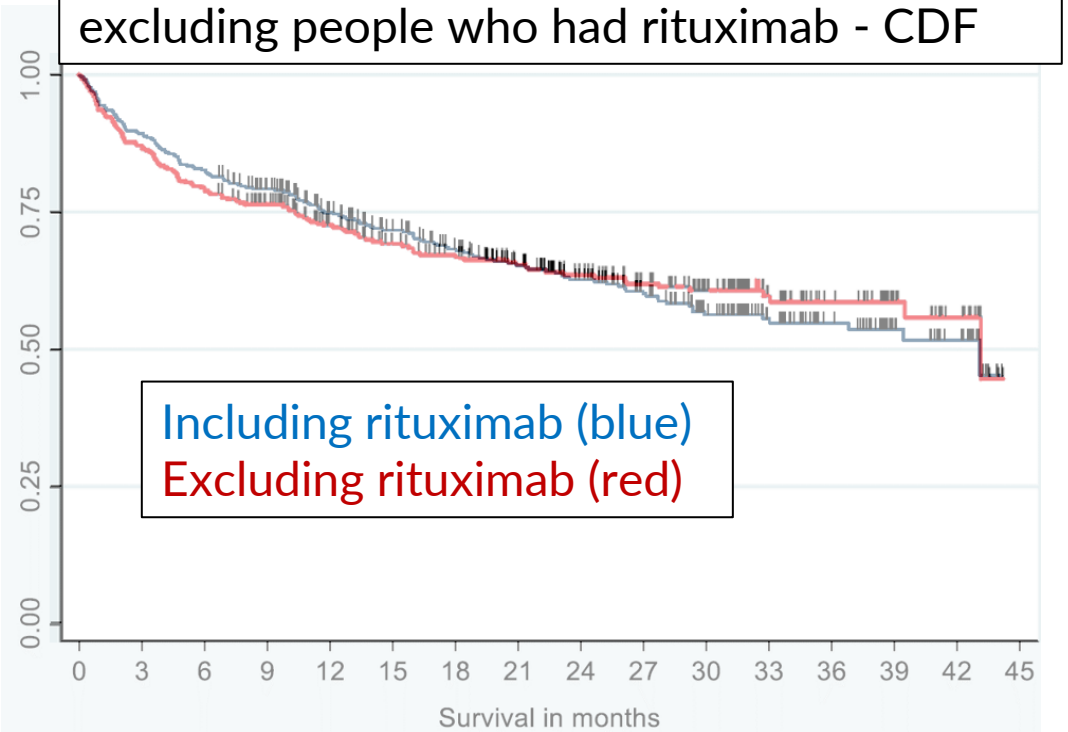
NICE National Institute for Health and Care Excellence

Generalisability of venetoclax data to UK practice [1]
Unclear due to use of venetoclax combinations and rituximab

Background
- Primary source of data for venetoclax in company's model is SACT CDF dataset. Some additional venetoclax patients identified from EAMS but not included in company model as not split by deletion/mutation status
- Evolving treatment pathway for CLL means that patients eligible for venetoclax monotherapy in future will have followed a different treatment pathway to patients in CDF

ERG comments
- Patients were allowed to switch from venetoclax monotherapy to venetoclax+rituximab (TA561, 2019)
- 80/406 patients in SACT CDF cohort had rituximab on or after earliest venetoclax start date and may have had additional benefit – unclear whether after stopping venetoclax monotherapy or not
- Including costs of rituximab slightly increases ICER
- Likely that few people in SACT CDF dataset would have had prior venetoclax – may not reflect current practice.
  →venetoclax efficacy as retreatment may be lower
  →patients may be different at baseline if had venetoclax before

Kaplan-Meier of overall survival including and excluding people who had rituximab - CDF



Abbreviations: EAMS, Early Access to Medicines Scheme; Systemic Anti-Cancer Therapy, SACT; ICER, incremental cost-effectiveness ratio

Generalisability of venetoclax data to UK practice [2]
Unclear due to use of venetoclax combinations and rituximab

Company
- Inappropriate to pool with EAMS data as not split by deletion/mutation status and patients likely to have had more previous treatment than UK population
- Expert opinion suggests venetoclax likely still to be effective on retreatment
- Consideration of updated treatment pathway is outside the scope of this review
- Reason for people having subsequent rituximab is unclear in SACT report
  - Median OS (43.1 months) remains the same when group with subsequent rituximab excluded
- Acknowledge limitations, but SACT CDF cohort is most appropriate efficacy data source in this appraisal

Stakeholder responses to technical engagement
- Data quality outside of company's control – SACT CDF data remains best UK data available
- Some patients may have had rituximab but effect appears minimal
- There is some evidence to show venetoclax is still effective on retreatment
- Venetoclax monotherapy most likely to be used in third line setting

ERG comments
- Recent publication suggests reduced response rates of later lines of venetoclax therapy
- Effects of rituximab and prior venetoclax have larger influence on extrapolations than on observed period

How should the potential generalisability issues be accounted for in decision-making?

Abbreviations: EAMS, Early Access to Medicines Scheme; Systemic Anti-Cancer Therapy, SACT

Uncertainty around best supportive care data [1]

Company's source of BSC data unchanged from TA487

Background

- In TA487, company used data from rituximab arm of trial 116 to approximate best supportive care (BSC)
- Committee preferred ERG approach of using post-progression survival data from idelalisib arm of 116 trial
- SACT report was expected to provide source of BSC data but did not

Company

- Retained use of data from rituximab arm of trial 116
- Better aligns with patients in SACT CDF data than it did with venetoclax trials as patients in SACT CDF have more advanced disease

ERG comments

- Not a suitable comparator because patients in trial 116 had other treatment options which may have improved their survival post-study
- Differences in eligibility criteria between SACT CDF and trial 116 e.g. previous treatments, previous transplant, time since progression
- Company did not present any updated information on trial 116
  - There is some updated follow-up although not reported in enough detail to use in model
- Company did not conduct a systematic search for alternative source of BSC data
  - ERG identified alternative sources of data
- Pooled deletion/mutation groups could have been considered as a scenario analysis, allowing comparison to other sources and inclusion of EAMS data

Stakeholder responses to technical engagement

- If trial 116 used, choice of arm may not be important due to significant crossover

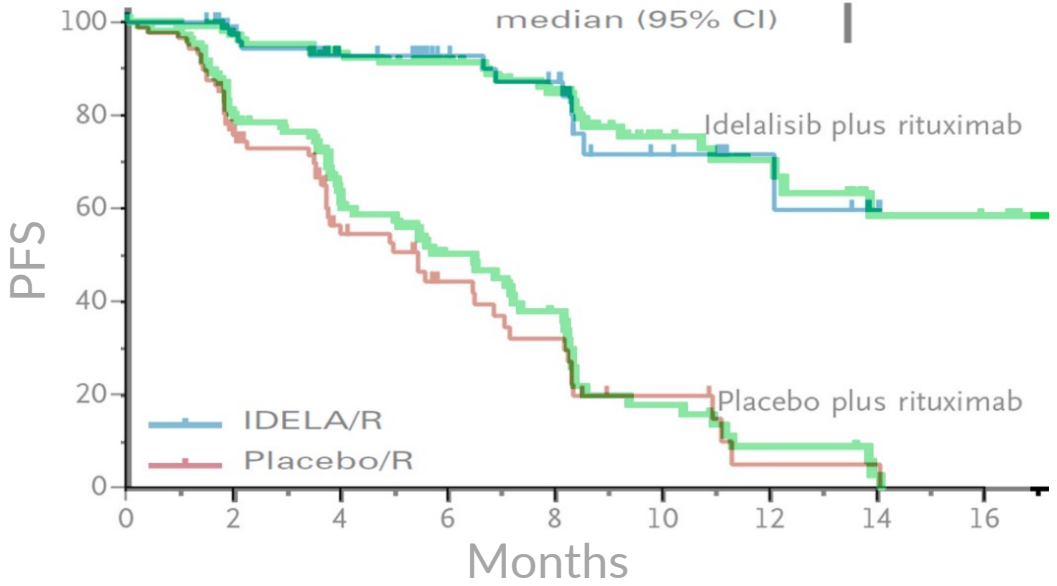
Abbreviations: BSC, best supportive care; SACT, Systemic Anti-Cancer Therapy

Uncertainty around best supportive care data [2]

ERG analyses of potential alternative sources of BSC data

Updated follow-up from trial 116 (ERG analysis)

- Pooled deletion/mutation status so cannot be used in economic model
- Suggests slightly better performance of rituximab than original data in overall population



Updated (green) vs old follow-up of progression-free survival from trial 116

Alternative sources of BSC data (ERG search)

- ERG considers most relevant alternative sources are Rigolin 2021 and Aarup 2020 as they both contain real world data

Table 5 Summary of most relevant alternative sources

Study (relevant sample size)	Post-progression survival details (reason for discontinuation)	Most common post-progression treatments
Aarup 2020 (n=86, Denmark)	Med OS = 18.2 months	Venetoclax (n=22) Idelalisib (n=10)
Rigolin 2021 (n~99, Italy)	Med OS = 15.5 months (progression), not reached (toxicities)	Not reported
Company – with del/mut	Med OS = 18 months	-
Company - non-del/mut	Med OS = 24 months	-

Are results from the alternative data sources informative?

Abbreviations: BSC, best supportive care; Med OS, median overall survival

Lack of matching-adjusted or naïve statistical comparison of venetoclax and best supportive care

ERG presents a statistical comparison

Background

- In TA487, company presented indirect comparison of venetoclax and BSC – no matching on baseline characteristics or eligibility criteria. Company did not present any further statistical comparison
- Committee: survival benefit of venetoclax compared with BSC likely to be biased in favour of venetoclax

ERG comments

- ERG presents analysis of pooled CDF and EAMS digitised dataset, excluding patients who had rituximab, compared with digitised post-progression survival plots from Rigolin and Aarup, combined
- Fitted a Cox proportional hazards model to produce hazard ratio of 0.57 (0.44-0.73) for OS
  - Scenario analysis applying this hazard ratio to BSC Weibull extrapolations substantially increases ICER
- Recognise that reported characteristics are difficult to compare, but similar concerns between SACT CDF and trial 116 populations

Company

- Limitations: inaccuracy of data in the analysis, differences between patients (baseline characteristics, previous and later therapies, different measures of disease severity, no split by deletion/mutation populations, no UK patients in Rigolin or Aarup)

How should the ERG scenario be considered in decision-making?

Abbreviations: BSC, best supportive care; EAMS, Early Access to Medicines Scheme

Cost effectiveness

NICE National Institute for Health and Care Excellence

Model structure

Partitioned survival model

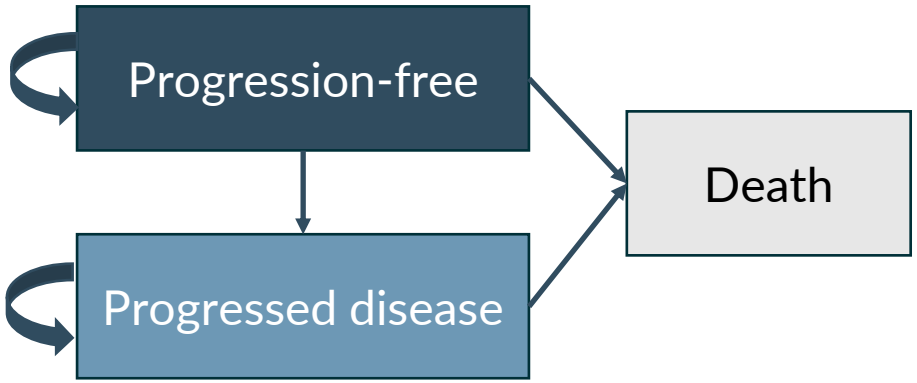
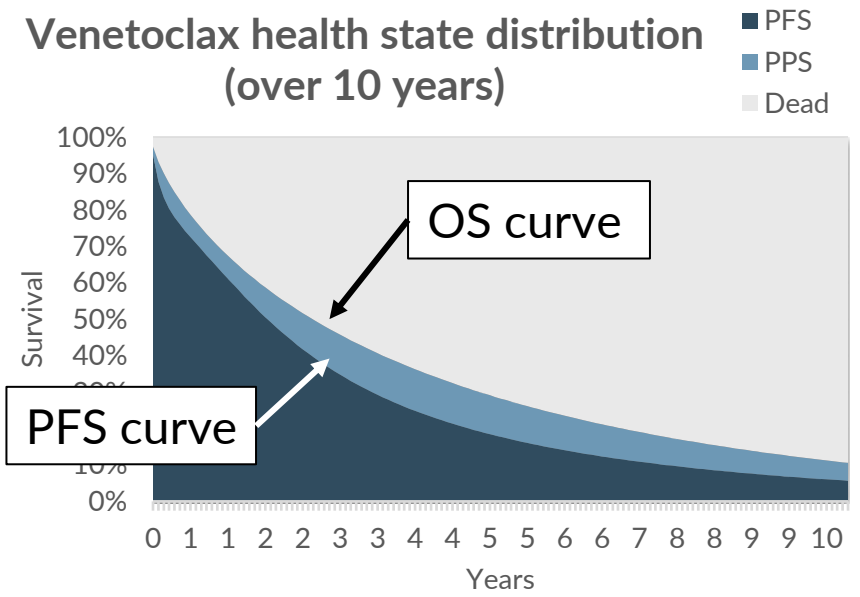


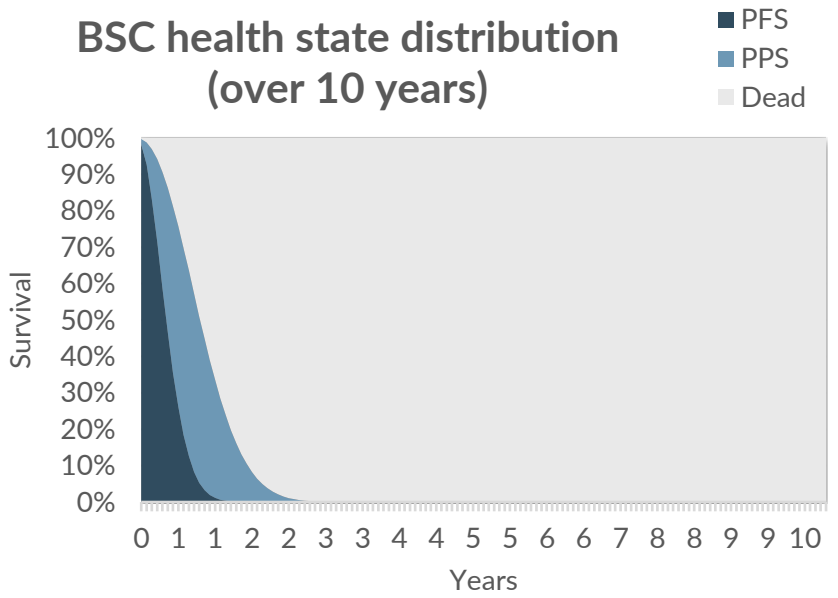
Table 6 Sources of data to populate the model

Treatment arm	PFS curve	OS curve
Venetoclax	Applied HR from TOT:PFS in venetoclax trials to TOT data from SACT CDF	OS data from SACT
BSC	PFS data from rituximab arm of trial 116	OS data from rituximab arm of trial 116

Abbreviations: PFS, progression-free survival; OS, overall survival; SACT, Systemic Anti-Cancer Therapy; PPS, post-progression survival; TOT, time on treatment; BSC, best supportive care

Summary of partitioned survival model (deletion/mutation population)





Post-progression survival modelling [1]

Post-progression survival is high in the company's original model

Company's pre-technical engagement model

- To extrapolate beyond the observed time period of data collection, company fitted parametric survival models to data recreated from SACT report – Weibull model selected

ERG comments

- Company's Weibull extrapolations model an inappropriate continuously decreasing hazard rate when OS and TOT data show increasing rate at end of follow up
- Lead to high estimates of venetoclax post-progression survival exceeding entire modelled BSC survival
- ERG fitted parametric curves to data from paper by Eyre et al. that reports post-progression survival times of 22 UK patients who had venetoclax
- Compared life years (capped at 20 years) of best fitting models with company's analyses
- Company's modelled venetoclax post-progression survival far exceeds Eyre estimates

Table 7 Life years in alternative scenarios

Scenario	Del/mut	Non-del/mut
Venetoclax post-progression LYs from company original model	1.80	2.44
Venetoclax post-progression LYs: ERG modelling of Eyre 2019	0.35 to 1.27 (depending on curve)	
BSC total LYs from company original model	0.95	1.80

Abbreviations: OS, overall survival; SACT, Systemic Anti-Cancer Therapy; BSC, best supportive care; LY, life years

Post-progression survival modelling [2]

Post-progression survival is high in the company's original model

ERG comments

- Presented transition probabilities over model time horizon to show how implied transition ratio gets stronger in favour of venetoclax, suggesting a large treatment benefit
- Presented scenario analysis where transition probabilities applied for venetoclax are estimated using weighted average of transition probabilities of venetoclax and BSC – to generate post-progression survival estimates more in line with Eyre

Company's response to technical engagement

- Patients in Eyre likely to have more advanced disease than patients who would have venetoclax
- **New survival modelling** incorporated into base case, with a lower post-progression survival due to more favourable PFS curve for venetoclax

ERG response: would prefer an OS extrapolation that models increasing hazard rate

OS transition probabilities for del/mut population

OS transition probabilities for non-del/mut population

Stakeholder responses to technical engagement

- Patients in Eyre had multiple rounds of chemoimmunotherapy and then ibrutinib as a last option before venetoclax
- Patients now would have had less chemotherapy

Is the company's or ERG's modelling of venetoclax overall survival more plausible?

Abbreviations: OS, overall survival; BSC, best supportive care

Inconsistent modelling of survival data [1]

Company modelled venetoclax and BSC differently

Company

- For venetoclax, fitted parametric models to data recreated from SACT report - independent models for each deletion/mutation group
- For BSC, one survival model fitted simultaneously to data for both deletion/mutation groups. For deletion/mutation group, estimated PFS and OS from Weibull model. For non-deletion/mutation group, applied hazard ratio from pooled data from venetoclax trials (PFS: 0.585, OS, 0.543)

ERG comments

- Not usually appropriate to use hazard ratio derived from venetoclax data applied to BSC model
- Estimate from venetoclax trials suggests more negative effect of deletion/mutation status than estimated in idelalisib appraisal
- Fitting parametric models simultaneously to venetoclax data for both subgroups would be more consistent

Company's response to technical engagement and updated modelling of venetoclax data

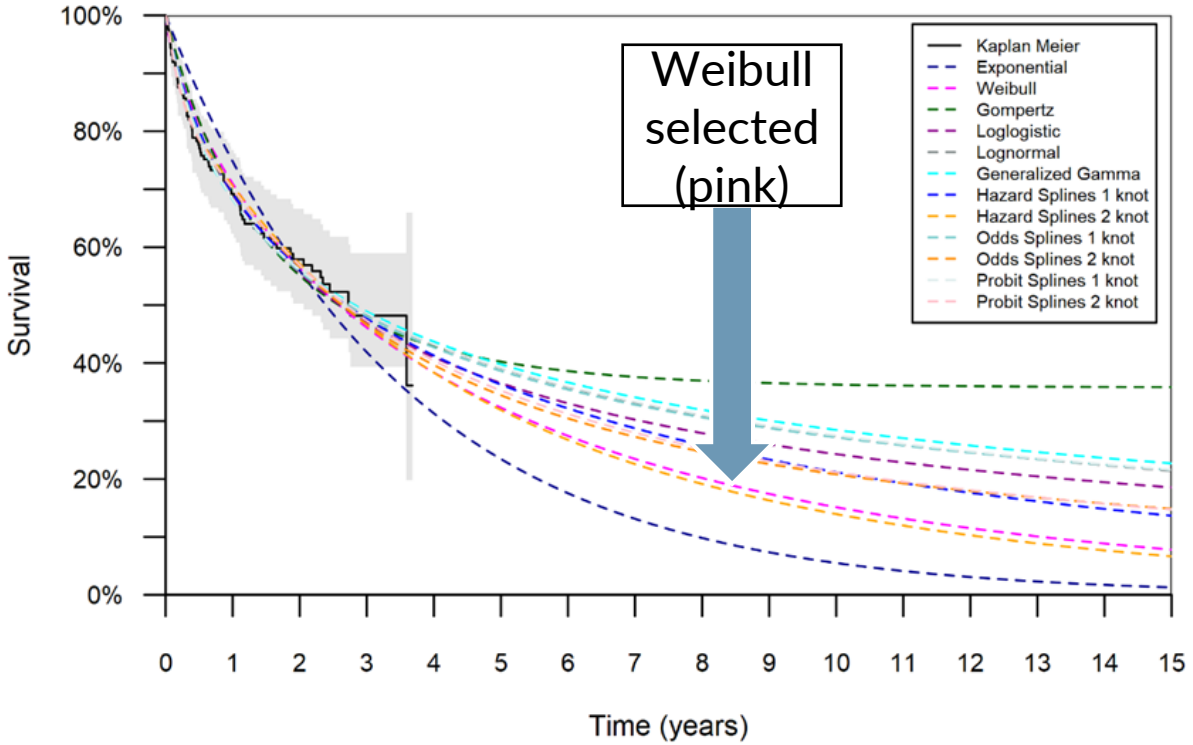
- Proportional hazards assumption held for OS and TOT, therefore fitted a single dependent model for venetoclax OS and TOT, including a hazard ratio for the deletion/mutation vs non-deletion/mutation groups
- Company also fitted further extrapolation models including generalised gamma and cubic spline models, which have a limited impact on the cost-effectiveness results
- **Base case model updated** to include dependent Weibull model for OS and normal spline 2-knot for TOT

Abbreviations: SACT, Systemic Anti-Cancer Therapy; BSC, best supportive care; PFS, progression-free survival; OS, overall survival; TOT, time on treatment

Inconsistent modelling of survival data [2]

Company's alternative venetoclax extrapolation curves – Weibull selected for overall survival

Deletion/mutation group



Non-deletion/mutation group

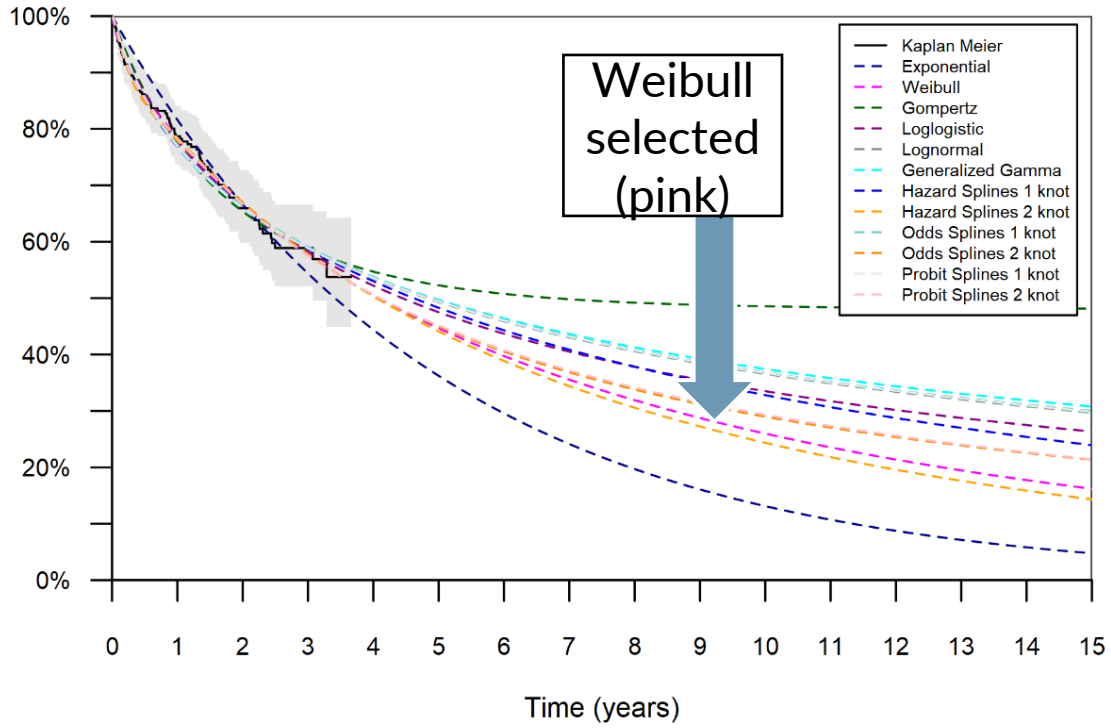


Table 10: Hazard ratios for effect of deletion/mutation status

	OS
Venetoclax, SACT CDF	0.52
Best supportive care	0.54

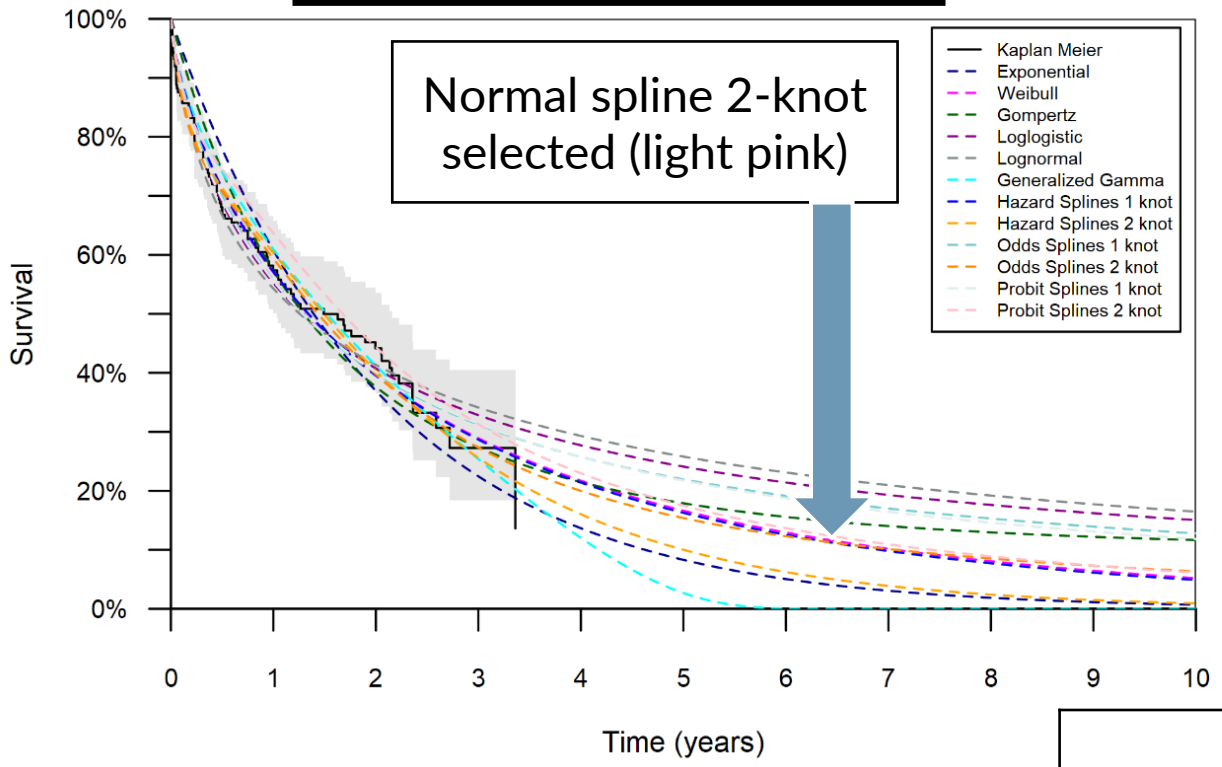
ERG comments

- New modelling still does not capture increasing hazard rate for deletion/mutation group

Inconsistent modelling of survival data [3]

Company's alternative venetoclax extrapolation curves – Normal spline 2-knot selected for time on treatment

Deletion/mutation group



Non-deletion/mutation group

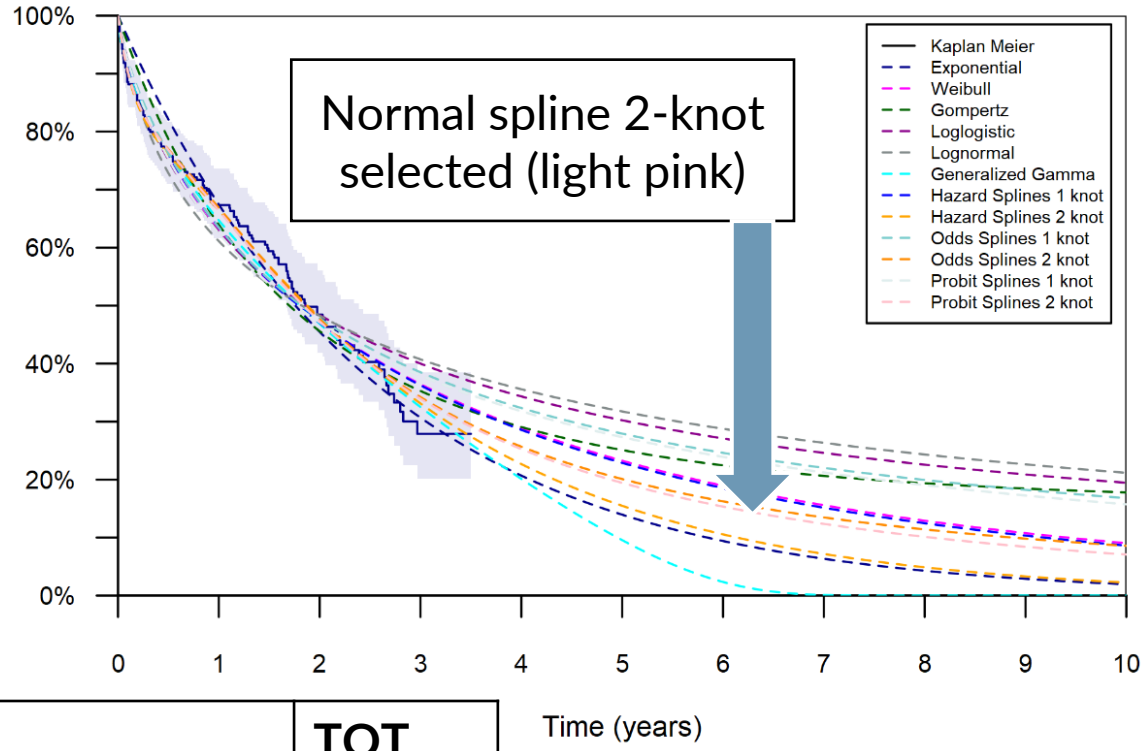


Table 11: Hazard ratios for effect of deletion/mutation status

	TOT
Venetoclax, SACT CDF	0.59
BSC	0.68

Is the company's updated modelling appropriate?

Use of time on treatment data to model progression-free survival [1]

Company updated modelling based on hazard ratio between PFS and TOT

Background

- PFS data unavailable from SACT so company used time on treatment (TOT) data to approximate PFS

ERG comments

- If patients stop venetoclax before disease progression, due to toxicity, modelled costs of venetoclax will be too low
- Using TOT is also inconsistent with BSC modelling

Company

- Estimated hazard ratio for TOT vs PFS from 2 of the venetoclax trials to demonstrate similarity of outcomes (separately for deletion/mutation groups)
  - Deletion/mutation group: hazard ratio (HR) = 1.20 (95% CI 1.00 – 1.50)
  - Non deletion/mutation group: HR = 1.40 (95% CI 0.89 – 2.40)
- **Base case model updated:** SACT CDF TOT data now used for TOT curve. PFS curve estimated by applying inverse of HR above to TOT curve. PFS curve is more favourable, reducing post-progression survival

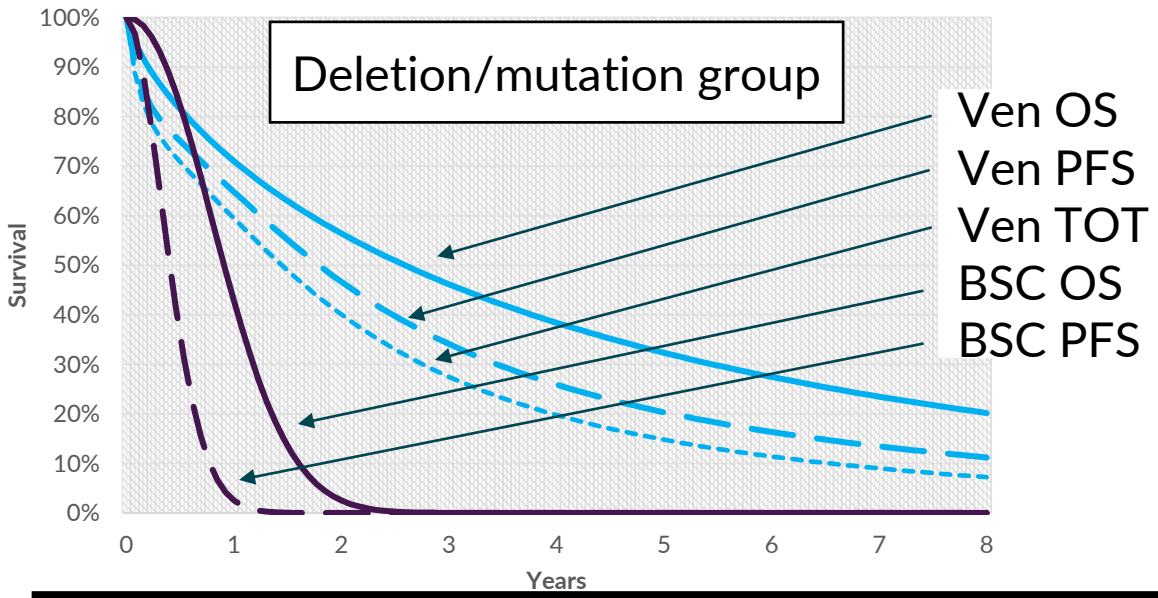
Stakeholder responses to technical engagement

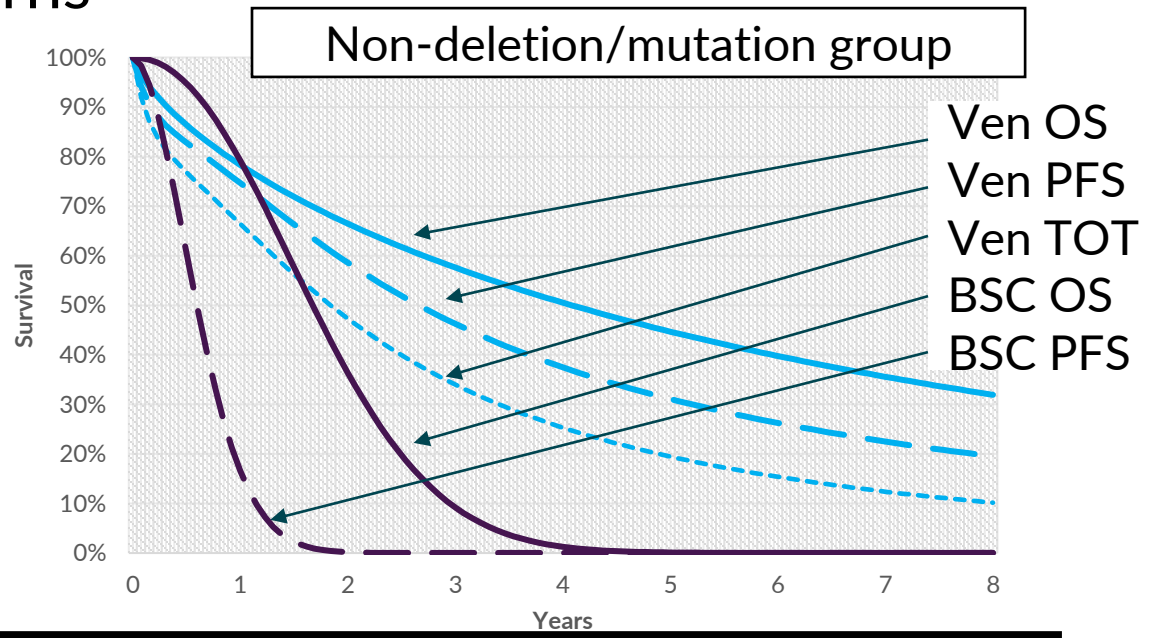
- Only way to measure progression in clinical practice is by time on treatment
- Patients may show early disease progression while still benefitting from and remaining on treatment

Abbreviations: PFS, progression-free survival; SACT, Systemic Anti-Cancer Therapy; BSC, best supportive care

Use of time on treatment data to model progression-free survival [2]

Company's new approach and ERG's concerns





ERG comments

- Now inconsistent with BSC modelling because PFS and TOT not modelled separately for BSC
- Unclear why company only used data from 2 of 3 venetoclax trials to calculate hazard ratios
- Unclear why company estimated HR separately for each deletion/mutation group – this will reduce PFS in non-del/mut population, decreasing efficacy of venetoclax
- Hazard ratio may actually vary over time but single HR used here
- Company applied HR actually as a risk ratio – ERG has corrected this error

Is the company's updated modelling of PFS and TOT for venetoclax appropriate?

Abbreviations: PFS, progression-free survival; SACT, Systemic Anti-Cancer Therapy; BSC, best supportive care; HR, hazard ratio

Cost-effectiveness results

Table 8 Incremental base case results, including PAS for venetoclax

Scenario	Incremental costs	Incremental QALYs	Deterministic ICER (venetoclax v BSC) (£/QALY)	Probabilistic ICER (venetoclax v BSC) (£/QALY)
Company's updated base case – deletion/mutation group	[redacted]	[redacted]	£44,121	£45,312
Company's updated base case – non-deletion/mutation group	[redacted]	[redacted]	£46,624	£48,290

Results do not include confidential commercial discounts for other treatments. Including these discounts increases the ICER and will be considered by committee in part 2.

No ERG base case presented as ERG considers it is not able to robustly improve on the company's assumptions — 4 scenarios provided

Abbreviations: PAS, patient access scheme; ICER, incremental-cost effectiveness ratio; QALY, quality-adjusted life year; BSC, best supportive care

Company's scenario analyses
Alternative extrapolations for OS and TOT

Results do not include confidential commercial discounts for other treatments

Table 9 Company's scenario analyses results, including PAS for venetoclax

Scenario	ICER (venetoclax v BSC) (£/QALY) Deletion/mutation group	ICER (venetoclax v BSC) (£/QALY) Non-deletion/mutation group
Company's updated base case	**£44,121**	**£46,624**
Using normal spline 2-knots for OS (dependent fit)	£40,262	£44,587
Using log-normal for OS (dependent fit)	£36,888	£40,478
Using log-logistic for OS (dependent fit)	£38,679	£42,043
Using odds spline 2-knot for OS (dependent fit)	£40,651	£44,703
Using hazard spline 1-knot for OS (dependent fit)	£40,138	£42,479
Using hazard spline 2-knot for ToT (dependent fit)	£39,202	£42,177
Using Weibull for ToT (dependent fit)	£45,099	£49,069
Using odds spline 2-knot for ToT (dependent fit)	£45,484	£48,078

Abbreviations: ICER, incremental-cost effectiveness ratio; BSC, best supportive care; QALY, quality-adjusted life year; OS, overall survival; TOT, time on treatment; PAS, patient access scheme

Summary of company base case and ERG scenarios

Table 10 Company base case and ERG scenario assumptions

Assumption	Company base case	ERG scenario
Patients having rituximab	Benefits included within SACT CDF data – additional costs not included	Included cost of rituximab over 6 months for 20% of patient population
Comparison of venetoclax and BSC	Two comparators are not directly compared in 1 survival analysis model	Estimated naïve hazard ratio (0.57) for venetoclax relative to BSC (from SACT CDF+EAMS compared with Rigolin+Aarup), and applied this to BSC extrapolations to derive those for venetoclax
Post-progression survival modelling	Updated survival modelling includes a much lower post-progression survival period than original base case	Transition probabilities amended to reduce venetoclax post-progression survival to align with Eyre paper
PFS and TOT	SACT CDF TOT data used for TOT curve. PFS curve estimated by applying hazard ratio to TOT curve	Removed applied hazard ratio for difference between PFS and TOT to show influence of the change

ERG could not present scenario using BSC modelling from TA487 as it could not be implemented in the company's technical engagement model

Abbreviations: BSC, best supportive care; SACT, Systemic Anti-Cancer Therapy

ERG's scenario analyses [1] Deletion/mutation group

Table 11 ERG's scenario analyses results, including PAS for venetoclax

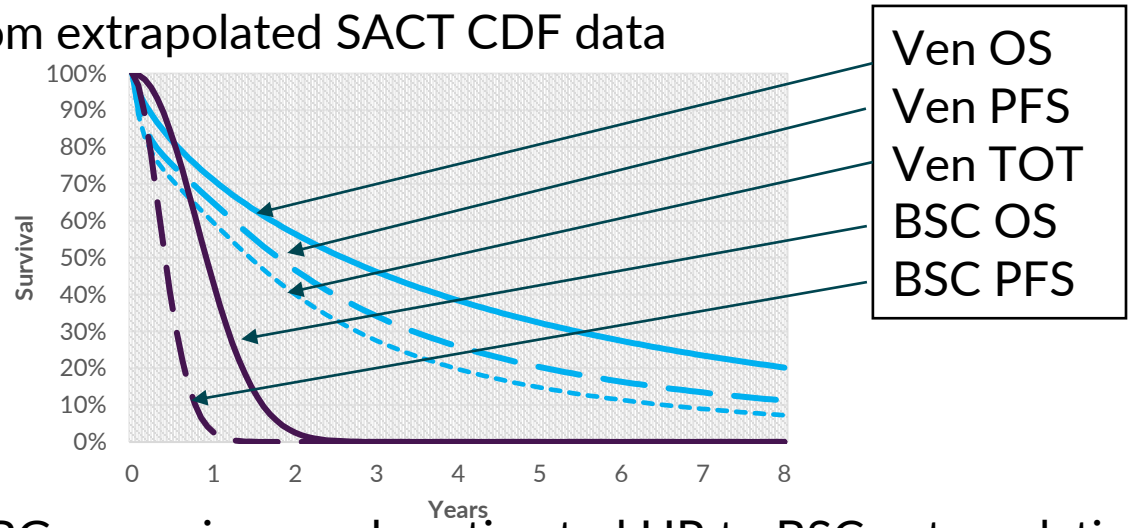
Scenario	Incremental costs	Incremental QALYs	ICER (venetoclax v BSC) (£/QALY)
Company's updated base case	[redacted]	[redacted]	**£44,121**
ERG corrected (applying difference between TOT and PFS as HR instead of risk ratio)	[redacted]	[redacted]	**£44,237**
1. Add costs for rituximab to venetoclax arm	[redacted]	[redacted]	£45,220
2. Estimated naïve hazard ratio (0.57) for venetoclax relative to BSC (from SACT CDF+EAMS compared with Rigolin+Aarup), and applied this to BSC extrapolations to derive those for venetoclax	[redacted]	[redacted]	£72,038
3. Reducing venetoclax post-progression survival to align with Eyre paper	[redacted]	[redacted]	£59,439
4. Setting PFS=TOT for venetoclax	[redacted]	[redacted]	£45,300

Results do not include confidential commercial discounts for other treatments

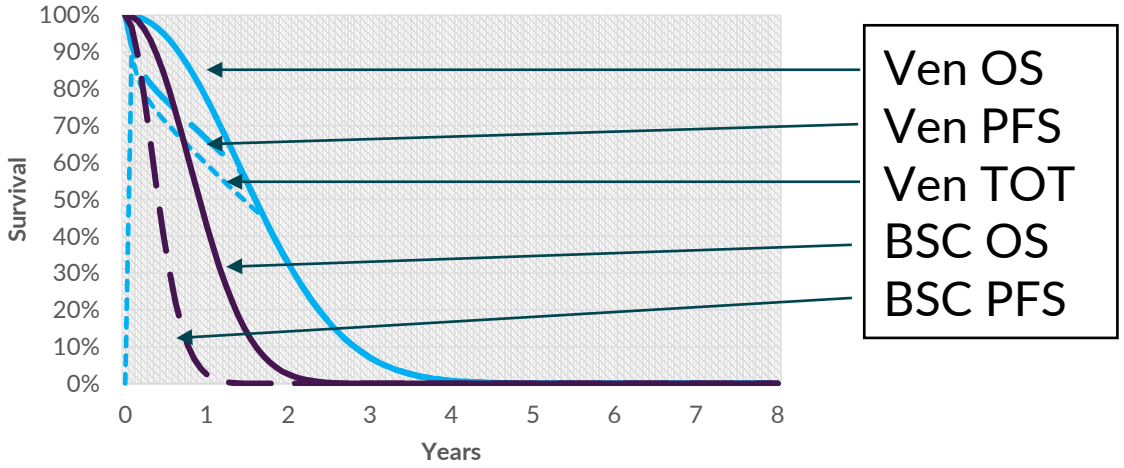
Abbreviations: ICER, incremental-cost effectiveness ratio; BSC, best supportive care; QALY, quality-adjusted life year; PAS, patient access scheme; SACT, Systemic Anti-Cancer Therapy

ERG's scenario analyses [2]
Deletion/mutation group – visual summary

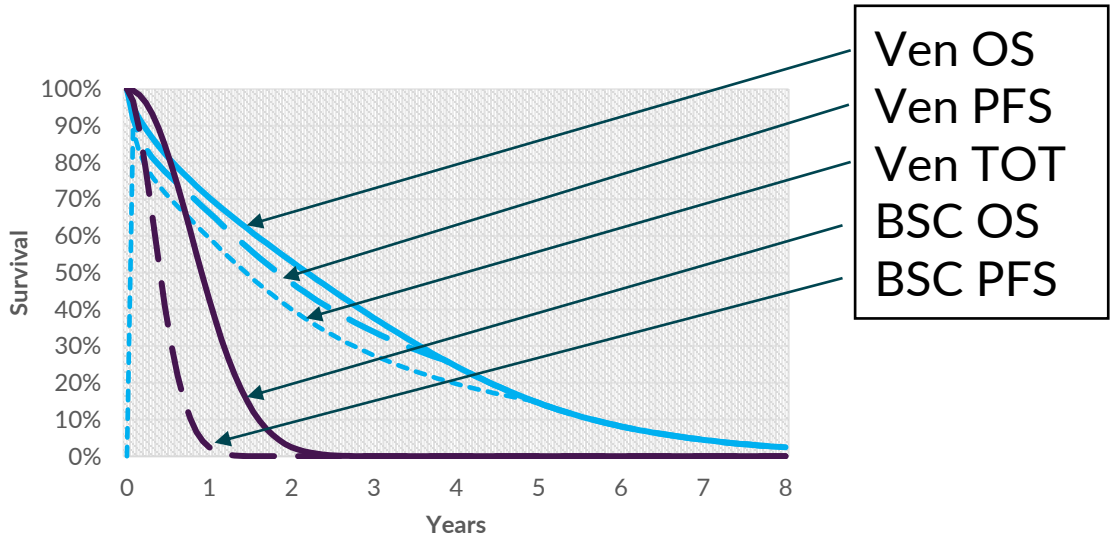
Company base case – venetoclax curves from extrapolated SACT CDF data



ERG scenario – apply estimated HR to BSC extrapolation – lowers survival estimate



ERG scenario – reducing venetoclax post-progression survival to align with Eyre paper



ERG's scenario analyses [3] Non-deletion/mutation group

Table 12 ERG's scenario analyses results, including PAS for venetoclax

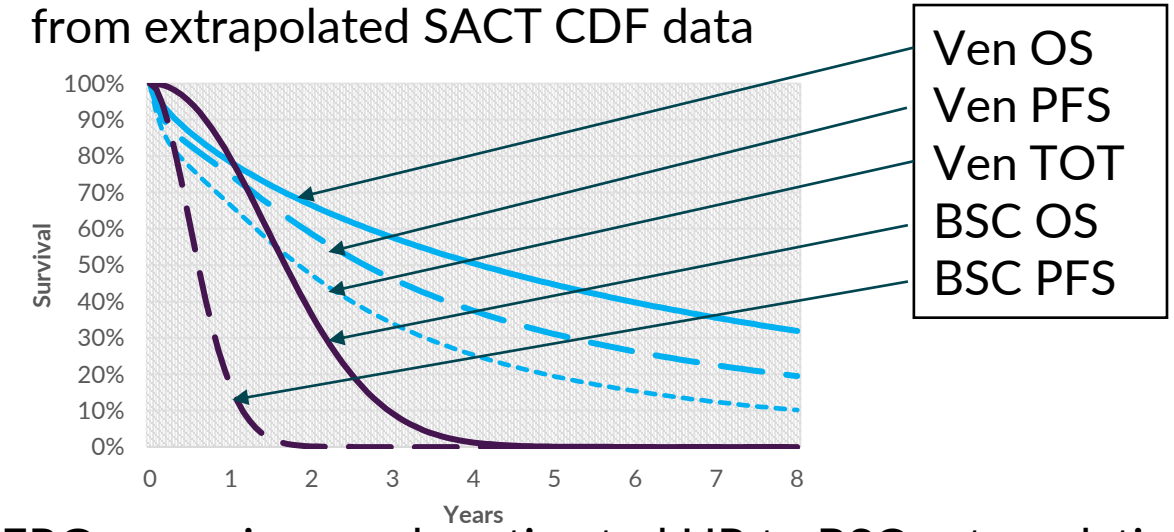
Scenario	Incremental costs	Incremental QALYs	ICER (venetoclax v BSC) (£/QALY)
Company's updated base case	[redacted]	[redacted]	**£46,624**
ERG corrected (applying difference between TOT and PFS as HR instead of risk ratio)	[redacted]	[redacted]	**£46,776**
1. Add costs for rituximab to venetoclax arm	[redacted]	[redacted]	£47,685
2. Estimated naïve hazard ratio (0.57) for venetoclax relative to BSC (from SACT CDF+EAMS compared with Rigolin+Aarup), and applied this to BSC extrapolations to derive those for venetoclax	[redacted]	[redacted]	£74,056
3. Combining OS transition probabilities to estimate long term OS for venetoclax	[redacted]	[redacted]	£62,862
4. Setting PFS=TOT for venetoclax	[redacted]	[redacted]	£49,024

Results do not include confidential commercial discounts for comparators

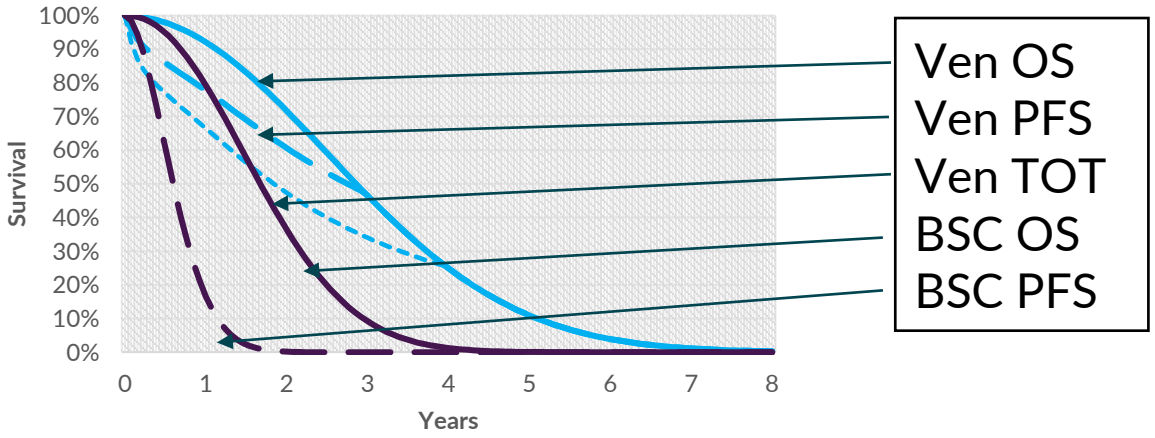
Abbreviations: ICER, incremental-cost effectiveness ratio; BSC, best supportive care; QALY, quality-adjusted life year; PAS, patient access scheme; SACT, Systemic Anti-Cancer Therapy

ERG's scenario analyses [4]
Non deletion/mutation group – visual summary

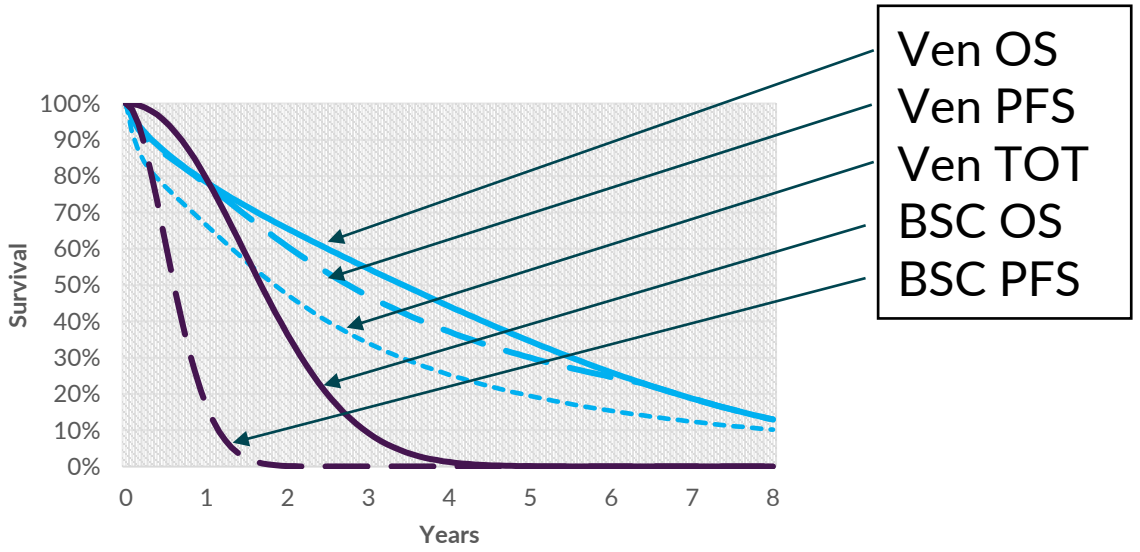
Company base case - venetoclax curves from extrapolated SACT CDF data



ERG scenario – apply estimated HR to BSC extrapolation – lowers survival estimate



ERG scenario – reducing venetoclax post-progression survival to align with Eyre paper



Key issues

Key: Large impact  Small/moderate impact  Unknown impact 

Table 13 Key issues

Issue	Resolved?	ICER impact
Generalisability of venetoclax SACT CDF data to UK practice	No – for discussion	
Uncertainty around best supportive care data	No – for discussion	
Lack of matching-adjusted or naïve statistical comparison of venetoclax and best supportive care	No – for discussion	
Source of baseline characteristics inputs	Yes	
Venetoclax post-progression survival modelling	No – for discussion	
Inconsistent modelling of survival data between venetoclax and best supportive care	Partially – for discussion	
Use of time on treatment data to model progression-free survival for venetoclax	Partially – for discussion	

Other considerations

Equality considerations

- A stakeholder identified that CLL is a disease of the elderly and if venetoclax is withdrawn, this could have a disproportionate effect for older people

Are there any equality considerations?

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