Zanubrutinib for treating Waldenström's macroglobulinaemia

Part 1 slides for public - redacted

Technology appraisal committee A, 9th August 2022

Chair: Jane Adam

Lead team: Steven Edwards, Andrew Champion, Richard Ballerand

Evidence assessment group: Kleijnen Systematic Reviews

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Company: BeiGene

NICE

ACM2 – Preliminary recommendation

*Zanubrutinib is recommended as an option for treating Waldenstrom's macroglobulinaemia in adults who have had at least 1 treatment, only if

- they would otherwise have treatment with bendamustine and rituximab
- the company provides it according to the commercial arrangement

*This is an optimised recommendation. The marketing authorisation for zanubrutinib is:

For treating 'adults with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy'.

Key issues 1

Draft recommendation for people who have had 1 or more previous therapies

Recommendation was optimised for the only group in which zanubrutinib demonstrated to be cost effective. Company has not updated its base case for people who have had previous therapies. There are consultation comments on how recommendation may affect treatment pathway.

- What determines the first treatment a person has? Does the draft recommendation impact a person accessing the most appropriate first-line treatment for them? Are there people for whom DRC as 1st treatment is not suitable?
- Can people have re-treatment with BR? If so what is the treatment pathway for this group?
- Has the full population covered by the marketing authorisation been considered? Is there clinical and cost effectiveness evidence for zanubrutinib if taken after several rounds of chemoimmunotherapy?

Treatment naïve population for whom chemoimmunotherapy is unsuitable

Company has provided new cost effectiveness estimates for this group

- What is/are the comparator(s) for this population?
- The company presents results using its previous modelling for BR or DRC as proxies for rituximab and applies hazard ratios from separate indirect comparison of zanubrutinib vs. rituximab to these curves to model zanubrutinib survival outcomes in this group. Are BR and DRC modelled arms appropriate proxies?
- Are there any equality issues?

Key issues 2

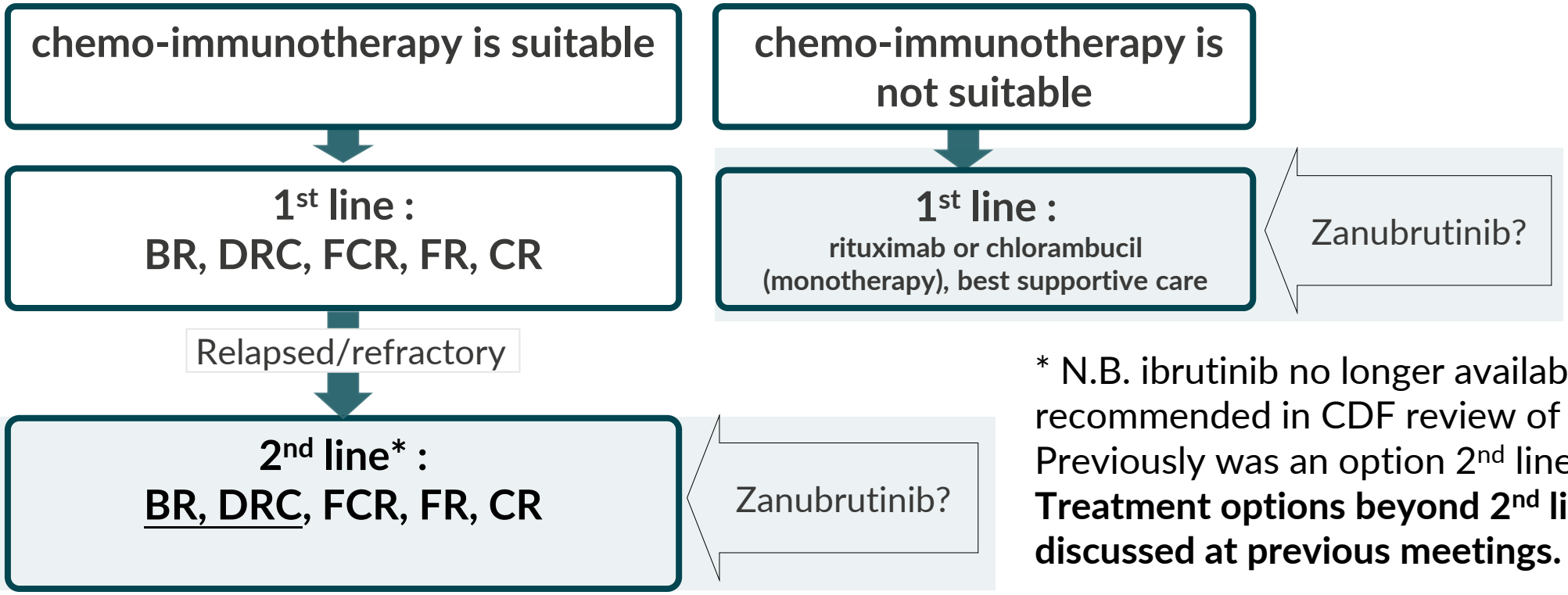
These issues from previous meeting remain relevant for today

- The MAIC indicates that DRC is more effective than BR given second line. This is key to the cost effectiveness estimates
- How reasonable is it to adjust downwards the effectiveness of BR and DRC to compensate for ibrutinib not being available as a follow on treatment. This is the principal area of disagreement between the company and ERG.

Zanubrutinib

Marketing authorisation	'Indicated for treatment of adults with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment 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 patient access scheme for zanubrutinib.

NHS Treatment pathway (as in NICE scope)



* N.B. ibrutinib no longer available 2nd line. Not recommended in CDF review of TA491. Previously was an option 2nd line-plus via CDF. **Treatment options beyond 2nd line not discussed at previous meetings.**

Committee conclusions at ACM1 and ACM2 (ACD sections 3.1, 3.2, 3.9):

- For relapsed or refractory disease, BR and DRC are the most relevant comparators when chemo-immunotherapy is suitable. Ibrutinib not a comparator + should not be included as follow-on treatment
- For first-line treatment, rituximab or chlorambucil are relevant comparators when chemoimmunotherapy is unsuitable
- Remains an unmet need for an effective and well-tolerated oral therapy.

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

Decision Problem- comparators

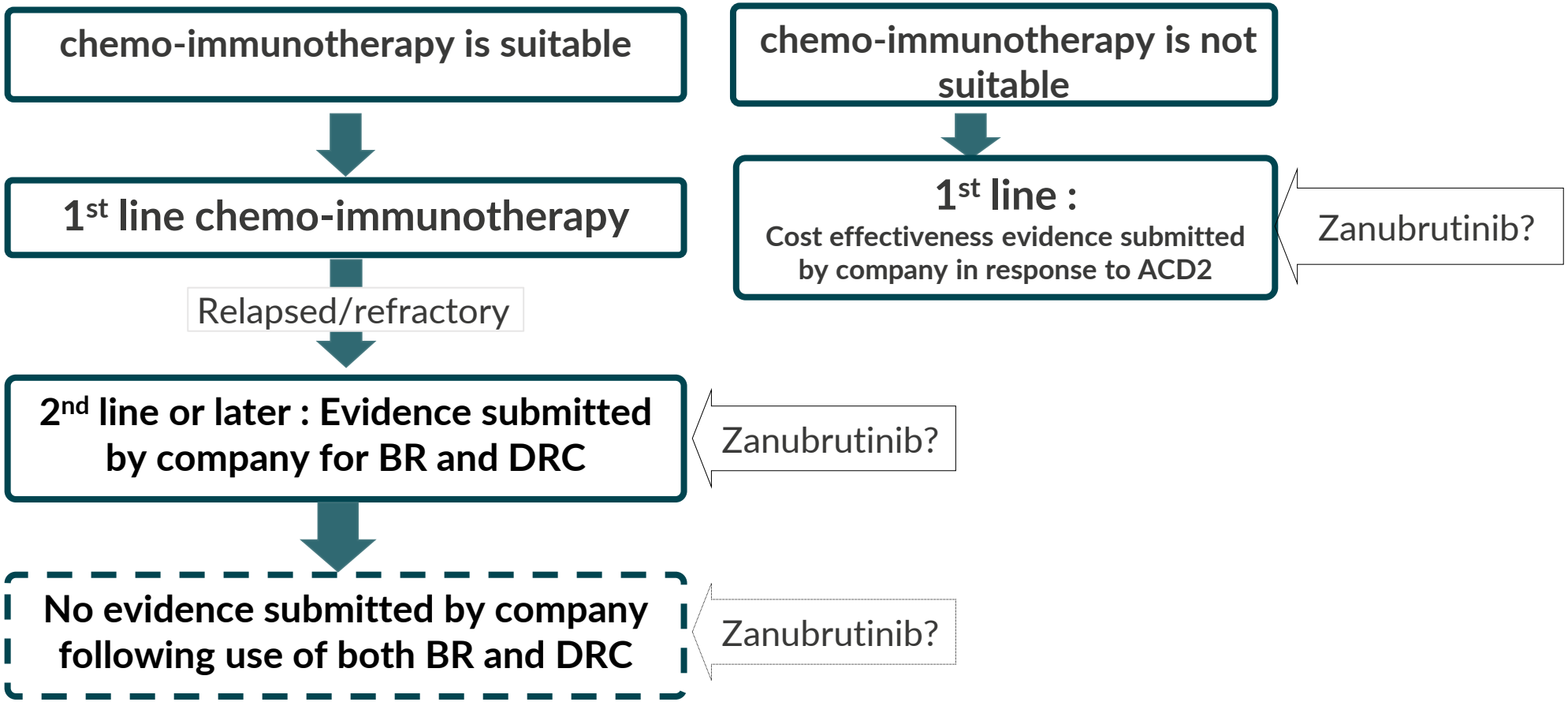
	Final scope issued by NICE	Evidence used in the model
Comparators	For people who have had at least one prior therapy: ○ BR ○ DRC ○ FR ○ FCR ○ Clad-R ○ ASCT in people for whom ASCT is suitable	BR and DRC only comparators used in the model for relapsed/refractory population.
	For people for whom chemo-immunotherapy is unsuitable: ○ chlorambucil ○ rituximab monotherapy ○ BSC	• No cost-effective evidence submitted for this population in the original company submission. • Company incorporated cost-effective analyses vs. rituximab monotherapy as part of ACD2 response.

ASCT = autologous stem cell transplantation; BR = bendamustine and rituximab; BSC = best supportive care, CDF = cancer drugs fund; Clad-R = cladribine and rituximab; DRC = dexamethasone, rituximab and cyclophosphamide; FCR = fludarabine, cyclophosphamide and rituximab; FR = fludarabine and rituximab;

Evidence submitted for committee consideration

Zanubrutinib marketing authorisation:

indicated for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.



BR = bendamustine rituximab; DRC = dexamethasone, rituximab, and cyclophosphamide; ICER = Incremental cost effectiveness ratios; QALY = Quality adjusted life year; WM = Waldenström's macroglobulinaemia

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
- Company presented indirect comparison with rituximab monotherapy during clarification but did not present a base case vs this comparator (**Company's new analysis today uses estimates from Gertz 2004/2009**).

Intervention	Trial/study	Population included in trial			Follow up
		Treatment naïve Chemoimmunotherapy not suitable	Treatment naïve Chemoimmunotherapy suitable/unknown	Relapsed refractory	
Zanubrutinib	**ASPEN vs ibrutinib** (zanubrutinib arm)	n/N=19/102		n/N= 83/102	19.47 months
Comparators if chemoimmunotherapy suitable (2nd line + treatments)					
BR	**Tedeschi 2015**			N=71	19 months
DRC	**Dimopoulos 2007/Kastritis 2015**		N=72 (suitable)		23.4 months/ 8 years
Comparator if chemoimmunotherapy unsuitable (1st line treatment)					
Rituximab	**Gertz 2004/Gertz 2009**		n/N=34/69 (unknown)	n/N= 35/69	Unknown

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

Recap of key evidence- indirect comparisons of OS & PFS

- Relapsed/refractory population
  - 2 methods for indirect, unanchored comparisons; MAIC and STC. Both highly uncertain.
  - Zanubrutinib improved OS and PFS against both BR and DRC, using both MAIC and STC with wide confidence intervals.
- Treatment naïve population
  - Company assumed same treatment benefit for zanubrutinib in treatment naïve population (where chemo-immunotherapy is unsuitable) as relapsed/refractory.

	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 (1st meeting)- company base case at 2nd meeting used MAIC
- Results suggest zanubrutinib is effective, but exact size of treatment effect highly uncertain because of limitations of indirect comparisons
- Assumption of equivalent efficacy between treatment naïve (where chemoimmunotherapy is unsuitable) and relapsed/refractory population may be reasonable but the exact size of the benefit in this population is uncertain because of the lack of direct or indirect evidence comparing zanubrutinib with the relevant comparators.

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

Recap of model- people who have had at least 1 prior therapy

Three-state partition survival model (pre-progression, progressed, dead). Company presented 3 modelled comparisons

comparisons	Clinical data	Committee comments
Zanubrutinib vs. BR	MAIC using data from study of BR in relapsed refractory population and ASPEN for zanubrutinib (majority had had prior treatment)	Comparison with BR robust because data for BR from people who had had previous treatment.
Zanubrutinib vs. DRC	MAIC using data from trial of DRC in treatment naïve population and ASPEN for zanubrutinib	Comparison with DRC uncertain because data for DRC from treatment naïve population.
Zanubrutinib vs. blend of BR and DRC	Weighted average of the ICERs from pairwise comparisons Rory Morrison Database in the absence of ibrutinib: 49% of people would have BR and 51% DRC.	Methodological difficulty with the blended comparator → relied on an assumption of the proportions of people who would have BR or DRC in clinical practice + underlying uncertainty of DRC comparison.

Committee conclusions (ACD section 3.12):

- It would take into account the cost-effectiveness results for both the blended and the pairwise comparisons.
- Also take into account the greater uncertainty around the estimates compared with DRC, and from the blended comparator.

BR = bendamustine rituximab; DRC = dexamethasone, rituximab, and cyclophosphamide; MAIC = matching adjusted indirect comparison

Extrapolated overall survival

<2 years follow up on Zanubrutinib from ASPEN. 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]

Overall survival extrapolation of zanubrutinib was consistent with observed data on ibrutinib at 5 years.

Company considered that its extrapolation of BR and DRC may overestimate survival so proposed an adjustment (next slide)

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

Recap- comparator overall survival adjustment

Company rationale for adjusting BR and DRC OS	ERG comments on company OS adjustment
• Original OS extrapolations for BR and DRC were validated by clinical expert on assumption that 72% of people would have follow-on ibrutinib. • An ERG clinical expert in the appraisal of ibrutinib for WM (TA795) suggested a 50% difference in survival at 6 years between ibrutinib and standard care plausible. Model for zanubrutinib estimates [redacted] difference. • Considers reduced risk for zanubrutinib should be at least as large as for ibrutinib • Company adjusted BR and DRC OS so that difference vs. zanubrutinib at 6 years 50%, absolute decrease of [redacted] in SoC OS vs. unadjusted	• People in the comparator trials were unlikely to have had follow on ibrutinib, so OS data would not have included effect of follow on ibrutinib. • Inclusion of follow-on treatment with ibrutinib in model was based on Rory Morrison Registry data up to 2018. • 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) • Adjustment not warranted.

Committee conclusions (ACD sections 3.9 and 3.13):

- It is reasonable to apply some adjustment to OS in the comparator arm, but not necessarily the adjustment proposed by the company.
- Level of this adjustment highly is uncertain.

BR = bendamustine rituximab; DRC = dexamethasone, rituximab, and cyclophosphamide; OS = overall survival

Recap: ICERS presented at ACM2

All results include updated patient access scheme (PAS) for zanubrutinib. Including comparator PAS increased these ICERs

Zanubrutinib vs.	Company (with adjustment of BR/ DRC OS)	ERG (no OS adjustment)
Blended comparator (49% BR and 51% DRC) probabilistic	£26,316	£37,393
Blended comparator (49% BR and 51% DRC) deterministic	£25,045	£34,463
BR deterministic	[redacted]	[redacted]
DRC deterministic	[redacted]	[redacted]

BR = bendamustine rituximab; DRC = dexamethasone, rituximab, and cyclophosphamide; ICER = Incremental cost effectiveness ratios; OS = overall survival; QALYs = Quality adjusted life year

Conclusions- people who have had ≥1 previous treatments

	Committee conclusions	ACD section
Acceptable ICER	Should be comfortably below £30,000 noting • Uncertainty around indirect comparisons and long-term survival • The likelihood that zanubrutinib was an effective treatment • Significant unmet clinical need • Patient and clinical experts are hugely supportive of the medicine, calling it a step-change in treatment.	3.13, 3.14
Most plausible ICER	• Took into account ICERs presented vs. BR, vs DRC and the blended comparator. • Some adjustment of post-progression survival in BR/DRC modelled arms may be reasonable but the level of adjustment is highly uncertain. • Confidential because of comparator confidential prices but only the ICER vs. BR was comfortably below £30,000, including some adjustment for comparator overall survival.	3.9, 3.13
Recommendation	• It was possible to recommend zanubrutinib in people who had had previous treatment and would otherwise have BR. This was because the ICER for this group was below £30,000 per QALY gained.	3.15

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BR = bendamustine rituximab; DRC = dexamethasone, rituximab, and cyclophosphamide; ICER = Incremental cost effectiveness ratio

Conclusions- population for whom chemo-immunotherapy is unsuitable

	Committee conclusions at ACM1 and ACM2	ACD section
Treatment pathway/comparators	People would typically have chlorambucil or rituximab when chemoimmunotherapy is not suitable.	3.6
Clinical effectiveness estimates	• There is uncertainty about whether WM responds to zanubrutinib in the same way in people unable to tolerate chemoimmunotherapy who have not had previous treatment as in people whose condition is relapsed or refractory after chemoimmunotherapy. • The assumption of equivalent efficacy for zanubrutinib between first- and second-line treatment may be reasonable. • The comparators (monotherapy when chemoimmunotherapy is unsuitable) may be less effective than chemoimmunotherapy, which would increase the potential benefit of zanubrutinib vs. the comparators for this group.	3.6
Cost effectiveness estimates	Unable to recommend zanubrutinib for the population for whom chemoimmunotherapy is unsuitable due to lack of an estimate for clinical and cost effectiveness compared to alternative therapies.	3.15

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WM = Waldenström's macroglobulinaemia

ACD consultation responses

Clinical experts, patient experts and web comments

Consultation comments
• Patient Expert • WMUK and Lymphoma Science subgroup- NCRI (joint response)* • BSH and RCPath (joint response)* • Company: BeiGene (manufacturer of zanubrutinib)   • Presented further analysis for people who are treatment naïve and for whom chemoimmunotherapy is unsuitable * These were provided by the clinical experts for this appraisal

Key themes have been summarised over the next few slides

BSH = British Society for Haemotology; RCPath = Royal College of Pathologists; NCRI = National Cancer Research Institute; SoC = standard of care; WM = Waldenström's macroglobulinaemia

Summary of consultation comments (1)

Patient expert and comments from WMUK, Lymphoma Science subgroup- NCRI, BSH and RCPath

Comments on the optimisation that zanubrutinib only recommended as an option for adults with WM if 'they would otherwise have treatment with bendamustine and rituximab' (in relapsed/refractory population)

"In practice these proposed recommendations will … reduce clinician/patient choice by channelling more patients into starting treatment with DRC. ***Why?*** *- no informed sensible patient will agree to starting treatment with BR when doing so would then probably mean having DRC next before state of the art treatment with Zanubrutinib is made available to them".*

People who would be disadvantaged:

- Patients who have already received BR in clinical practice (approx. 50% of patients with WM in the UK receive BR as first-line therapy according to Rory Morrison Registry (2021))
- People who have experienced an early failure of BR who cannot be retreated with BR. These people have a poor prognosis and a particular unmet need for effective follow on treatment
- People for whom BR would be the most appropriate 1st treatment option because of patient characteristics or disease-related characteristics (next slide)
- People being treated in centres where clinician prescribing habits are to prefer BR first
- People whose clinician, in light of the draft recommendations, selects front-line DRC to have access to zanubrutinib who would be better served by having BR first.

BCSH = British Committtee for the standards in Haematology; BR = bendamustine rituximab; BSH = British Society for Haemotology; CDF = cancer drugs fund; DRC = dexamethasone, rituximab, and cyclophosphamide; NCRI = National Cancer Research Institute; RCPath = Royal College of Pathologists; WM = Waldenström's macroglobulinaemia

Summary of consultation comments (2)

Comments from WMUK, Lymphoma Science subgroup- NCRI, BSH and RCPath

Comments on the optimisation that zanubrutinib only recommended as an option for adults with WM if 'they would otherwise have treatment with bendamustine and rituximab' (in relapsed/refractory population)

Instances in which BR would be preferred as 1st treatment option:

Patient characteristics

- Age and consideration of toxicity of treatment, in WM there is a high rate of people dying of other causes than WM alone. BR rarely used in frailer people or people with co-morbidities

Disease related factors

- Prefer BR if person has hyperviscosity, cryoglobulinaemia, AI amyloidosis (as per latest BCSH Guidelines for the Diagnosis and Management of WM- A British Society for Haematology Guideline, 2022)
- Instances where need rapid response. BR gives a more rapid response than DRC and is particularly important if person has hyperviscosity when rituximab is deferred. Also if people have bulky disease.
- Potential increased risk of second primary cancers if bendamustine used as a second option in previously treated lymphoma.

BCSH = British Committtee for the standards in Haematology; BR = bendamustine rituximab; BSH = British Society for Haemotology; CDF = cancer drugs fund; DRC = dexamethasone, rituximab, and cyclophosphamide; NCRI = National Cancer Research Institute; RCPath = Royal College of Pathologists; WM = Waldenström's macroglobulinaemia

Summary of consultation comments (3)

Comments from WMUK, Lymphoma Science subgroup- NCRI, BSH and RCPath

Comments on the optimisation that zanubrutinib only recommended as an option for adults with WM if 'they would otherwise have treatment with bendamustine and rituximab' (in relapsed/refractory population)

Note some people in clinical practice could have re-treatment with BR (although noted there may be some clinical reluctance to use same chemotherapy again due to toxicity/efficacy concerns).

Suggested further definition of group who would otherwise have BR in recommendations

1) patients who would otherwise be eligible for BR including those who have not previously received this treatment or received this > 2 years ago and did not experience significant toxicity
2) patients who experienced early treatment failure after BR for whom re-treatment is not recommended and novel therapy is needed. This includes BR treated patients who failed to achieve PR/CR, or experienced PD within 24 months, and/or developed significant toxicity. (N.B. this group was estimated by stakeholder to be ~ 10% of people suitable for chemoimmunotherapy).

BCSH = British Committtee for the standards in Haematology; BR = bendamustine rituximab; BSH = British Society for Haemotology; CDF = cancer drugs fund; DRC = dexamethasone, rituximab, and cyclophosphamide; NCRI = National Cancer Research Institute; RCPath = Royal College of Pathologists; WM = Waldenström's macroglobulinaemia; PR= partial response; CR = complete response; PD progressed disease.

Summary of consultation comments (4)

Patient experts and comments from WMUK, Lymphoma Science subgroup- NCRI, BSH and RCPath

Treatment naïve population (where chemoimmunotherapy is unsuitable)

- Concerned no recommendation is made for this group
- In patients for whom chemoimmunotherapy is unsuitable, life expectancy is likely to be shorter for reasons such as co-morbidities or frailty. Not having access to zanubrutinib prevents them from having an effective therapy that can be well tolerated by elderly frail patients or those with co-morbidities.
- No reason to suppose that first-line treatment with zanubrutinib would be less effective than if a patient had received one or more earlier treatments with either BR or DRC.
- Irrespective of whether company provided evidence for this group denying patients access to a step-change treatment is "*unlawful discrimination as WM is a cancerous disability*".
- Accept the limited evidence in this setting as well as the imprecise definition of 'unsuitable for chemoimmunotherapy'. In the absence of the opportunity to assess patients at front-line, the chance of seeking the answer to this question is slim. If unable to recommend zanubrutinib, propose a consideration of a pre-defined setting in which front-line zanubrutinib is permitted and data collection undertaken to enable a better understanding in this group.

BR = bendamustine rituximab; BSH = British Society for Haemotology; DRC = dexamethasone, rituximab, and cyclophosphamide; NCRI = National Cancer Research Institute; RCPath = Royal College of Pathologists; WM = Waldenström's macroglobulinaemia

Company: group for whom chemoimmunotherapy unsuitable– rituximab is key comparator

- Company's clinical expert: neither rituximab of chlorambucil monotherapy are commonly used in clinical practice in the UK.
- Company uses rituximab rather than chorambucil as comparator:
  - UK Rory Morrison registry data (2021) shows that rituximab is more widely used than chlorambucil in the front-line setting for the treatment for WM (11% vs 4%).
  - British Society for Haematology WM guidelines (2021) describe chlorambucil monotherapy as having *"a very limited role"* in contemporary first-line therapy, whereas rituximab is noted to be *"generally well tolerated but associated with modest response rates."*
  - Concerns around the toxicity of chlorambucil (clinical expert opinion).
  - Company's MAIC indirectly demonstrates superior efficacy of rituximab compared to chlorambucil. PFS HR for zanubrutinib vs rituximab monotherapy is higher than that of zanubrutinib vs chlorambucil monotherapy, with values of [redacted](95% CI [redacted]) and [redacted] (9% CI [redacted]), respectively.
  - Better survival outcomes also for rituximab monotherapy vs chlorambucil monotherapy for 1st line treatment chronic lymphocytic leukemia. HR of 0.69 (95% CI: 0.51 - 0.91) (Mato et al. 2018).
  - Company expects that if zanubrutinib is cost effective relative to rituximab monotherapy, it will also be cost effective relative to chlorambucil monotherapy.

CI = confidence interval; HR = hazard ratio; MAIC = matching adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; WM = Waldenström's macroglobulinaemia;

Company: group for whom chemotherapy is unsuitable company modelling approach

	Approach	Comments
PFS and OS rituximab	Used BR or DRC modelled arms →assumes rituximab has same efficacy	• In ACD2 committee: "the comparators (monotherapy when chemoimmunotherapy is unsuitable) may be less effective than chemoimmunotherapy".
PFS and OS zanubrutinib	• Applied hazard ratios from MAIC comparing zanubrutinib with rituximab • PFS HR [redacted] [95% CI [redacted]]; OS [redacted] [95% CI [redacted]] • Adjustment of BR or DRC OS applied (as base case in last meeting)	• Notes HR for zanubrutinib vs. rituximab lower than HR zanubrutinib vs. BR or DRC • Considers estimate from MAIC conservative given the MAIC analyses included the full ASPEN ITT population (mostly relapsed/refractory) supported by committee conclusion that zanubrutinib is at least as effective in treatment naïve setting compared to relapsed/refractory setting
Costs rituximab	Only included rituximab costs from BR and DRC (proxies for rituximab) arms	-

BR = bendamustine rituximab; CI = confidence interval; DRC = dexamethasone, rituximab, and cyclophosphamide; HR = hazard ratio; MAIC = matching adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; WM = Waldenström's macroglobulinaemia;

Cost effectiveness results: company base case for treatment naïve group

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

Key assumptions

- Rituximab monotherapy efficacy and safety equalised to BR or DRC data
- Indirect comparison: MAIC (PFS and OS HRs for zanubrutinib vs rituximab)
- Adjustment of rituximab survival [[redacted] percentage point decrease at 6 years] in SoC).

	Probabilistic			Deterministic		
	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER
Zanubrutinib vs. rituximab (BR dataset as proxy)	[redacted]	[redacted]	£22,475	[redacted]	[redacted]	£21,341
Zanubrutinib vs. rituximab (DRC dataset as proxy)	[redacted]	[redacted]	£28,165	[redacted]	[redacted]	£26,646

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: ERG base case for treatment naïve group

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

Key assumptions:

- Rituximab monotherapy efficacy and safety equalised to BR or DRC data
- Indirect comparison: MAIC (PFS and OS HRs for zanubrutinib vs rituximab)
- No adjustment of rituximab OS

	Probabilistic			Deterministic		
	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER
Zanubrutinib vs. rituximab (BR dataset as proxy)	[redacted]	[redacted]	£25,250	[redacted]	[redacted]	£23,570
Zanubrutinib vs. rituximab (DRC dataset as proxy)	[redacted]	[redacted]	£36,378	[redacted]	[redacted]	£34,084

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 for treatment naïve group (1)

Company scenarios	Inc. cost	Inc. QALYs	ICER vs. SoC
Company base case (BR dataset as proxy)	[redacted]	[redacted]	£21,341
Scenario 1: [redacted] percentage point decrease in survival at 6 years in SoC arm rather than [redacted] (equates to 45% lower than zanubrutinib arms)	[redacted]	[redacted]	£22,402
Scenario 2: [redacted] percentage point decrease in survival at 6 years in SoC arm rather than [redacted] (equates to 40% lower than zanubrutinib arms)	[redacted]	[redacted]	£23,968

BR = bendamustine rituximab; ICER = Incremental cost effectiveness ratios; QALYs = Quality adjusted life year; SoC standard of care

Cost effectiveness results: Company scenario analyses for treatment naïve group (2)

Company scenarios	Inc. cost	Inc. QALYs	ICER vs. SoC
Company base case (DRC dataset as proxy)	[redacted]	[redacted]	£26,646
Scenario 1: [redacted] percentage point decrease in survival at 6 years in SoC arm rather than [redacted] (equates to 45% lower than zanubrutinib arms)	[redacted]	[redacted]	£27,818
Scenario 2: [redacted] percentage point decrease in survival at 6 years in SoC arm rather than [redacted] (equates to 40% lower than zanubrutinib arms)	[redacted]	[redacted]	£29,608

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

Key issues 1

Draft recommendation for people who have had 1 or more previous therapies

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- What determines the first treatment a person has? Does the draft recommendation impact a person accessing the most appropriate first-line treatment for them? Are there people for whom DRC as 1st treatment is not suitable?
- Can people have re-treatment with BR? If so what is the treatment pathway for this group?
- Has the full population covered by the marketing authorisation been considered? Is there clinical and cost effectiveness evidence for zanubrutinib if taken after several rounds of chemoimmunotherapy?

Treatment naïve population for whom chemoimmunotherapy is unsuitable

Company has provided new cost effectiveness estimates for this group

- What is/are the comparator(s) for this population?
- The company presents results using its previous modelling for BR or DRC as proxies for rituximab and applies hazard ratios from separate indirect comparison of zanubrutinib vs. rituximab to these curves to model zanubrutinib survival outcomes in this group. Are BR and DRC modelled arms appropriate proxies?
- Are there any equality issues?

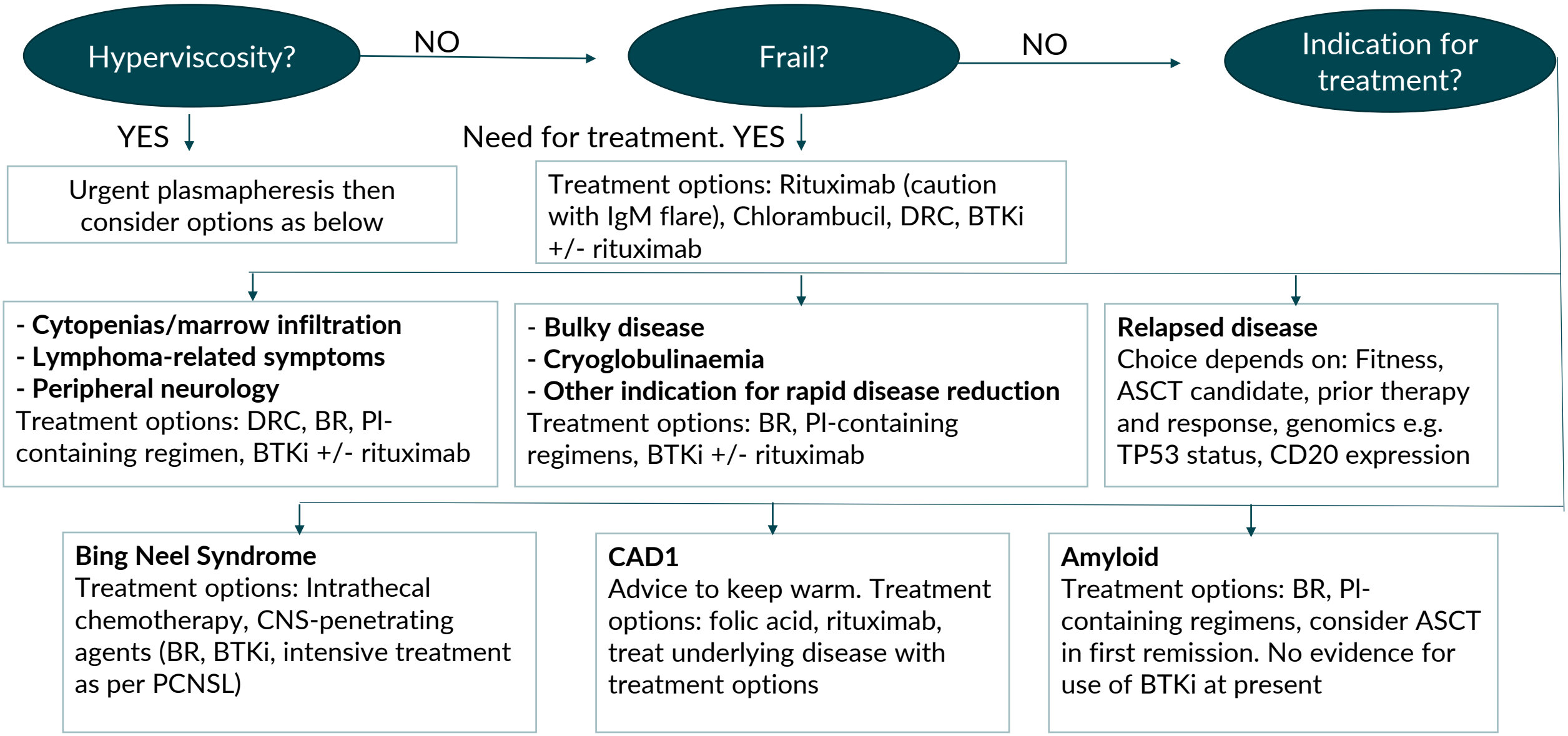
Key issues 2

These issues from previous meeting remain relevant for today

- The MAIC indicates that DRC is more effective than BR given second line. This is key to the cost effectiveness estimates
- How reasonable is it to adjust downwards the effectiveness of BR and DRC to compensate for ibrutinib not being available as a follow on treatment. This is the principal area of disagreement between the company and ERG.

Back up slides

BSH guideline- management of WM



NICE

Diagram adapted from BSH guidelines (2022); ASCT = autologous stem cell transplant; BR = bendamustine rituximab; BTKi =bruton tyrosine kinase inhibitor; CNS = central nervous system; DRC = dexamethasone, rituximab, and cyclophosphamide; IgM = immunoglobulin M; PCNSL = primary central nervous system lymphoma