For public

Ibrutinib for treating chronic lymphocytic leukaemia [ID749]

Single Technology Appraisal

3rd meeting: 6 August 2016

2nd meeting: 6 April 2016

1st meeting: 3 February 2016

Technology Appraisal Committee B

Lead team: Ray Armstrong, Ken Stein, Dani Preedy

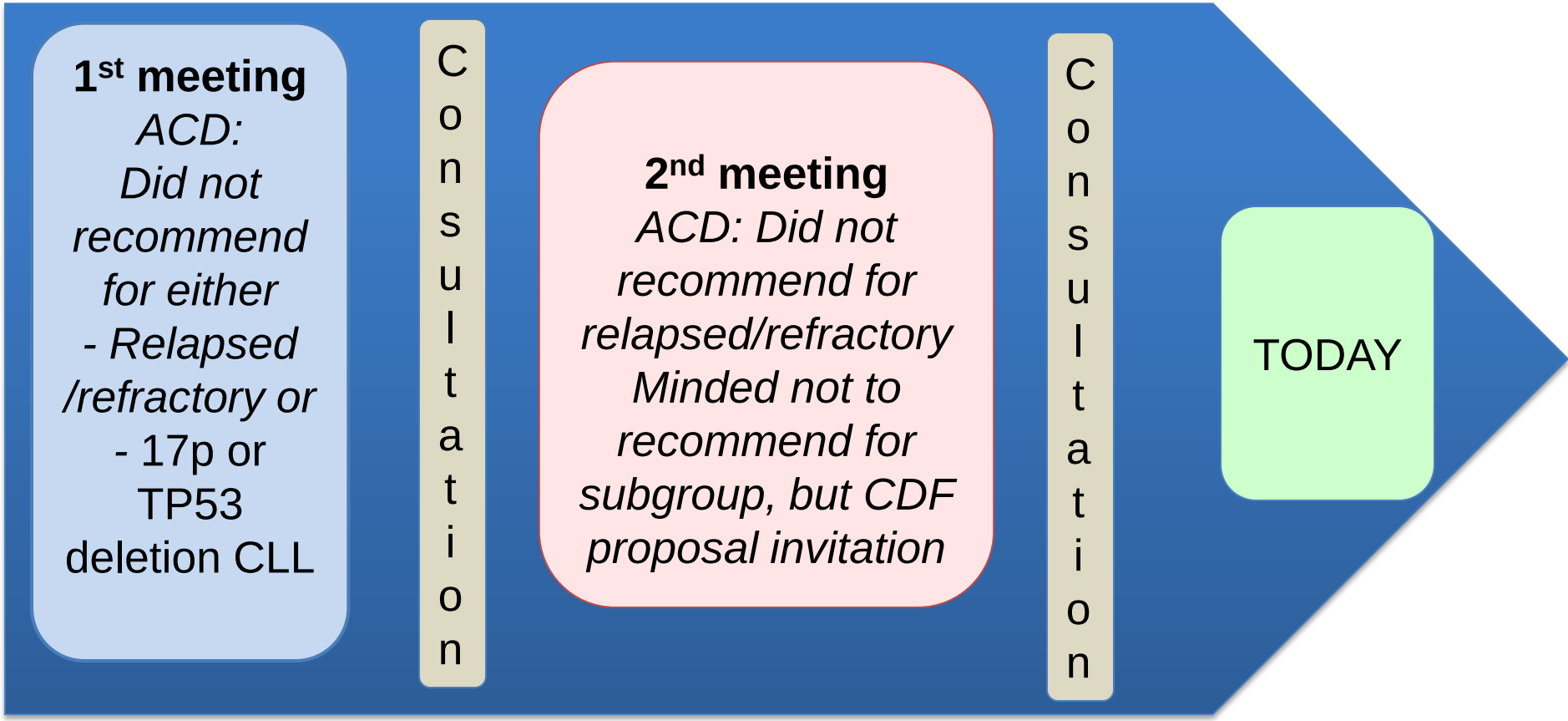
Evidence Review Group: Aberdeen HTA Group

Company: Janssen

NICE team: Raisa Sidhu

Experts: George Follows, Peter Hillmen, Molly Fletcher and Nick York

History of appraisal



ACD2: preliminary recommendations

1.1: Ibrutinib is not recommended for treating chronic lymphocytic leukaemia in adults without a 17p deletion or TP53 mutation.

1.2: Appraisal committee is minded not to recommend ibrutinib as an option for treating chronic lymphocytic leukaemia in adults with a 17p deletion or TP53 mutation. The committee invites the company to submit a proposal for inclusion in the Cancer Drugs Fund.

Since consultation, company has chosen not to accept invitation and has not submitted a CDF proposal noting:
'do not believe that better data than this already available data source could be obtained through the CDF'

Ibrutinib

- Inhibits Bruton's tyrosine kinase
- Marketing authorisation:
  - 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy
    - 1st line
    - 2nd line
  - At least 1 prior therapy
    - 2nd line
- Oral: 3 once daily
- £55,954.50 per year
- Confidential patient access scheme (PAS)

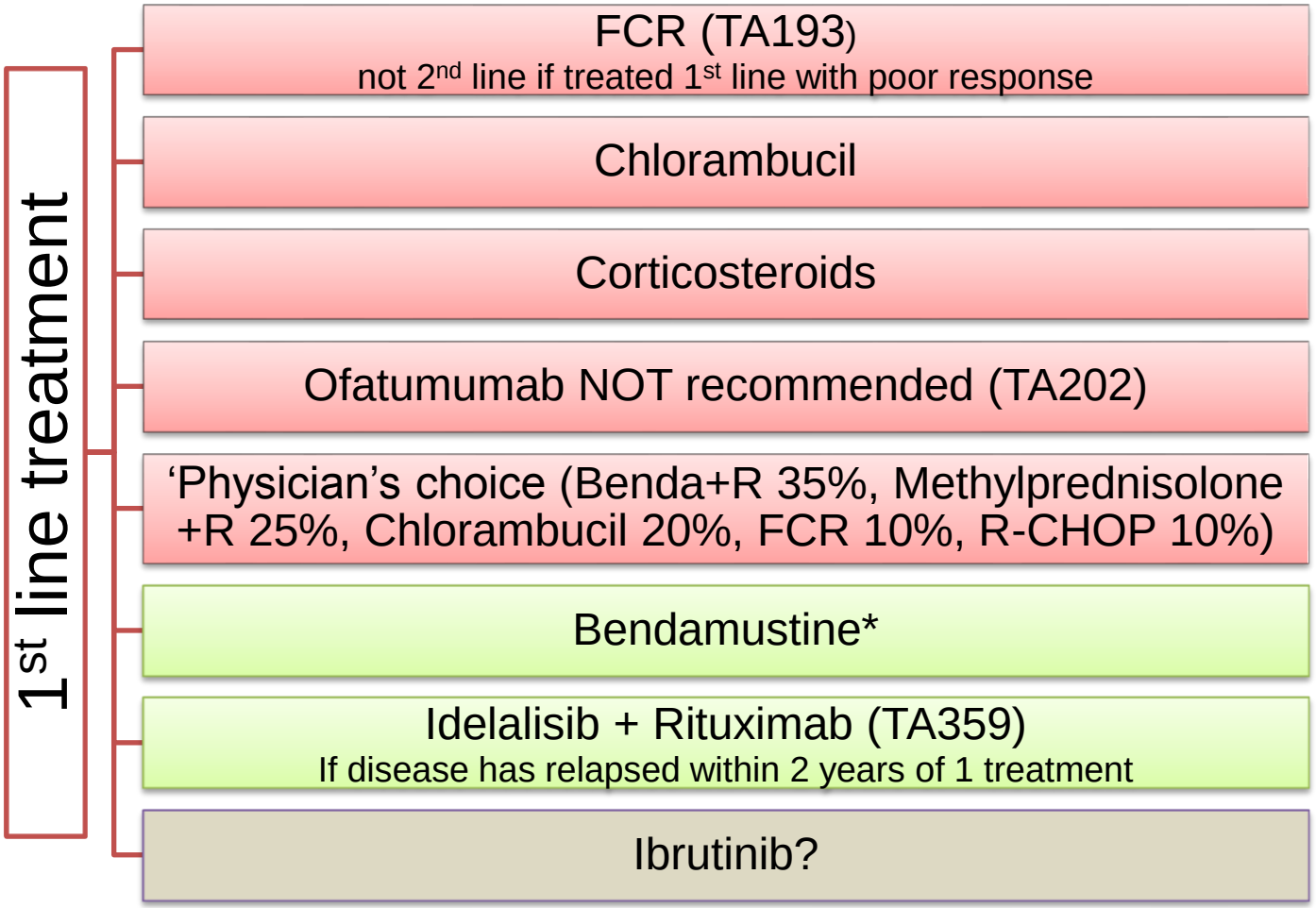
Scope and Decision Problem

Population	Relapsed or refractory CLL		17p or TP53 deletion CLL
Type	NICE Scope	Company Submission	NICE scope + Company
Intervention	Ibrutinib		
Comparator	• FCR • Idelalisib +R • Bendamustine (+/-R) • Chlorambucil (+/- R) • Corticosteroids + R • Rituximab alone for refractory disease • BSC	<u>Base case</u> • Physician's choice (blended comparator) <u>Additional analysis</u> • Idelalisib + R • Bendamustine (+/-R) • Ofatumumab	• Alemtuzumab + corticosteroids • Idelalisib + R • BSC
Outcomes	Overall survival; progression-free survival; response rates; adverse effects of treatment; HRQoL		

BSC - best supportive care; FCR – Fludarabine, cyclophosphamide and rituximab; R - Rituximab

Relapsed Refractory (Without 17p deletion or TP53 mutation) 2nd line treatment and place for ibrutinib

Comparators agreed (green) not agreed (red) by Committee



** Recommended by NICE 1st line only*

‘Physician’s choice’
company comments

- “..most relevant comparator for ibrutinib, as demonstrated by the lack of a standard of care”
- “..composition reflects the mix and proportion of therapies that were used in the physician’s choice arm of Österborg, 2014 but was adjusted further to include only treatments relevant to UK clinical practice”
- 43 patients in trial
- ‘Patients in the physician’s choice arm who developed disease progression during the study could receive OFA salvage therapy for up to 12 months of treatment.’ 46% of patients died in ofatumumab arm vs. 63% in physician choice arm.
- Not adjusted for cross-over, but conservative

Ref: BresMed. Health Technology Assessment Strategy for Ibrutinib for the Treatment of Relapsed/Refractory CLL Summary Report Advisory Board, 2015.
Osterborg abstracts only 2014
Osterborg et al. Leukemia & Lymphoma, 57:9, 2037-2046, 2016

Physician's choice in submission and in Osterborg

Contents

- Bendamustine + rituximab – 35%
- Methylprednisolone + rituximab – 25%
- Chlorambucil – 20%
- Fludarabine and cyclophosphamide + rituximab (FCR) – 10%
- Cyclophosamide, doxorubicin, vincristine and prednisolone + rituximab (R-CHOP) – 10%

Table 2. Treatment regimens administered in the PC arm.

Treatment regimen	PC ($n = 43$)
Alemtuzumab-based therapy, *n* (%)	11 (26)
Combination therapy[a]	5 (12)
Monotherapy	6 (14)
Alkylator-based therapy, *n* (%)	12 (28)
Combination therapy	12 (28)
Monotherapy	0
Bendamustine-based therapy, *n* (%)	5 (12)
Combination therapy	4 (9)
Monotherapy	1 (2)
Chlorambucil-based therapy, *n* (%)	4 (9)
Combination therapy	3 (7)
Monotherapy	1 (2)
Fludarabine-based therapy, *n* (%)	6 (14)
Combination therapy	5 (12)
Monotherapy	1 (2)
Glucocorticoid-based therapy, *n* (%)	3 (7)
Combination therapy	0
Monotherapy	3 (7)
Rituximab-based therapy ± prednisone therapy	2 (5)
Combination therapy	2 (5)
Monotherapy	0

PC, physicians' choice.

Patients in the PC treatment arm could have received more than 1 study drug. Treatment regimens in the PC arm were classified using a hierarchical order (for example, regimens containing fludarabine and alemtuzumab were classified as alemtuzumab-based therapy rather than fludarabine-based therapy).

1st line treatments and place for ibrutinib **With** 17p deletion or TP53 mutation

Alemtuzumab +/- corticosteroids	Idelalisib + rituximab (TA359)	Best supportive care	**Ibrutinib?**

From summary of product characteristics for idelalisib as of June 2016: “Idelalisib is indicated in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL):

- who have received at least one prior therapy, or
- for continuing treatment in patients with 17p deletion or *TP53* mutation who were unsuitable for chemo-immunotherapy and who had already initiated Idelalisib as first line treatment

Note: provisional EMA advice not to start treatment with idelalisib in this subpopulation

Key trial RESONATE open label RCT
comparator not in NICE scope

Relapsed or refractory CLL with at least 1 prior therapy, ECOG 0 or 1 and inappropriate for purine analogues (e.g. fludarabine) included 127 with 17p deletion

Ibrutinib (n=195)

Ofatumumab (n=196)
116 crossed over

1° endpoint: PFS
Assessed independently + locally until interim analysis then only locally

Tx duration	Ibrutinib until disease progression; Ofatumumab up to 6 months only
Crossover	Permitted at disease progression; 116/191
Quality of life	EORTC QLQ-30, FACiT-F, EQ-5D
Stopped	Stopped early at planned interim analysis 146 PFS events
When analysed	9.4 months median interim analysis and **trial stopped early**; 16.0 months median after trial post study monitoring 30 month data provided at last meeting but not in modelling

Summary of RESONATE results

✔ = chosen for modelling base case

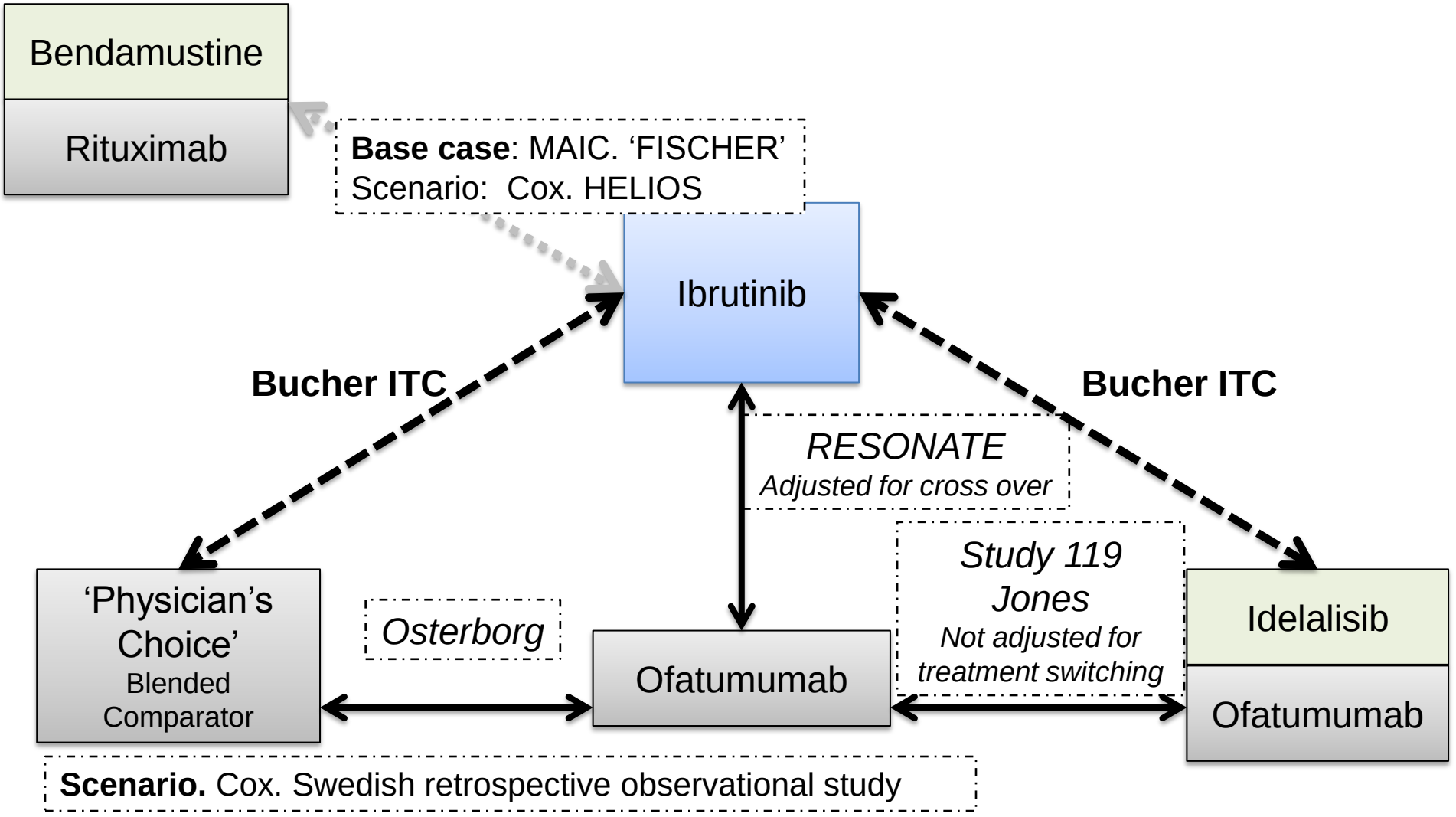
	Whole population		Deletion mutation	
		Median follow-up (months)		Median follow-up (months)
Progression free survival				
Ibrutinib median PFS	Not reached	9.4	Not reached	
Ofatumumab median PFS	8.1	9.4	5.8	
Hazard ratio (ITT)	0.22	9.4	0.25	9.4
Hazard ratio (ITT)	xxx ✔	16.0	xxx ✔	16.0
Overall survival				
Ibrutinib median OS	Not reached	16.0		
Ofatumumab median OS	Not reached	16.0		
Hazard ratio (ITT)	xxx	16.0	Not available	
Hazard ratio (Rank Preserving Structural Failure Time, RPSFT)	xxx ✔	16.0	xxx ✔	16.0

Summary of evidence for ibrutinib

for 17p no evidence for 1st line or for TP53

	Relapsed or refractory fludarabine-inappropriate	Treatment-naïve and have 17p deletion or TP53 mutation
RCTs	RESONATE	RESONATE - 2nd line data only - 17p deletion only
Uncontrolled Not randomised	1. PCYC1102 2. PCYC1103 3. PCYC117 4. Farooqui, 2014	Farooqui (n=33) - 1st line only

Company's results: ibrutinib vs. comparators



ITC = indirect treatment comparison
MAIC = Matched adjusted indirect comparison
Cox= Proportional hazard modelling

Note: Idelalisib + **rituximab** recommended by NICE on basis of 'study 116'
HR OS: 0.34, 95% CI 0.19 to 0.60, p=<0.001

AA

Indirect comparison analyses and results

✔ = chosen for modelling base case ★ preferred by Committee

Comparator	Used in model	Type	Data ibrutinib	Data comparator	HR PFS (95% CI)	HR OS (95% CI)
Bendamustine + rituximab	Base-case	MAIC 22 variables n=30	RESONATE Patient level data	Fischer (2011), 1 arm trial of **bendamustine + R,** study level data	**xxx** ✔	**xxx** ✔
	Company Scenario	Cox	RESONATE n=195 Patient level data	HELIOS, Ibrutinib+ benda+R vs. **bendamustine +R** Patient level data	**xxx** ★	**xxx** ★
Idelalisib + ofatumumab	Base-case	ITC Bucher method	RESONATE adjusted for cross over	Jones, 2015 not adjusted for treatment switching	**0.39** (0.23- 0.67) ✔	**0.50** (0.24 - 1.04) ✔
	ERG scenario	ITC Bucher method	RESONATE **Not** adjusted for crossover	Jones, 2015 Not adjusted for switching	0.39 (0.23- 0.67) ★	0.58 (0.26–1.30) ★

Committee's conclusions clinical

Populations	1. CLL without a 17p deletion or TP53 mutation who have had at least 1 round of previous treatment, and 2. CLL with a 17p deletion or TP53 mutation (1st or 2nd)
Comparators	1. Previously treated: Idelalisib + R, bendamustine 2. TP53 and 17p: Idelalisib +R Not : Physician's choice and ofatumumab FCR, chlorambucil, rituximab monotherapy, corticosteroids
RESONATE	Data immature medians for OS and PFS not reached; effective vs. ofatumuamb, but uncertain
Cross over	Reasonable to adjust RESONATE for cross-over, but not without adjusting other trials in network
Bendamustine	Committee preferred approach using Cox
Idelalisib	Study 119 (Jones et al): Idela+Ofa, not idela+Rituximab; ofatumumab as proxy for rituximab accepted by Committee
TP mutation	Generalise data from 17p deletion to TP53
Results from network	Ibrutinib more effective than bendamustine Ibrutinib benefit over idela+R unclear Ibrutinib better tolerated than idela+R

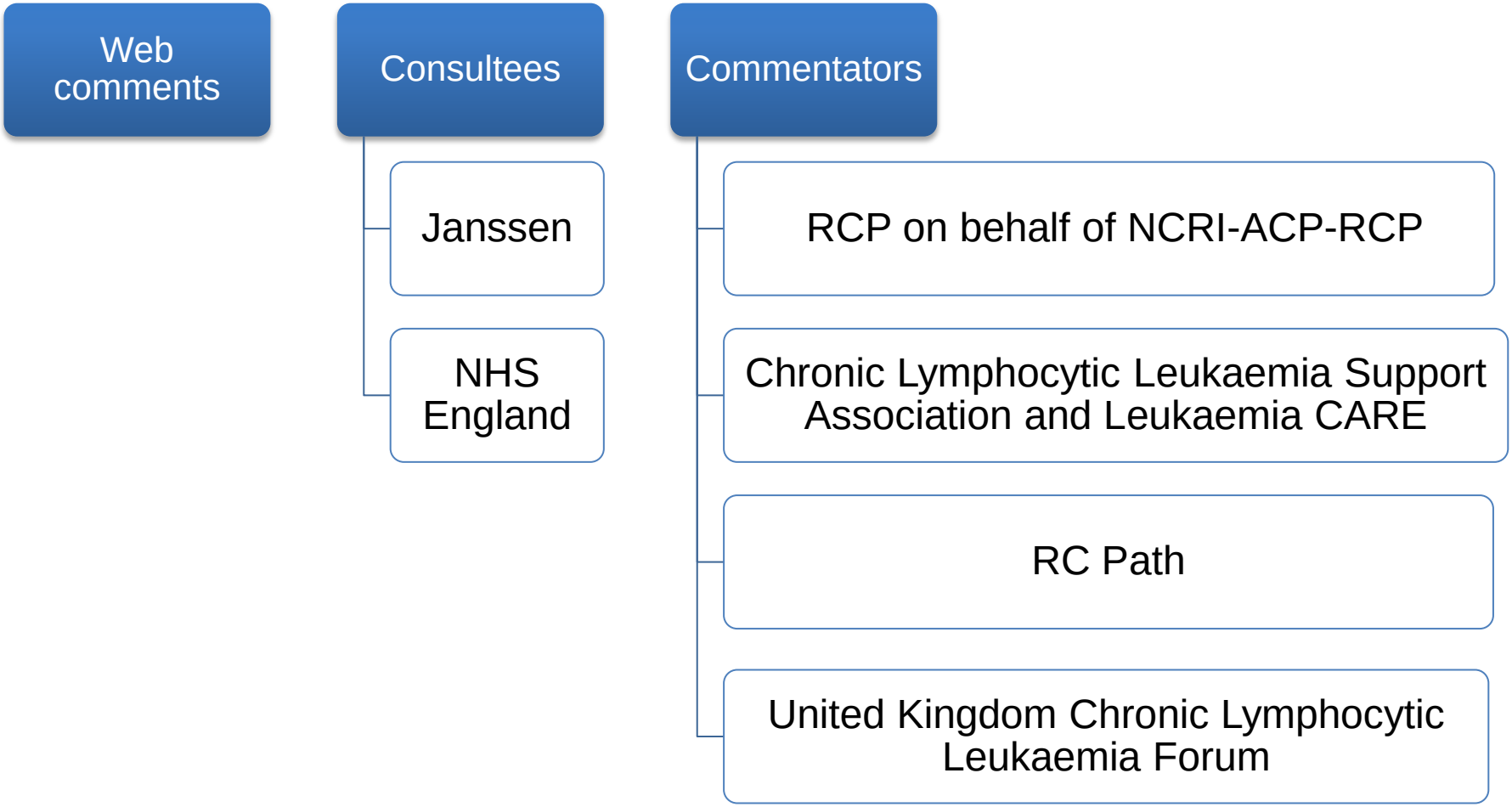
Committee's conclusions cost

Extrapolating PFS	Key driver of cost effectiveness Considerable extrapolation Committee noted 'improbably long periods in progressed disease' with company's preferred **Weibull** function Committee noted ERG suggested **exponential** function provided a more credible period of time in progressed disease
Extrapolating overall survival	Original company model predicted 10 times as many patients who have ibrutinib would be alive after 20 years compared with patients having idelalisib + rituximab: improbable During consultation to ACD1 company agreed with committee that Weibull function provided best fit
Treatment duration	Time to progression determines treatment duration, which in turn determines the cost of treatment; treatment beyond progression occurs in the NHS
Benefit over time	Company's base case assumes ibrutinib benefit constant over time; committee considered scenario limiting benefit to 5 years
Key ERG's analyses	Using the exponential function to extrapolate the overall survival and progression-free Kaplan-Meier survival curves from RESONATE and not adjusting for crossover

Committee's conclusions cost (2)

Costs	Of routine follow-up determined by disease response to treatment as measured in RESONATE; corrected by company
Utilities	After 1st consultation, the company provided age-adjusted utility values, and chose a lower utility value in the post progression state (0.60)
End of life	Criteria met, on balance
Innovation	Yes

Comments on ACD2



Main points from consultation
+ if addressed by Janssen

Main points	New evidence?
Magnitude of ibrutinib's treatment effect	No, 30 months data seen previously (Also 9.4 month and 16 month) **No change to model**
Comparators	Marketing data **No change to model**
Adjusting for cross over	Median overall survival from a trial with ofatumumab as a comparator 'Wierda et al.' 2010. **No change to model**
17p deletion/TP53 mutation	Abstract from European Haematology Association (EHA) Congress **No change to model**

Magnitude of ibrutinib's treatment effect

Immature data

Consideration	Consultation comments
Immature data Median PFS and OS not reached; reflects successful treatment but uncertainty because of greater proportion of the modelled time horizon depended on extrapolations	At a median of 30 months follow-up in the RESONATE trial, patients treated with ibrutinib have not yet reached median OS and xxx of patients remain alive Indicates significant step forward for patients; inappropriate to view as uncertainty.

Consideration	Consultation comments
Considerable uncertainty around the PFS and OS benefits of ibrutinib compared idelalisib plus rituximab; ibrutinib likely to offer preferable toxicity profile • NMA based on comparison with idelalisib plus ofatumumab; unable to establish equivalence with I+R • Concerns with immature data **Uncertain benefits of ibrutinib compared with I+R unlikely to warrant the significant additional acquisition cost**	• Idelalisib toxicity – significant concern, life threatening infections • Ibrutinib 'clearly superior both in terms of toxicity and efficacy' • 'Most effective drug for treating relapsed / refractory CLL with an excellent side effect profile' • Appropriate to assume I+O equivalent to I+R • *Company:* • Median OS not reached at 30 month follow up; unprecedented benefits. Idelalisib recommended with a median OS of 21.6 months Methodological challenges resulted from a lack of publically available data on I+R trials; represents uncertainty that Janssen cannot address

⊙ Issues to discuss:

- Does Committee think ibrutinib is more effective than idelalisib?
- Does Committee think the current estimates over or under estimate level of effect?

Comparators

Comparators company comments

- Company submitted ibrutinib to NICE ‘7 days before idelalsib guidance released’
  - N.b. Janssen requested that appraisal be delayed to await more mature data; NICE agreed.
- ‘Clinicians agree that both physicians choice and ofatumumab relevant comparators’
  - N.b. committee has concluded that neither are relevant comparators
- ‘Unreasonable for the committee to expect Janssen to have been able to generate evidence against IR. It is unfair …’
  - N.b. Indirect comparisons frequent in NICE appraisals.
- ‘Latest market research data from May 2016 shows xxx of patients receiving idelalisib, xxx bendamustine and the remainder a mix of chemoimmunotherapy regimens that we have previously described as physicians’ choice’.
  - N.b physicians’ choice in submission includes bendamustine

Contraindications and special warnings

SPC	**Idelalisib 24 Jun 2016**	**Ibrutinib 1 Jun 2016**
Contra-indications	Hypersensitivity	Hypersensitivity, St. John's Wort
Bleeding-related	None	Major haemorrhagic events, some fatal. Warfarin or other vitamin K antagonists should not be administered with ibrutinib
Infections	Infections, some fatal. 'Should not be initiated in patients with any evidence of ongoing systemic bacterial, fungal, or viral infection. 'Prophylaxis for Pneumocystis jirovecii pneumonia should be administered to all patients throughout treatment.'	'Patients should be monitored for fever, neutropenia and infections and appropriate anti-infective therapy should be instituted as indicated'
Liver	Liver function tests in all patients every 2 weeks for the first 3 months	None

Comparators previously treated population

Comparator	ACD Considerations	Consultation comments
Idelalisib + rituximab	**Main comparator.** In the absence of ibrutinib, clinicians would offer idelalisib + rituximab	Less likely to be used because of infection-related deaths
Bendamustine	No longer available through CDF; difficult to obtain, but offered with rituximab for some patients	Bendamustine is not available in England for this indication *n.b. marketing data as of May 2016 still used*
Ofatumumab	No longer available through CDF Not recommended by NICE Not a comparator	Only 'replaced' when ibrutinib became available; only approved and funded drug when trial started
Physician's choice (includes bendamustine)	Not representative of UK treatments; blended comparator Not a comparator	Company maintains it is relevant as no single standard of care; not a blended comparator as taken from single trial

⊙ Issues to discuss:

- Has the committee seen evidence or arguments to change its decision on each of these 4 comparators in this population?

Comparators untreated population with 17p/TP53 mutation

Comparator	ACD Considerations	Consultation comments
Alemtuzumab	Marketing authorisation now limited only to MS so difficult to obtain; not a comparator	No comments
Idelalisib + rituximab (I+R)	Recommended by NICE, but provisional EMA advice to not start treatment with I+R in this population No other treatment options, and company did not provide any other comparison (such as best supportive care). Noting EMA advice provisional, I+R only available comparator	Idelalisib + rituximab 'entirely inappropriate' as instructed by MHRA not to use it for this indication

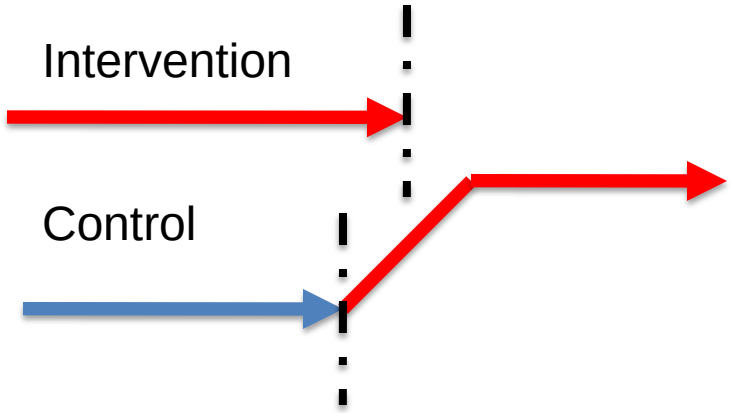
⊙ Issues to discuss:

- Does committee agree that idelalisib + rituximab not a comparator?
- Is physician choice a proxy for no treatment options?
- Is committee able to make a decision based on the evidence presented?

Adjusting for cross-over and treatment switching

‘Crossover’ and ‘treatment switching

1st line treatment

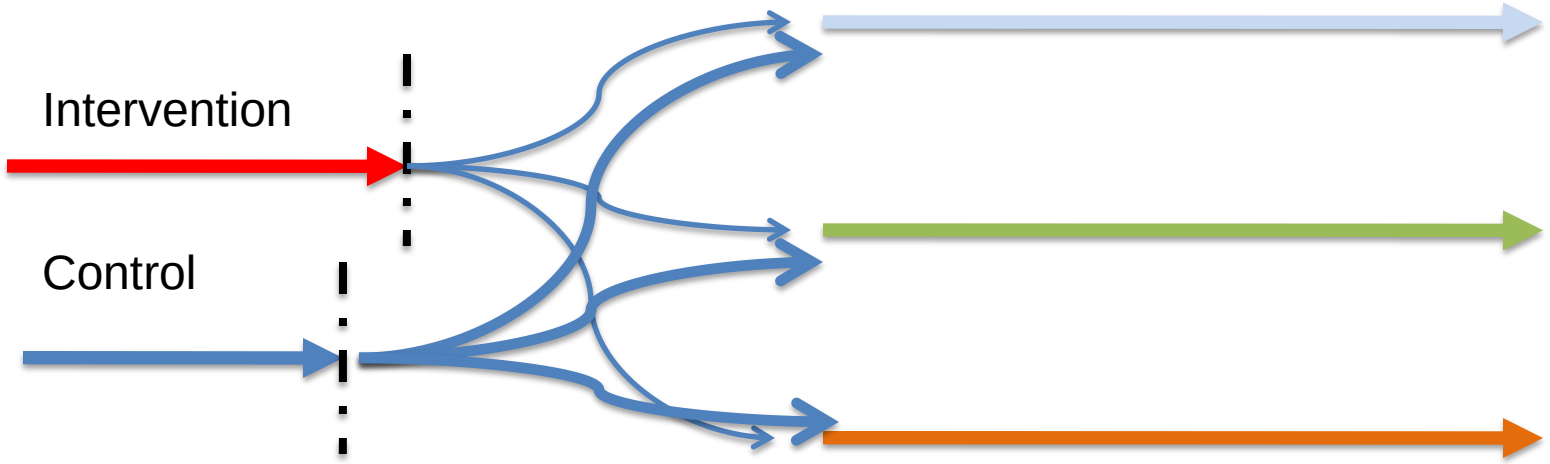


Progression = End of treatment
End of randomised portion of study

‘Crossover’ and ‘treatment switching

Ist line treatment

2nd, 3rd etc. line treatment



Progression = End of treatment
End of randomised portion of study

Adjusting for cross over

- ‘Janssen urges the Committee to follow NICE DSU guidance, …by accepting that adjustment for cross-over must be taken into account under these circumstances.’ (for RESONATE)

- ‘Study 119, the Committee has further stated that while no cross-over from the control arm (ofatumumab) to the experimental arm (IO) occurred, progressed patients may have left the trial and received other life-extending therapies. Adjustment for this type of “cross-over” (to treatment arms outside of the study) is not recommended by NICE DSU guidance, ..’

  - N.b. From Gilead (idelalisib) comments on 1st ACD:
    ‘119 trial was open label and patients receiving ofatumumab monotherapy were likely to switch to other available therapies. During the time of the study RESONATE was un-blinded and a compassionate use programme for ibrutinib was made available…. Patients that did not respond well to ofatumumab may have withdrawn from the study prior to their PFS assessment (because they had knowledge of the treatment they were receiving).’

Decision Support Unit

This TSD focuses upon adjusting survival time estimates in the presence of treatment switching from the control treatment onto the experimental treatment. In some circumstances it may be desirable to also adjust for switching from the experimental treatment onto the control treatment, or for switching onto other alternative therapies – although often such switches may represent realistic treatment pathways that do not require adjustment within an economic evaluation context. RPSFTM and IPE methods are designed to cope with

Don't need to adjust if:

1. 'realistic treatment pathways' i.e. treatments routinely offered in the NHS
2. Treatment does not extend life

If both are present, appropriate to adjust for treatment switching

⊙ Does the committee maintain that adjusting only RESONATE data for crossover is inappropriate?

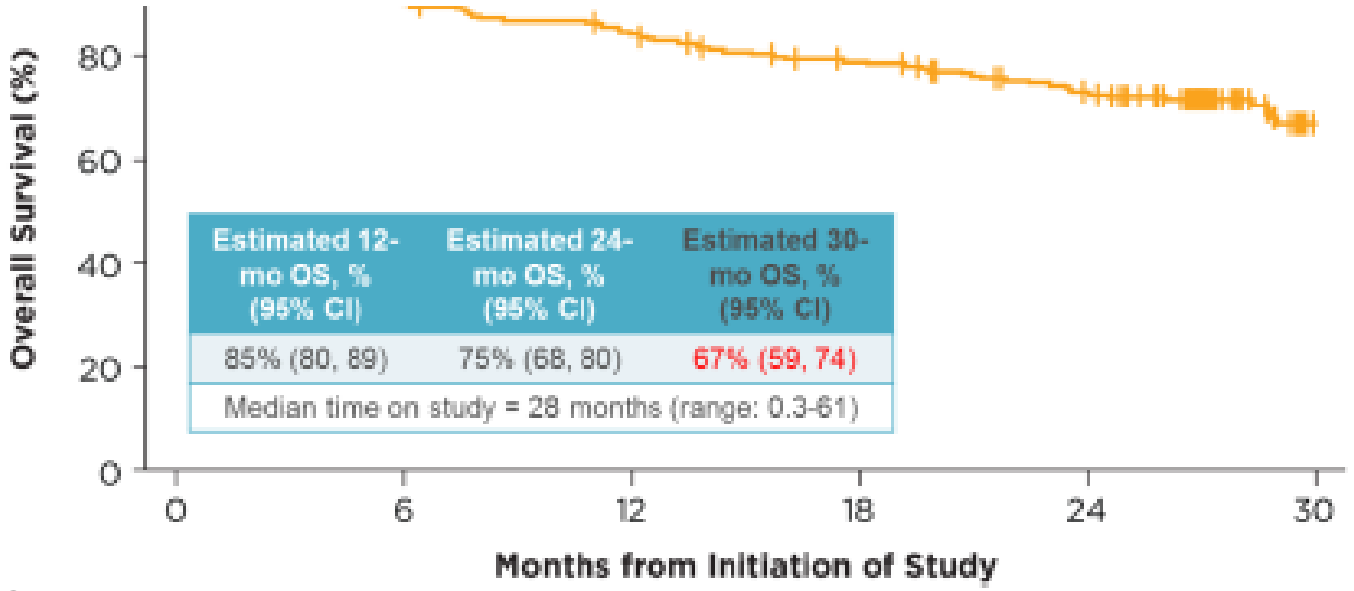
Ref: Nicholas R Latimer1 Keith R Abrams Nice DU Technical Support Document 16: Adjusting survival t ime estimates in the Presence of treatment switching
TSD = Technical support document P 46

17p deletion/TP53 mutation

New evidence 17p
company declines CDF

Company: 'By applying to the CDF and by nature of the disease, it is unlikely that data "certainty" in terms of reaching median PFS or median OS would be attainable over a short time period (e.g. two years).'

Instead, company submitted data from a study of 243 patients with 17p (both treatment naive and relapsed/refractory), showing median PFS and OS not yet met at 30 month follow-up.



Ref: Given by company only as 'Recent European Haematology Association (EHA) Congress'

Part 2