Zanubrutinib for treating Waldenström's macroglobulinaemia

Part 1 slides for public – redacted

Technology appraisal committee A, 7th June 2022

Chair: Jane Adam

Lead team: Steven Edwards, Andrew Champion, Richard Ballerand

Evidence assessment group: Kleijnen Systematic Reviews

Technical team: Alex Sampson, Mary Hughes, Janet Robertson

Company: BeiGene

NICE

ACM1 – Preliminary recommendation

Zanubrutinib is not recommended, within its marketing authorisation, for treating Waldenstrom's macroglobulinaemia in adults after at least 1 therapy or as first-line treatment when chemoimmunotherapy is unsuitable.

Key issues

At first meeting company included costs of follow on treatment with ibrutinib in SoC arm, **now removes these costs** but provides OS adjustment for SoC to remove potential benefits of follow on ibrutinib

Issue	ICER impact

Company: external validation of comparator (BR and DRC) modelled overall survival based on current practice in which follow-on ibrutinib is available (CDF only, now negative recommendation subject to appeal)
• Should survival for SoC (BR and DRC) be adjusted (as well as cost of ibrutinib) to remove potential treatment benefit from **ibrutinib as a subsequent treatment**? If so,
  • Is the method the company used to make the adjustment valid?
  • Is the value of the adjustment appropriate (adjusts so overall survival at 6 years in SoC arm will be 50% of that in zanubrutinib arm)
	Moderate. Removing this assumption increases the ICER

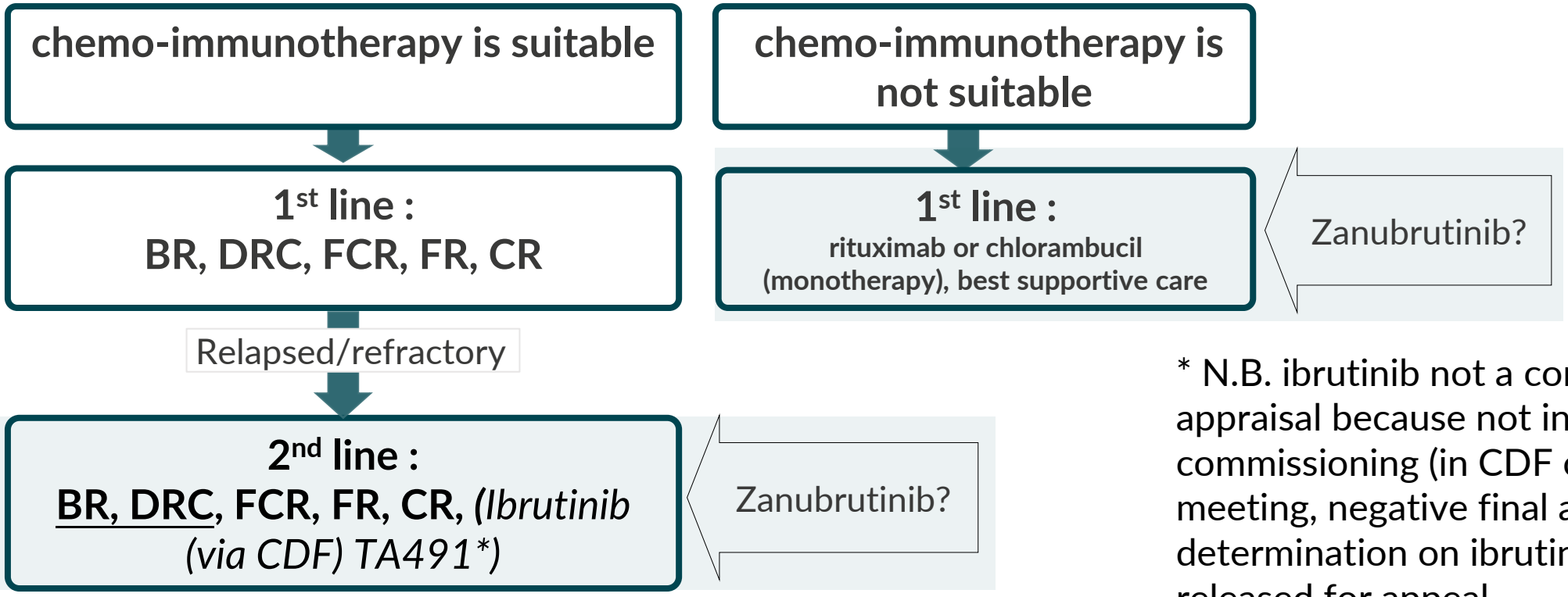
Company's base case is a weighted blended ICER of its pairwise comparisons of zanubrutinib vs. BR and vs. DRC • As the BR population was similar to the ASPEN population (mostly relapsed/refractory), is the **BR comparison, both the BR and DRC pairwise comparisons, or a blend of the two acceptable** for decision making?	Moderate Lowest ICER is vs. BR, Highest is vs. DRC

BR = bendamustine rituximab; DRC = dexamethasone, rituximab, and cyclophosphamide; MAIC = matching adjusted indirect comparisons; OS = overall survival; R/R = relapsed/refractory; SoC = standard of care; STC = simulated treatment comparisons; WM = Waldenström's macroglobulinaemia;

Zanubrutinib

Marketing authorisation	Monotherapy for people with Waldenström's macroglobulinaemia (WM) who have had at least one prior therapy, or first line for patients unsuitable for chemo-immunotherapy.
Mechanism of action	Selective inhibitor of Bruton's tyrosine kinase (BTK), stopping B-cell (lymphocyte) proliferation and promoting cell death
Dose	320 mg daily
Administration	Capsules, **taken orally**
List price	£4,928.65 (120 80mg capsules). Company has agreed a revised patient access scheme for zanubrutinib (since ACM1).

NHS Treatment pathway (as in NICE scope)



* N.B. ibrutinib not a comparator in this appraisal because not in routine commissioning (in CDF only). Since 1st meeting, negative final appraisal determination on ibrutinib has been released for appeal.

- **Committee conclusions at ACM1 (ACD sections 3.1, 3.2, 3.11):**
  - BR and DRC accepted as two treatments most commonly used (excluding ibrutinib)
  - Ibrutinib not a comparator + should not be included as follow on treatment-not established practice
  - BR and DRC are the key comparators for cost-effectiveness analysis
  - Remains an unmet need for an effective and well-tolerated oral therapy

BR = bendamustine rituximab; CDF = cancer drugs fund; DRC = dexamethasone, rituximab cyclophosphamide; FCR = fludarabine, cyclophosphamide rituximab; FR = fludarabine rituximab; CR = cladribine + rituximab

Sources of evidence

- No trial directly compared zanubrutinib with comparators (main trial of zanubrutinib compared with ibrutinib, but ibrutinib not a comparator for this appraisal)
- Data for BR and DRC came from different populations

	Intervention	Trial/study	Population	Follow up
	Zanubrutinib	**ASPEN vs ibrutinib** (Cohort 1)	• Treatment-naïve, chemo-immunotherapy **not** suitable) n/N=19/102 • Relapsed refractory n/N = 83/102	19.47 months
Comparators	Bendamustine rituximab (BR)	**Tedeschi et al. 2015**	Relapsed/refractory N=71	19 months
Comparators	Dexamethasone rituximab and cyclophosphamide (DRC)	**Dimopoulos et al. 2007/Kastritis et al. 2015**	Treatment-naïve (and for whom chemo-immunotherapy **is** suitable) N=72	23.4 months and 8 years respectively

- No evidence presented for comparators for the population who are treatment-naïve and for whom chemo-immunotherapy is not suitable (that is, rituximab or chlorambucil monotherapy)

BR = bendamustine rituximab; DRC = dexamethasone, rituximab, and cyclophosphamide

Recap of key evidence: indirect comparisons of OS & PFS

- 2 methods for indirect, unanchored comparisons; originally used MAIC, then STC. ERG noted both indirect comparisons highly uncertain
- Zanubrutinib improved OS and PFS against both BR and DRC, using both MAIC and STC with wide confidence intervals. Slightly more favourable results for zanubrutinib from STC, but broadly consistent results.
- Company assumed same treatment benefit for zanubrutinib in treatment naïve population (where chemo-immunotherapy is unsuitable) as relapsed/refractory (despite small numbers of patients in ASPEN and different comparators - rituximab or chlorambucil monotherapy)

	Progression free survival		Overall survival	
	BR	DRC	BR	DRC
MAIC: HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

- **Committee conclusions (ACD sections 3.5 and 3.6):**
  - Committee preferred MAIC to STC, but noted they gave broadly consistent results (N.B. company has updated its base case to use data from MAIC)
  - Results suggest zanubrutinib is effective, but exact size of treatment effect highly uncertain because of limitations of indirect comparisons
  - Assumption of equivalent treatment benefit in treatment naïve (where chemoimmunotherapy is unsuitable) and R/R population was likely to be conservative, underestimating benefit of zanubrutinib given first line.

BR = bendamustine rituximab; CI = confidence interval; DRC = dexamethasone, rituximab, and cyclophosphamide; MAIC = matching adjusted indirect comparisons; OS = overall survival; PFS = progression-free survival; STC = simulated treatment comparisons

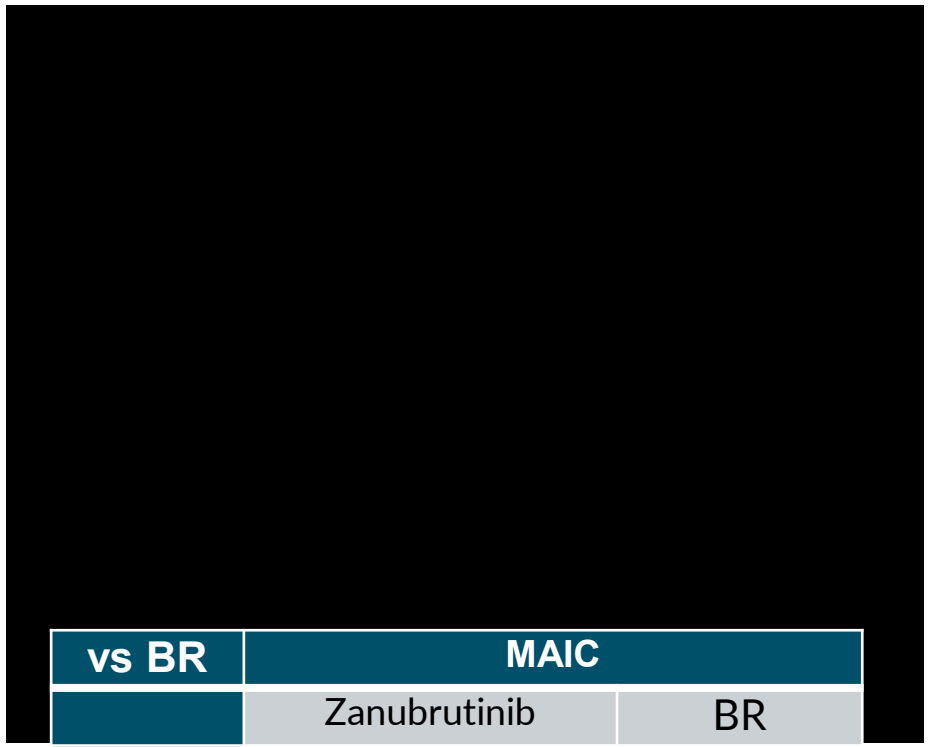
Recap of model

	Company	ERG	Committee conclusions
Model	Three-state partition-survival model (pre-progression, progressed, dead)		Appropriate for decision making
Comparators – entry regimen	Weighted average of the 2 pairwise comparisons to reflect 'standard care' (49% BR & 51% DRC)	Presented weighted average and results from the 2 pairwise comparisons	Took both blended and pairwise into account in decision making. Comparison of zanubrutinib with BR may have been more reliable than the comparison with DRC, but both BR and DRC are comparators.
Indirect comparison informing model	STC	MAIC	Preferred MAIC both methods are uncertain, but MAIC more transparent
Subsequent treatment options	BR, DRC and ibrutinib	Excluded costs of ibrutinib	Ibrutinib costs should be excluded
Treatment waning	No treatment effect cut-off	5 year treatment effect cut off	Do not apply treatment effect cut off – not plausible

Extrapolated overall survival

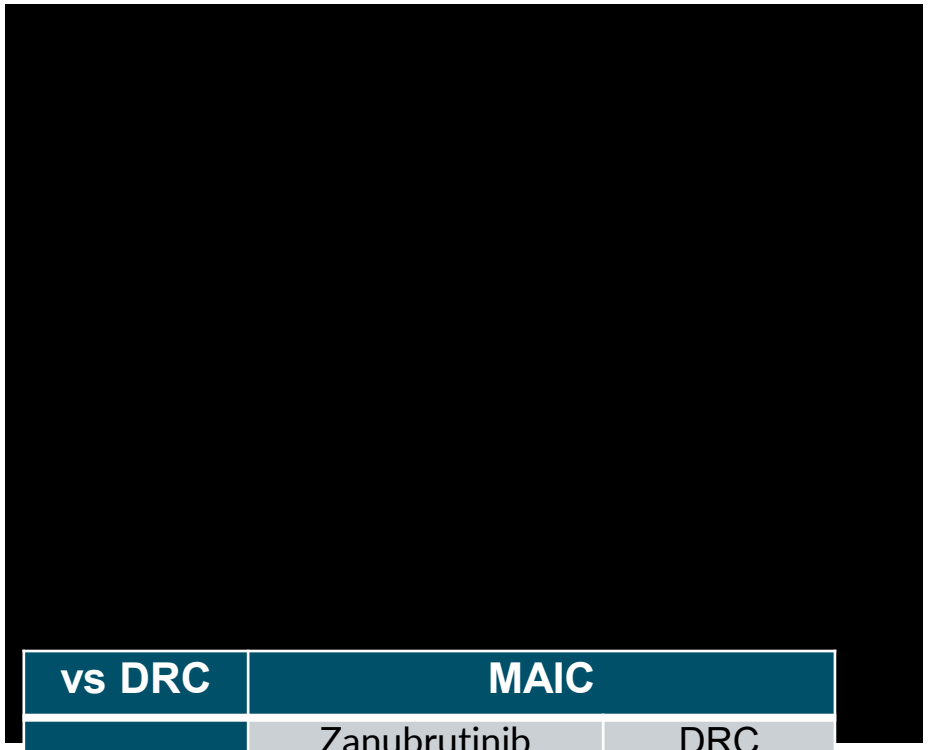
<2 years follow up on Zanubrutinib available from ASPEN. WM is slowly progressing and median overall survival not reached in trial. ERG concerned extrapolation from immature data is uncertain

Zanubrutinib (red) vs BR (blue)



vs BR	MAIC	
	Zanubrutinib	BR
	Exponential	Weibull
5yr	[redacted]	[redacted]
10yr	[redacted]	[redacted]

Zanubrutinib (red) vs DRC (grey)



vs DRC	MAIC	
	Zanubrutinib	DRC
	Dependent gamma	
5yr	[redacted]	[redacted]
10yr	[redacted]	[redacted]

WM= Waldensrom's macroglobulinaemia; BR = bendamustine rituximab; CI = confidence interval; DRC = dexamethasone, rituximab

Comments on plausibility of extrapolated overall survival

Observed data from trials:

[redacted]

Zanubrutinib

- <2 years follow up on Zanubrutinib from ASPEN
- Company: long term survival with zanubrutinib likely be similar to observed long-term OS data for ibrutinib from study 1118E
- In model at 5 years [redacted] alive in zanubrutinib arm. 5 year data from study 118E suggests 87% alive on ibrutinib

BR and DRC

- ERG: Data for BR and DRC came from studies carried out before ibrutinib licensed so no follow on ibrutinib
- Company: choice of distribution used to extrapolate OS informed by expert opinion on survival in current practice, where 72% of people have ibrutinib (via CDF) after BR or DRC. So, may overestimate BR and DRC overall survival if ibrutinib not included as follow on treatment

- **Committee conclusions (ACD sections 3.8 and 3.11):**
  - Accepted survival projections for zanubrutinib, noting limitations of underpinning data
  - Doubtful there is a need to adjust post-progression survival in BR/DRC modelled arms if remove ibrutinib as follow on treatment

Committee conclusions

	Committee conclusions at first meeting	ACD section
Clinical effectiveness estimates	Uncertainty because of • Immaturity of trial data for zanubrutinib • Limitations of indirect comparisons + the indirect comparisons were carried out in different populations for each comparator	3.13
Most plausible ICER	• Took into account ICERs presented vs. BR, vs DRC and the blended comparator. • Confidential because of comparator confidential prices but all ICERs were above £30,000 per QALY gained	3.13
Acceptable ICER	Should be comfortably below £30,000 noting • Uncertainty around clinical effectiveness estimates • Significant unmet clinical need for people with Waldenstrom's macroglobulinaemia • Patient and clinical experts are hugely supportive of the medicine, calling it a step-change in treatment • Despite uncertainties, zanubrutinib had a large treatment effect compared with BR and DRC	3.14

ACD consultation responses

Clinical experts, patient experts and web comments

Consultation comments

• Patient Expert
• WMUK
• Janssen (manufacturer of cladribine and ibrutinib)
• Company: BeiGene (manufacturer of zanubrutinib)
  • Increased PAS discount
  • Has proposed adjustment of overall survival of comparators based on ERG's clinical expert statements in ID3778 (ibrutinib CDF review of TA491) to account for ibrutinib not being available as follow on treatment
  • Provided scenario analysis for variation in BR / DRC use

Key themes have been summarised over the next few slides

Summary of consultation comments (1)

Patient experts and comments from WMUK

Comments on quality of life

Patient quality of life:

- Undergoing chemoimmunotherapy can have “detrimental and traumatic consequences”.
- Patients “overwhelmingly prefer” an oral treatment due to the better quality of life and lack of side effects vs. chemotherapy.
- Zanubrutinib enables patients to live well with WM, leading as fulfilling and normal lives as possible
- WM currently has no alternative oral treatments available – only hospital based
- Increasingly younger WM patients with families and working lives are recognised within WM demographic.

Carers quality of life:

- Zanubrutinib minimises hospital visits which are often arduous and rely on network of family and friends.

“Patients describe Zanubrutinib as a 'game changer', 'step change' treatment which has an immediate effect on their well being and ability to return to their normal lives.”

WM = Waldenström’s macroglobulinaemia;

Summary of consultation comments (2)

Patient experts and web comments from WMUK

Unmet need and disease prevalence

- Zanubrutinib would address a significant unmet need
- It is more clinically effective than chemo-immunotherapy options and better tolerated, and is an oral therapy
- The majority of WM patients who have had or are having a BTK inhibitor have previously endured detrimental and traumatic chemo-immunotherapy – had a BTK inhibitor been available 1st line clinical outcomes and quality of life could have been better

Cost savings

- Not clear if associated cost savings have been taken into account, and value of freeing-up human resources in an already overstretched NHS.
- Price has clearly been the determining factor in the recommendation – urge collaboration between NICE and BeiGene to resolve

WM = Waldenström's macroglobulinaemia;

Summary of consultation comments (3)

Janssen (manufacturer of ibrutinib) suggests that available data for ibrutinib is relevant to support the clinical effectiveness of zanubrutinib

Treatment naïve population (where chemoimmunotherapy is unsuitable)
• There was no comparison of zanubrutinib with chlorambucil or rituximab monotherapy in the treatment naïve population, and therefore the relative clinical benefit of zanubrutinib in this population is unclear • However, data on ibrutinib in WM and CLL supports assumption that treatment naïve patients would do at least as well as those with R/R disease
Indirect treatment comparison
• Hazard ratio for progression-free survival (PFS) for ibrutinib vs standard of care in TA491 was 0.25. Also supported by other relevant ibrutinib data (e.g. ibrutinib in combination with rituximab vs rituximab). • These figures give credibility to the low hazard ratios generated by both the zanubrutinib STC and MAIC, and the results from MAIC "may in fact be deemed conservative".

CLL = chronic lymphocytic leukaemia; MAIC = matching adjusted indirect comparisons; R/R = relapsed/refractory; STC = simulated treatment comparisons; WM = Waldenström's macroglobulinaemia;

ACD consultation: company rationale for adjusting BR and DRC extrapolated overall survival

Company agreed to remove costs of follow on treatment with ibrutinib, but says its modelling of BR and DRC overall survival (OS) may still include clinical benefits of follow on ibrutinib, and needs adjustment

Company's rationale:

- Reiterated that original OS extrapolations for BR and DRC were validated by clinical expert on assumption that 72% if people would have follow on ibrutinib
- Suggest that the model for zanubrutinib estimates less of a survival benefit vs. standard care than was considered plausible in the appraisal of ibrutinib at 6 years.
- The reduced risk for zanubrutinib should be at least as large as for ibrutinib, given that the ASPEN has demonstrated comparable efficacy and improved tolerability

Ibrutinib appraisal ID3778 CDF review of TA491	Company's model for zanubrutinib

• ERG clinical experts indicated that, at 6 years, people with R/R WM receiving ibrutinib would have double the survival probability of people treated with standard care (50% less survival at 6 years).	• Committee's preferred assumptions in this appraisal give the following estimates:
	  • [redacted]% patients receiving zanubrutinib are alive at 6 years
	  • [redacted]% of patients in SoC are alive at 6 years
	• This is a [redacted]% reduction, vs the 50% reduction suggested in the ibrutinib appraisal.

BR = bendamustine rituximab; CDF = Cancer Drugs Fund; DRC = dexamethasone, rituximab, and cyclophosphamide; OS = overall survival; R/R = relapsed/refractory; SoC = standard of care; WM = Waldenström's macroglobulinaemia;

ACD consultation: company approach for adjusting BR and DRC extrapolated overall survival

- Company uses same parametric distributions to extrapolate BR and DRC overall survival but adjusts these curves so that the survival at 6 years is 50% of that in the modelled zanubrutinib cohort at this time.
- This adjustment:
  - gives absolute decrease of [redacted] in SoC OS at 6 years compared with unadjusted
  - generates [redacted] undiscounted total life years for SoC, which company consider is clinically plausible

BR = bendamustine rituximab; CDF = Cancer Drugs Fund; DRC = dexamethasone, rituximab, and cyclophosphamide; OS = overall survival; SoC = standard of care; WM = Waldenström's macroglobulinaemia;

ERG comments on company comparator overall survival adjustment

- People in the comparator trials were unlikely to have had follow on ibrutinib, so overall survival data would not have included effect of follow on ibrutinib
  - For DRC Dimopoulos et al (2016) included people between 2002 and 2006, before ibrutinib received its marketing authorisation in 2014
  - For BR, Tedeschi et al (2015) was submitted for publication in 2014 and very unlikely people were subsequently treated with ibrutinib
- Follow on treatment with ibrutinib in the model was based on Rory Morrison Registry data up to 2018
- Selection of curve for extrapolation may be biased if based on expected survival if follow on ibrutinib is available, but:
  - Extrapolation of BR is with the second most pessimistic curve (Weibull). Using the most pessimistic (gamma) has a minor effect on results. (DRC was extrapolated with gamma)
- It is unclear whether the committee accepted the assumptions from the ERG's clinical expert in the appraisal of ibrutinib that survival at 6 years on standard care would be half of survival on ibrutinib
- ERG considers the overall survival adjustment to be arbitrary, but notes it has been implemented correctly

Cost effectiveness results: company revised base case

All results include updated patient access scheme for zanubrutinib. The results with comparator confidential discounts will be considered in Part 2

Key assumptions

- Indirect comparison: MAIC
- Subsequent treatment with ibrutinib: no ibrutinib costs included but [redacted] reduction in SoC overall survival at 6yrs to align with estimates in ibrutinib appraisal
- No treatment waning
- SoC weighting: 49% BR and 51% DRC

	Probabilistic			Deterministic		
	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER
Zanubrutinib vs. standard of care	[redacted]	[redacted]	£26,316	[redacted]	[redacted]	£25,045

The company considers the blended SoC comparator is most appropriate rather than separate pairwise comparisons vs. BR and DRC. ICER vs. BR is [redacted] vs. DRC is [redacted]

BR = bendamustine rituximab; DRC = dexamethasone, rituximab, and cyclophosphamide; ICER = Incremental cost effectiveness ratios; QALYs = Quality adjusted life year; SoC standard of care

Company's revised base case but without adjustment of comparator OS – ERG preferred

Key assumptions

- Indirect comparison: MAIC
- Subsequent treatment with ibrutinib: no ibrutinib costs and no adjustment to OS
- No treatment waning
- SoC weighting: 49% BR and 51% DRC

	Probabilistic			Deterministic		
	Incremental costs (£)	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER
Zanubrutinib vs. standard of care	[redacted]	[redacted]	£37,393	[redacted]	[redacted]	£34,463

The company consider the blended SoC comparator is most appropriate rather than separate pairwise comparisons vs. BR and DRC. ICER vs BR [redacted]; ICER vs DRC [redacted]

BR = bendamustine rituximab; DRC = dexamethasone, rituximab, and cyclophosphamide; ICER = Incremental cost effectiveness ratios; QALYs = Quality adjusted life year; SoC standard of care

Cost effectiveness results: Company scenario analyses

Company scenarios	Inc. cost	Inc. QALYs	ICER vs. SoC
Company base case	[redacted]	[redacted]	£25,045
Scenario 1: STC methodology for ITC rather than MAIC	[redacted]	[redacted]	£24,822
Scenario 2: ibrutinib subsequent treatment costs excluded and [redacted] percentage point decrease in survival at 6 years in SoC arm rather than [redacted] (equates to 45% lower than zanubrutinib arms)	[redacted]	[redacted]	£26,849
Scenario 3: Odds k=1 curve for DRC OS rather than generalised gamma (this was the company's preferred curve for extrapolating DRC OS data from the STC)	[redacted]	[redacted]	£24,921
Scenario 4: 40%:60% BR:DRC split for SoC rather than 49%:51%*	[redacted]	[redacted]	£25,724
Scenario 5: 60%:40% BR:DRC split for SoC rather than 49%:51%*	[redacted]	[redacted]	£24,151

* These scenarios were carried out to account for potential variation of use of BR and DRC across centres in UK. Company's clinical expert said reasonable to assume that usage of BR and DRC may vary between 40-60%

BR = bendamustine rituximab; DRC = dexamethasone, rituximab, and cyclophosphamide; ITC = indirect treatment comparison; MAIC = matching adjusted indirect comparisons; OS = overall survival; STC = simulated treatment comparisons

Key issues

At first meeting company included costs of follow on treatment with ibrutinib in SoC arm, **now removes these costs** but provides OS adjustment for SoC to remove potential benefits of follow on ibrutinib

Issue	ICER impact

Company: external validation of comparator (BR and DRC) modelled overall survival based on current practice in which follow-on ibrutinib is available (CDF only, now negative recommendation subject to appeal)
• Should survival for SoC (BR and DRC) be adjusted, (as well as cost of ibrutinib) to remove potential treatment benefit from **ibrutinib as a subsequent treatment**? If so,
  • Is the method the company used to make the adjustment valid?
  • Is the value of the adjustment appropriate (adjusts so overall survival at 6 years in SoC arm will be [redacted] of that in zanubrutinib arm)
	Moderate. Removing this assumption increases the ICER

Company's base case is a weighted blended ICER of its pairwise comparisons of zanubrutinib vs. BR and vs. DRC • As the BR population was similar to the ASPEN population (mostly relapsed/refractory), is the **BR comparison, both the BR and DRC pairwise comparisons, or a blend of the two acceptable** for decision making?	Moderate Lowest ICER is vs. BR, Highest is vs. DRC

BR = bendamustine rituximab; DRC = dexamethasone, rituximab, and cyclophosphamide; MAIC = matching adjusted indirect comparisons; OS = overall survival; R/R = relapsed/refractory; SoC = standard of care; STC = simulated treatment comparisons; WM = Waldenström's macroglobulinaemia;