NICE National Institute for Health and Care Excellence

For public

Zanubrutinib for Waldenström's macroglobulinaemia

Lead team presentation

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ERG: Kleijnen Systematic Reviews

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Company: BeiGene

Date: 12th April 2022

Key clinical issues

- *Only direct comparative evidence is against ibrutinib (available via CDF → outside scope).*
- *Indirect comparisons have been made vs. BR and DRC*
- *Company present cost effectiveness results using a blended comparator of 49%BR + 51%DRC*
- *For adults who can have chemo-immunotherapy, zanubrutinib is positioned second line (after relapse or becoming refractory to first line therapy)*
- *For adults for whom chemotherapy is unsuitable, zanubrutinib is positioned first line*
- *BR trial was for a relapsed/refractory population but DRC was a for treatment naïve population.*

Population for whom chemo-immunotherapy is suitable

- Is the BR comparison, or both the BR and DRC comparisons the most relevant?
- Is a 'standard of care' comparator, with 49% BR and 51% DRC, consistent with UK clinical practice (in absence of ibrutinib)?
- Is the clinical effectiveness of zanubrutinib vs BR or DRC expected to be different?

Indirect comparisons

- Are the PFS and OS estimates from the STC and MAIC plausible?
- Is there any strong reason to favour one method of indirect comparison over another?

Population for whom chemo-immunotherapy is unsuitable

- Is the clinical effectiveness of zanubrutinib in this population likely to be similar to those people who have had a previous treatment? What proportion of people will be in this group?

BR = bendamustine rituximab; CDF = cancer drugs fund; DRC = dexamethasone, rituximab cyclophosphamide

Waldenström's macroglobulinaemia (WM): background

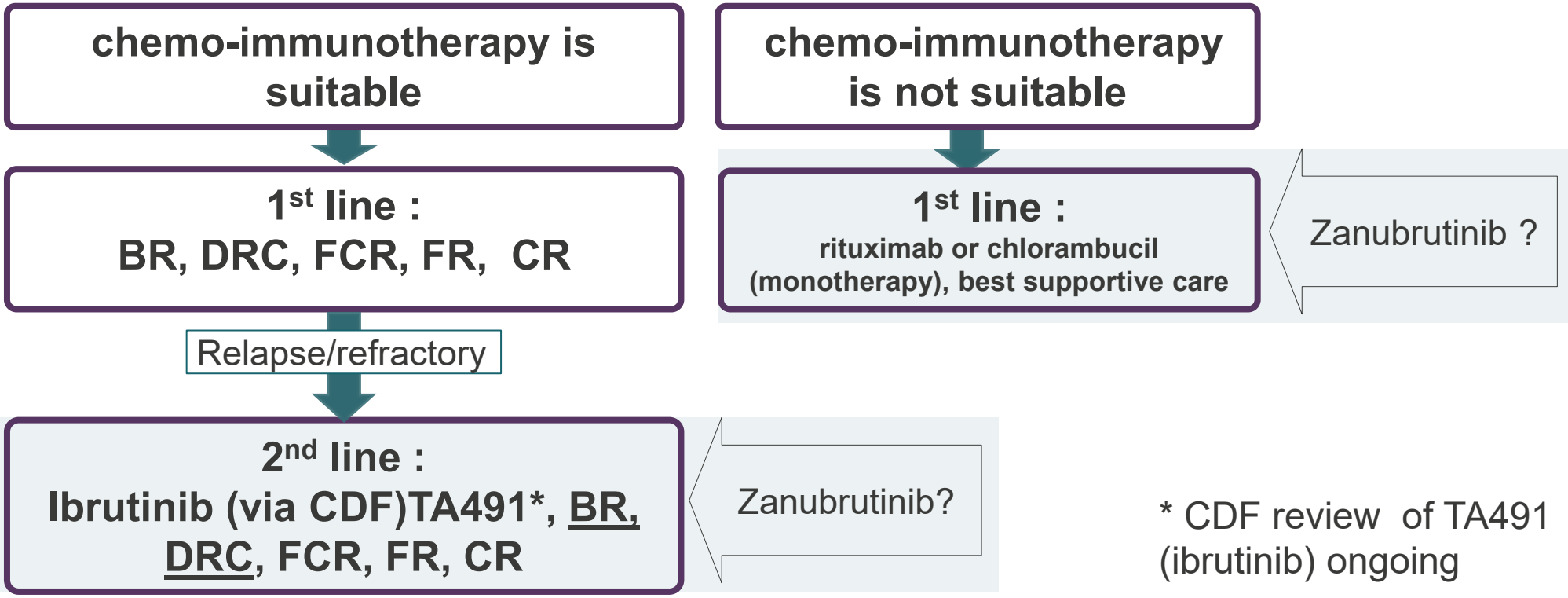
WM is a rare, slow-growing lymphatic cancer which mainly affects older people

- Rare type of non-Hodgkin's lymphoma, affecting the lymphatic system
- Symptoms include severe fatigue, night sweats, frequent/persistent infections, breathlessness, weight loss
- Develops slowly, usually asymptomatic at first. Many people diagnosed at an advanced stage
- More men affected, and usually 70 years and older
- Slowly progressive: median overall survival is around 16 years from symptom onset. Nearly half die from causes unrelated to WM.
- In England around 330 people diagnosed annually
- Data collected in the Cancer Drugs Fund showed 823 people had treatment with ibrutinib (also a BTK inhibitor)

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). The company has agreed a patient access scheme for zanubrutinib.

NHS Treatment pathway (as in NICE scope)



* CDF review of TA491 (ibrutinib) ongoing

- **Expert opinion:**
  - No well defined pathway, first line, BR and DRC most common
  - Relapsed/ refractory treatment variable, depends on patient-specific factors.
  - Majority started on ibrutinib since available in CDF.
  - Vast experience of this drug class (ibrutinib in CDF plus other indications)

Key question: For what proportion of patients would chemo-immunotherapy not be suitable?

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

Decision problem

	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 • For people for whom chemo-immunotherapy is unsuitable: ○ chlorambucil ○ rituximab monotherapy ○ BSC	Not in line with the NICE scope. BR and DRC only comparators used in the model. Other comparators excluded *"not widely used and have tolerability issues".* After technical engagement, company used a combined comparator to represent standard care (49% BRC, 51% DRC), based on Rory Morrison registry data. Ibrutinib was included as a subsequent treatment after BR or DRC, but cannot be considered as it is in the CDF Assumed equivalent effectiveness in treatment naïve (if chemoimmunotherapy unsuitable) vs. relapsed/refractory

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;

Comments: not all comparators in scope in company's decision problem

NOTE in the trial zanubrutinib was compared with ibrutinib: outside scope because in CDF

The company and ERG disagree on comparators used in this appraisal

Company:

- BR and DRC reflect standard of care for the vast majority of patients
- Additional indirect comparisons [MAICs] for FCR, FR, chlorambucil and rituximab performed but were not included because of differences in study populations
- Ibrutinib should be considered a subsequent treatment option as looking 8yrs forward (assumes availability)

ERG:

- ASCT should have been included
- Results for the MAICs in the company submission do not differ from the additional MAICs in the clarification response
- Exploratory analyses provided during clarification could have been included in the model

Clinical Expert:

- Comparators are aligned with what is used most frequently in the UK and advised by the latest BSH guidelines

Key question:

- **Is a 'standard of care' comparator, with 49% BR and 51% DRC consistent with UK clinical practice (in absence of ibrutinib)**

ASCT = autologous stem cell transplantation; BR = bendamustine and rituximab; Clad-R = cladribine and rituximab; DRC = dexamethasone, rituximab and cyclophosphamide; FCR = fludarabine, cyclophosphamide and rituximab; FR = fludarabine and rituximab

Patient organisation perspective

Zanubrutinib meets a significant unmet meet for patients, improving quality and length of life

Joint submission from WMUK and Lymphoma Action:

Impact of WM

- Fear of relapse and lack of treatment options affects wellbeing
- Viewed as a disease of the elderly, but increasingly seen in working-age people with active lives
- Symptoms like severe pain, extreme fatigue, reduced mobility and infections have significant impact on quality of life
- "Watch and wait" stressful for patients, family and carers

People would like

- An effective, well tolerated treatment that provides long-term disease control.
- Ability to continue/restart normal daily activities.
- Treatments which are easy to take at home or while travelling.
- Improved quality and length of life
- A treatment option for patients where current options are unsuitable (e.g. too frail or chemo-resistant disease)

Zanubrutinib

- Continuous oral therapy, taken at home
- 'Game-changer' & 'lifeline'
- Extends life, improves QOL and reduces health needs
- Better response quality & less toxicity compared to ibrutinib[1]
- Well tolerated and fulfils an unmet need
- Significantly fewer complications (then existing chemo-based treatments)

1. Tam, C. S. et al. (2020) The ASPEN study. Blood, 136(18), 2038-2050.

Patient and carer perspectives

Zanubrutinib meets a significant unmet meet for patients, improving quality and length of life

Collected by WMUK and Lymphoma Action

"It's simply a world away from chemo, let alone a stem cell transplant, with all the resultant side effects and hospitalisations"

"Both patients and carers affected by this condition are acutely aware of the finite number of therapies available to us and, as treatment cycles take place, this narrows our choices as intolerance increases, or effectiveness diminishes."

"I was able to have an immediate benefit which has been ongoing. I now functioning as normal, from being unable to climb the stairs at home without having to sit down on the bed, I am now walking 100 miles per month with ease."

"Zanubrutinib has been a complete game changer for me. I have not felt this well in many years and I am so happy to have an oral daily drug to take in place of chemotherapy infusions."

"Patients we have surveyed consider zanubrutinib an effective treatment, well tolerated, with rapid response, associated with an excellent QOL with limited side effects."

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QoL = quality of life

Professional organisation perspectives

Zanubrutinib is well tolerated, improves QoL, extends PFS and likely extends length of life

Submissions received from:

- British Society Haematology/ Royal College Pathologists and UCLH NHS FT

Efficacy

- This is a **stepwise improvement** in treatment options for patients
- BTK inhibitors are **new class of drugs** for WM
- Will improve both progression free survival and likely overall survival
- Trials outcomes good, but just looking at response rate and degree of response may underestimate activity and duration of benefit

Benefits:

- Zanubrutinib will improve QoL (more patients will be able to tolerate it than chemoimmunotherapy).
- Where chemoimmunotherapy is unsuitable, due to early relapse or toxicity concerns, this opens up a new treatment option
- Adverse events consistent known about this class of drug. In trial zanubrutinib had a more favourable safety profile than ibrutinib which anecdotally matches clinical experience
- Oral therapy, taken at home : important for WM patients who susceptible and vulnerable to infections, + reduces “chair time” + “nursing time”
- Many die from other causes: important to an oral option with meaningful and durable response & minimises toxicity

PFS = progression-free survival; QoL = quality of life; WM = Waldenström’s macroglobulinaemia

Evidence sources - zanubrutinib

Main evidence: One trial vs ibrutinib, two single arm: only data from vs ibrutinib used in model

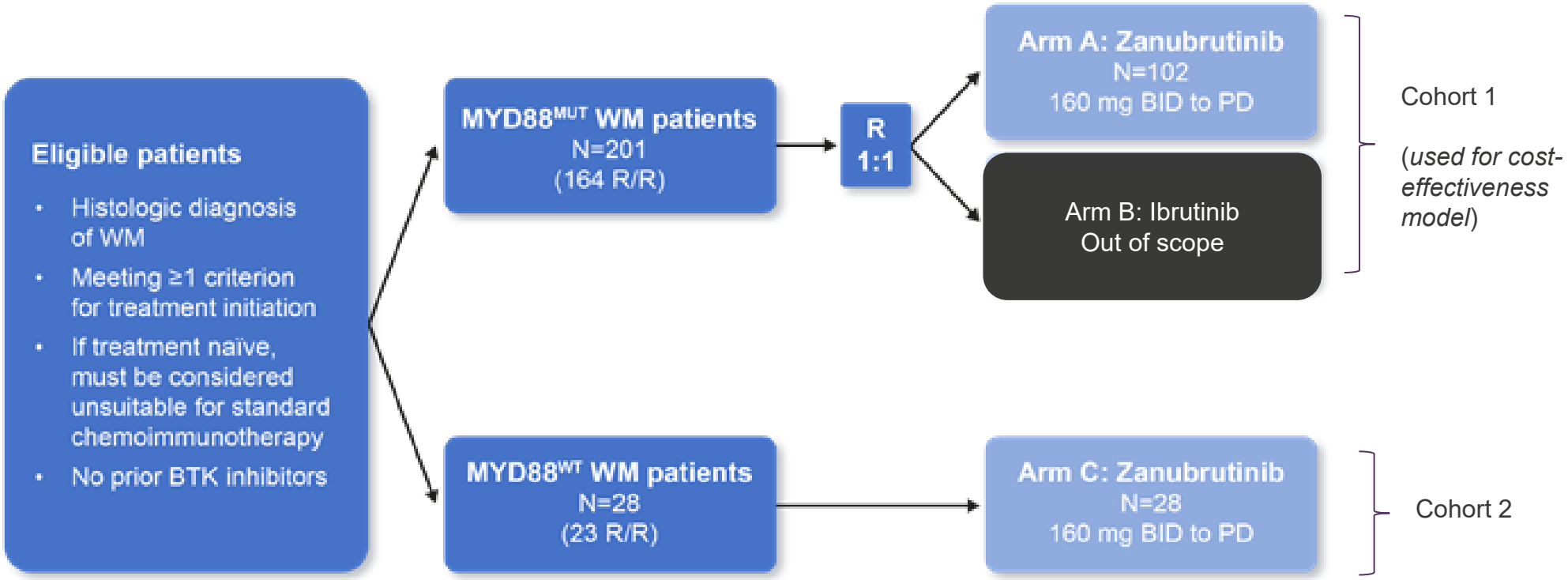
Trial	Intervention/ comparator	Population	Sample size	Median follow up	Use in model?
ASPEN (Cohort 1)	Zanubrutinib vs ibrutinib	Mixed treatment-naïve (unsuitable for chemo-immunotherapy) and relapsed/refractory WM. All *MYD88*^{MUT}	Treatment naïve: 37 Relapsed/ refractory: 164	19.47 months	Yes *(PFS, OS & pre-progression utility)* Aug 2019 data cut

Supporting evidence (for validation):

Trial	Intervention/ comparator	Population	Median follow up
ASPEN (Cohort 2)	Zanubrutinib	Mixed (n=28)	17.87 months
BGB-3111-AU-003 (phase 1/2 trial)	Zanubrutinib	Mixed (n=73)	48 months

ASPEN study

Main evidence on zanubrutinib comes from a randomised study vs ibrutinib (both BTK inhibitors)



- Cohort 1 patients with *MYD88*^{MUT} randomised to zanubrutinib or ibrutinib.
- In clinical practice 90% have *MYD88*^{MUT}
- Primary outcome: very good partial response/complete response (independent review)
- Progression free survival = secondary outcome
- Overall survival = exploratory outcome

BID = twice a day; R/R = relapsed or refractory; *MYD88*^{MUT} = Myeloid differentiation primary response gene 88 mutant; *MYD88*^{WT} Wild-type myeloid differentiation primary response gene 88; PD = progressive disease; R = randomised; WM = Waldenström's macroglobulinaemia

ASPEN study – baseline characteristics

Zanubrutinib arm, Cohort 1

Demographic/baseline characteristic	Zanubrutinib (N=102)
Median age (min, max), years	70.0 (45, 87)
Gender, n (%)	
Male	69 (67.6)
ECOG PS	
0/1	96 (94.1)
2	6 (5.9)
Prior lines of therapy, n (%)	
0	19 (18.6)
1-3	76 (74.5)
>3	7 (6.9)
Source: CS, Table B.2.7, page 33.	

- Median age was 70
- Vast majority had an ECOG 0 or 1
- 18.6% were treatment naïve
- 14% of all study participants (Cohorts 1 & 2) were from the UK

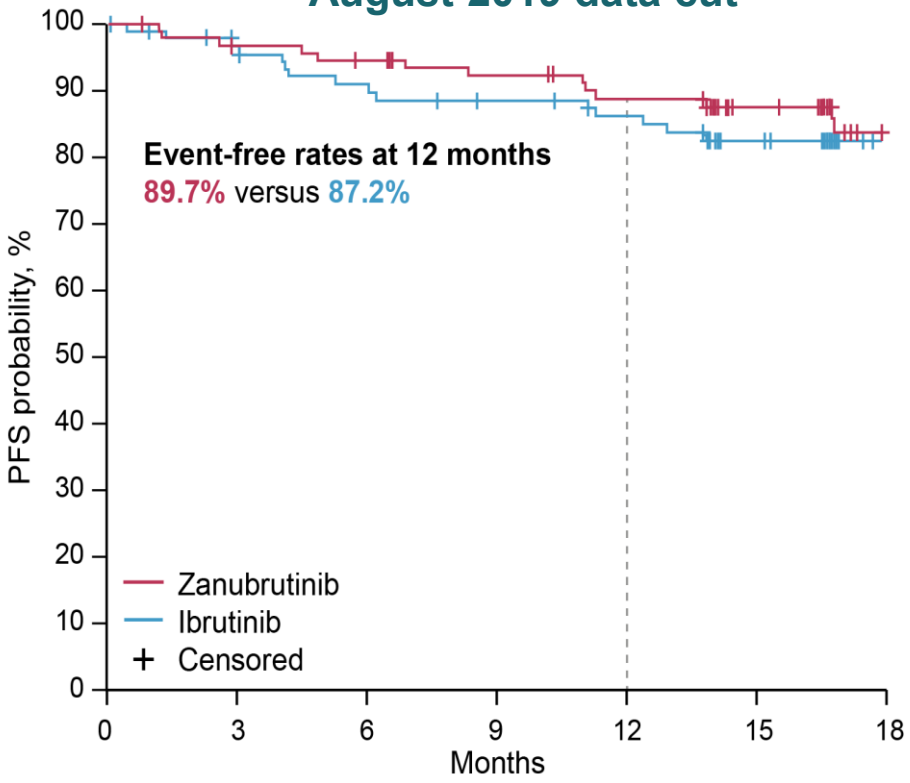
Professional group comments. Trial population reflects the patient population in the UK. Despite the median age of the patient population being 70, the maximum age was 87 … with a range of performance scores and also some were heavily pre-treated

CXCR4 = C-X-C Motif Chemokine Receptor 4; ECOG PS = Eastern Cooperative Oncology Group performance status; MYD88 = myeloid differentiation primary response gene 88; n = number of patients in the category; N = number of patients evaluable; WHIM = warts, hypogammaglobulinemia, infections, myelokathexis; WT = wild-type

ASPEN study results - efficacy

Zanubrutinib demonstrated comparable efficacy to ibrutinib; median PFS/OS not reached in either arm

PFS in Cohort 1 (ITT analysis set)
August 2019 data cut



Response in Cohort 1 (ITT analysis set)

Assessment	Zanubrutinib (N=102)	Ibrutinib (N=99)
CR, n (%)	0 (0.0)	0 (0.0)
VGPR, n (%)	29 (28.4)	19 (19.2)

- 12-month PFS and OS data were comparable between zanubrutinib and ibrutinib (89.7% vs. 87.2%, and 97.0% vs 93.9%).
- Zanubrutinib demonstrated an equivalent VGPR rate to ibrutinib (28.4% versus 19.2%) and was achieved at an earlier median time of 4.8 months vs 7.4 months. 0% had complete response in either arm.

- Updated efficacy data was provided during clarification (cut-off Aug 2020), which was in line with the 2019 results. However these analyses were investigator assessed (not by independent review committee). [redacted]

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ITT = intention-to-treat; OS = overall survival; PFS = progression-free survival; VGPR = very good partial response rate; CR= complete response

Subgroups: treatment naïve

More limited data available, but may expect similar treatment response as patients with relapsed refractory disease

- Evidence for treatment naïve patients based on 19 participants in the zanubrutinib arm
- Appears to show **comparable treatment effect** as in patients with relapsed refractory disease, with a **similar proportion of patients achieving a very good partial response** (treatment naïve: 26% vs. relapsed/refractory: 29%).
- Company: treatment naïve patients typically have a better prognosis
- Clinical expert:
  - Huge unmet need for people for whom chemo-immunotherapy is unsuitable
  - Whilst treatment naïve numbers are small, they do at least as well as those with relapsed/refractory disease
- ERG: results of the economic analyses will be less reliable for the treatment naïve population
- Only second line use funded for ibrutinib in the Cancer Drugs Fund

Key question:
Is the clinical effectiveness likely to be similar for people for whom **chemo-immunotherapy is unsuitable** (and therefore may receive zanubrutinib as their first treatment) and people who have had a previous treatment?

MYD88^{MUT} = Myeloid differentiation primary response gene 88 mutant; *MYD88*^{WT} Wild-type myeloid differentiation primary response gene 88; VGPR = very good partial response rate; R/R = relapsed/refractory; WM = Waldenström's macroglobulinaemia

Main evidence sources - comparators:

Absence of head-to-head data with comparators therefore indirect treatment comparisons.

Comparator trials not the same population as covered by the MA for zanubrutinib and trial populations different for each comparator.

- Indirect comparison 1: zanubrutinib vs BR in relapsed/refractory population
- Indirect comparison 2: zanubrutinib vs DRC in treatment naïve population

Trial	Intervention/ comparator	Population	Sample size	Median follow up	Follow up treatment
Tedeschi et al. 2015	Bendamustine rituximab (BR)	Relapsed/ refractory	71	19 months	Unclear. No suggestion of ibrutinib. Not approved at time of study
Dimopoulos et al. 2007 / Kastritis et al. 2015	Dexamethasone rituximab and cyclophosphamide (DRC)	Treatment-naïve (and for whom chemo-immunotherapy suitable)	72	23.4 months per Dimopoulos et al. 2007; 8 years per Kastritis et al. 2015	

For each comparison, two indirect comparison methods used

- Simulated treatment comparison (STC) (used in company base case after technical engagement)
- Matching adjusted indirect comparison (MAIC) (company's original submission: preferred by ERG)

Key question: Is the data from the BR comparison, or both the BR and DRC comparisons the most relevant?

BR = bendamustine and rituximab; DRC = dexamethasone, rituximab and cyclophosphamide; WM = Waldenström's macroglobulinaemia

Indirect treatment comparison results:

Zanubrutinib [redacted] against both BR and DRC, using both approaches (MAIC & STC). Hazard ratios differ by approach used and comparator. Wide confidence intervals around hazard ratios

Progression free survival

Overall survival

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

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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

Indirect comparisons – areas of uncertainty

Issue	Company rationale	ERG comments
Unable to adjust for all prognostic factors	• General limitation of a MAIC • Consistently showed survival benefit of zanubrutinib, both before and after matching adjustment	• Not enough data to match on all prognostic variables (e.g. ECOG performance status) • Unknown, but potentially substantial bias, could affect all results • But, little evidence of substantial bias in favour of zanubrutinib
Which method (STC or MAIC) more reliable?	• Following consultation with SCHARR expert, Company believes STC to produce more reliable and less biased results than MAIC • STC gives larger sample size (as they rely on extrapolation rather than reweighting)	• PFS and OS are immature • not all prognostic factors and effect modifiers could be considered in either comparison method • Both the MAIC and the STC are subject to bias, but ERG prefers to stick with the original MAIC

Key questions:
- **Are the hazard ratio estimates plausible?**
- **Is there a strong argument for using one method over the other (MAIC or STC)?**

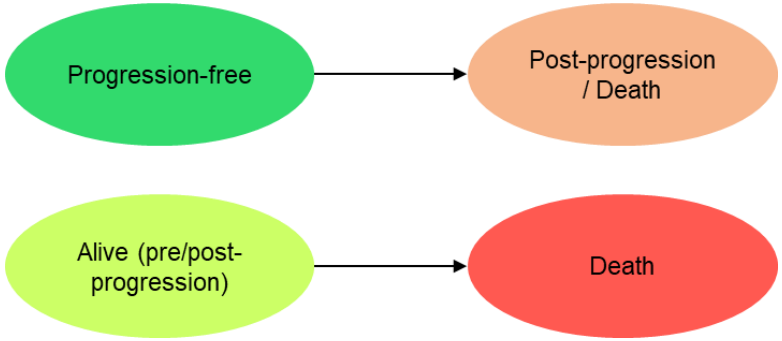
Key cost effectiveness issues

- Are the modelled outcomes based on data from the STC and MAIC plausible (for both PFS and OS), and which is the preferred comparison method?
- NICE position statement says that ibrutinib should not be included as subsequent treatment. Does committee consider that post-progression survival for BR and DRC is not reliant on subsequent ibrutinib and so these costs should be removed?
- Given the lack of evidence regarding long-term duration of treatment effect, should treatment effect cut-off be applied to PFS and OS?

Company's cost effectiveness model

Model type:	Three-state partition-survival model
Modelled patient characteristics	ASPEN ITT population
Source of PFS & OS curves	Simulated treatment comparison (ASPEN, Tedeschi et al. 2015, Dimopoulos et al. 2007 / Kastritis et al. 2015)
Source of utilities	Pre-progression: ASPEN Post-progression utility decrement: from NICE appraisals for ibrutinib in non-WM lymphoma
Comparison method (pre-TE)	Zanubrutinib vs. DRC and Zanubrutinib vs. BR (separate pairwise)
Comparison method (post TE)	Zanubrutinib vs. standard of care (weighted average of DRC & BR)

Modelled patient transitions in three-state PSM



Cycle length = 28 days
Time horizon = 30 years

The company made a number of updates to its base case in response to the ERG report, and this presentation shows revised base case **after** engagement.

BNF = British National Formulary; ITT = intention-to-treat; PSM = partitioned survival model; PSSRU: Personal Social Services Research Unit

Extrapolation of PFS and OS

ERG concerned trial data for zanubrutinib PFS and OS immature

Extrapolation of PFS

- Dependent exponential – chosen because lowest BIC & alignment with time-to-treatment discontinuation

Extrapolation of OS

- For comparison with BR used exponential distribution for zanubrutinib arm and Weibull for BR arm – chosen because clinically plausible mean OS and clinically plausible hazard pattern
- For comparison with DRC used flexible odd K1 model to extrapolate STC data (has better fit to observed OS hazards than standard parametric distributions). Dependent gamma for MAIC
- Hazards of all parametric survival models fall **below background mortality hazards** and background mortality is then assumed to apply.

ERG comments

- Only a small number of PFS and OS events had occurred at the time of this appraisal and many patients were censored - therefore extremely difficult to make long-term predictions.
- The driving factor in the model is likely **short-to-medium term OS** and the **timepoint background mortality takes over** in the zanubrutinib arm, rather than long-term extrapolation
- unclear if the company adjustment (i.e. the use of Odds k=1 model) is fully consistent with NICE DSU guidance, so prefer original parametric distributions (note minimal effect on ICER)

Plausibility of modelled overall survival

Company suggests that long term survival with zanubrutinib may be similar to observed long-term OS data for ibrutinib

Proportion of people predicted to be alive at 5 and 10 years in model

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

vs DRC	STC		MAIC	
	Zanubrutinib	DRC	Zanubrutinib	DRC
	Flexible odd K1 model		Dependent gamma	
5yr	[redacted]	[redacted]	[redacted]	[redacted]
10yr	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Source. Company technical engagement submission: Ibrutinib - digitised KM data from Treon et al. 2021; BR – digitised KM data from Tedeschi 2015; DRC – digitise KM data from Kastritis et al. 2015; zanubrutinib - ASPEN ITT trial. Abbreviations: OS = overall survival; R/R = relapsed or refractory

Company:

- Whilst the OS data for zanubrutinib is immature, it is comparable to the long-term ibrutinib OS data (from clinical trial).
- Long-term survival as a result of treatment with ibrutinib should be expected, with mean extrapolated undiscounted survival ranging from 18.40 to 18.88 years (considering all-cause mortality).
- **CE:** Given the very similar outcomes seen between ibrutinib and zanubrutinib, confident that extrapolation could be made from the longer term ibrutinib studies

ERG comments on lifelong treatment effectiveness: model driver

ERG and company disagree about whether treatment effect changes while on treatment

ERG issue: Assumption of lifelong treatment effectiveness may not be justified and preferred assumption is treatment effectiveness cut-off at 5 years (HR=1 at this point) for PFS and OS. Notes 5 year point arbitrary.

Company:

- Base case assumes no treatment effect cut-off
- Clinical data shows treatment effect persists whilst on treatment.
- ERG's 5yr assumption is extremely pessimistic and results in sudden loss of treatment benefit
- Leads to rate of progression and death for zanubrutinib being equivalent to BR or DRC - unrealistic given treatment with BTKi has resulted in long-term OS benefit in WM
- No such "kink" has ever been observed before in real-world settings
- Feedback obtained from a UK clinical expert deemed this clinically unrealistic.
- Treatment effect cut-off was not applied in six previous BTKi CLL and mantle cell lymphoma appraisals.

ERG:

- Assumption based on past appraisals is suboptimal, but so is the assumption of a lifelong treatment effect.

CE:

- Bar giving someone "extra time" as this is an extra line of effective therapy that otherwise would not be available to them, do not believe it would lead to lifelong treatment effectiveness.

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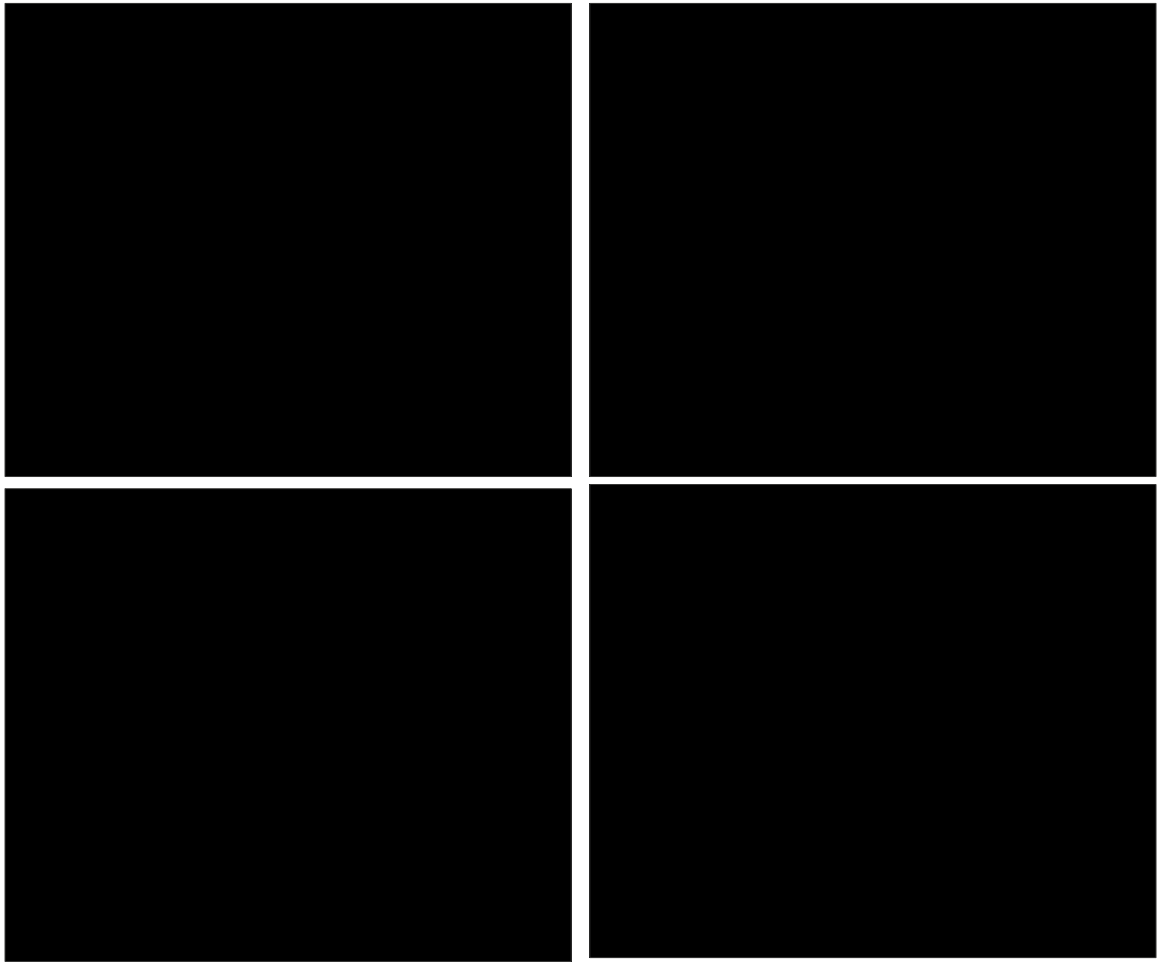
BR = bendamustine rituximab; CE = clinical expert; DRC = dexamethasone, rituximab, and cyclophosphamide OS = Overall survival; WM = Waldenström's macroglobulinaemia ; CLL, chronic lymphocytic leukaemia

Assumption of 5-year treatment effect cut-off

Implementation of 5yr cut off for treatment effect has clear effect on PFS & OS

No stopping rule proposed for zanubrutinib. ERG cited previous appraisal where 5-year treatment effect cut-off was applied to all patients while on treatment, based on clinical opinion (TA627 - Lenalidomide with rituximab for previously treated follicular lymphoma)



Key question:

Should a treatment effect cut off be applied to PFS/OS, and if so, what should it be?

- Is it reasonable to assume that the treatment stops working while still taking it?
- What is the basis for assuming all benefit ceases at 5yrs, while on drug?
- Common assumption in immunotherapies appraisals that the effect wears off 3 years after stopping

BR = bendamustine rituximab; DRC = dexamethasone, rituximab, and cyclophosphamide; PFS = Progression-free survival

Subsequent treatments

Company based the distribution of subsequent treatments on first report from Rory Morrison Database

Treatment regimen at model entry	Subsequent treatment use, %	Subsequent treatment distribution, % *(based on Rory Morrison data, adjusted to sum 100%)*		
		Ibrutinib	BR	DRC
Zanubrutinib	86[a]	0.0	60.4	39.6
BR	86[a]	72.0	0.0	28.0
DRC	86[a]	75.0	25.0	0.0

a The estimate of 86% was based on the proportion of patients receiving third-line treatment among patients progressing from second-line treatment for WM based on UK clinical experts' opinions, reported in UK NICE TA491 (ibrutinib in WM).

ERG base case: remove costs of ibrutinib after BR or DRC to align with NICE scope.

Company base case: ERG base case removes costs of ibrutinib without removing benefits. Reducing post-progression survival when removing ibrutinib as subsequent treatment results in lower ICER for zanubrutinib.

Key question:

- **Does committee consider that post-progression survival for BR and DRC is not reliant on subsequent ibrutinib and so these costs should be removed?**

Utility values: not a key model driver

Disease state	Utility value	Source of utility value
Pre-progression	0.791	ASPEN (EQ-5D- 5L cross walked to 3L (Van Hout method)
Progressed disease	0.611	Not enough data from ASPEN, so utility decrement (0.18) estimated based on previous NICE appraisals of ibrutinib (TA491, TA502)

- *Company used a smaller decrement for* **progressed disease utility** *in their original base case (0.1) (based on appraisals of ibrutinib for CLL TA429 and WM TA491) but accepted the increased decrement proposed by the ERG (0.18)* ***ERG:*** acknowledge it is not evidence based and is uncertain

- **Pre-progression utility** higher than general UK population values
- ***Company****:* Fatigue is not sufficiently addressed by EQ-5D
- Differences in clinical and real-world settings and geographical locations between ASPEN and UK.
- Value is not above the general population utility when you consider adverse events
- Results are not particularly sensitive to this parameter
- **ERG**: it is unknown to what extent the utility values used in the model are applicable to the UK population.
- **CE:** This is a statistical "quirk" and would not be clinically realistic.
- **PE:** "restored my quality of life, not dissimilar to the one I enjoyed prior to diagnosis"

Disutility values for adverse events from TA491, and TA429 (hypertension)

CE = clinical expert

Cost effectiveness results: Company base case after technical engagement

- ICER is a weighted average of the 2 pairwise comparisons to reflect 'standard care' (49% BR and 51% DRC)

	Probabilistic			Deterministic		
	Incremental costs (£)	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER
Zanubrutinib vs. standard of care	[redacted]	[redacted]	£21,023	[redacted]	[redacted]	£20,054

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

Comparison of company vs ERG exploratory base case

= differences

Parameter	Base case	
	Company	ERG
Comparators – entry regimen	Weighted average of the 2 pairwise comparisons to reflect 'standard care' (49% BR & 51% DRC)	
Subsequent treatment option	BR, DRC and ibrutinib	BR & DRC
Treatment waning	No treatment effect cut-off	5 year cut-off
Pre-progression utilities	Agreed use of age-adjusted utility values	
Post-progression utilities	Agreed a utility decrement of 0.18	
Indirect treatment comparison method	STC	MAIC

NICE

AE = adverse events; BR = bendamustine rituximab; DRC = dexamethasone, rituximab, and cyclophosphamide; OS = overall survival; PFS = Progression-free survival; STC = simulated treatment comparisons

Impact of ERG preferred assumptions on company base case

Company base case ICER (deterministic)		£20,054
Company base case assumption	**ERG preference**	**Assumption impact on company base case ICER (£)**
Ibrutinib costs and benefits included as **subsequent treatment option**	Ibrutinib costs excluded	+£23,971
No **treatment effect cut-off**	Assume treatment effect 5yr cut-off	-£10,973
Use of **STC** instead of MAIC	MAIC	+£6,785
No treatment effect cut-off + ibrutinib costs & benefits included	Assume 5-year cut-off and exclude ibrutinib costs	+£34,108
ERG exploratory base case (weighted ICER)		£78,383

ICER = Incremental cost effectiveness ratios; MAIC = matching adjusted indirect comparisons; STC = simulated treatment comparisons

Cost effectiveness results: ERG exploratory base cases

ERG preferred assumptions - Probabilistic

	Total costs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER
Zanubrutinib (weighted)	[redacted]	[redacted]	[redacted]	[redacted]	£86,675
SoC	[redacted]	[redacted]			

ERG preferred assumptions - deterministic

	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Weight results (49% BR, 51% DRC)					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	£78,383
SoC	[redacted]	[redacted]			

NICE

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

Key cost effectiveness issues

- Are the modelled outcomes based on data from the STC and MAIC plausible (for both PFS and OS), and which is the preferred comparison method?
- NICE position statement says that ibrutinib should not be included as subsequent treatment. Does committee consider that post-progression survival for BR and DRC is not reliant on subsequent ibrutinib and so these costs should be removed?
- Given the lack of evidence regarding long-term duration of treatment effect, should treatment effect cut-off be applied to PFS and OS?

Back-up slides

Cost effectiveness results: ERG exploratory base cases

ERG preferred assumptions - Probabilistic

	Total costs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER
Zanubrutinib (weighted)	[redacted]	[redacted]	[redacted]	[redacted]	£86,675
SoC	[redacted]	[redacted]			

	Total costs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER
Zanubrutinib (match BR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BR	[redacted]	[redacted]			
Zanubrutinib (match DRC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DRC	[redacted]	[redacted]			

NICE

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

Cost effectiveness results: ERG exploratory base cases

ERG preferred assumptions - deterministic

	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Weight results (49% BR, 51% DRC)					
Zanubrutinib	[redacted]	[redacted]	[redacted]	[redacted]	£78,383
SoC	[redacted]	[redacted]			

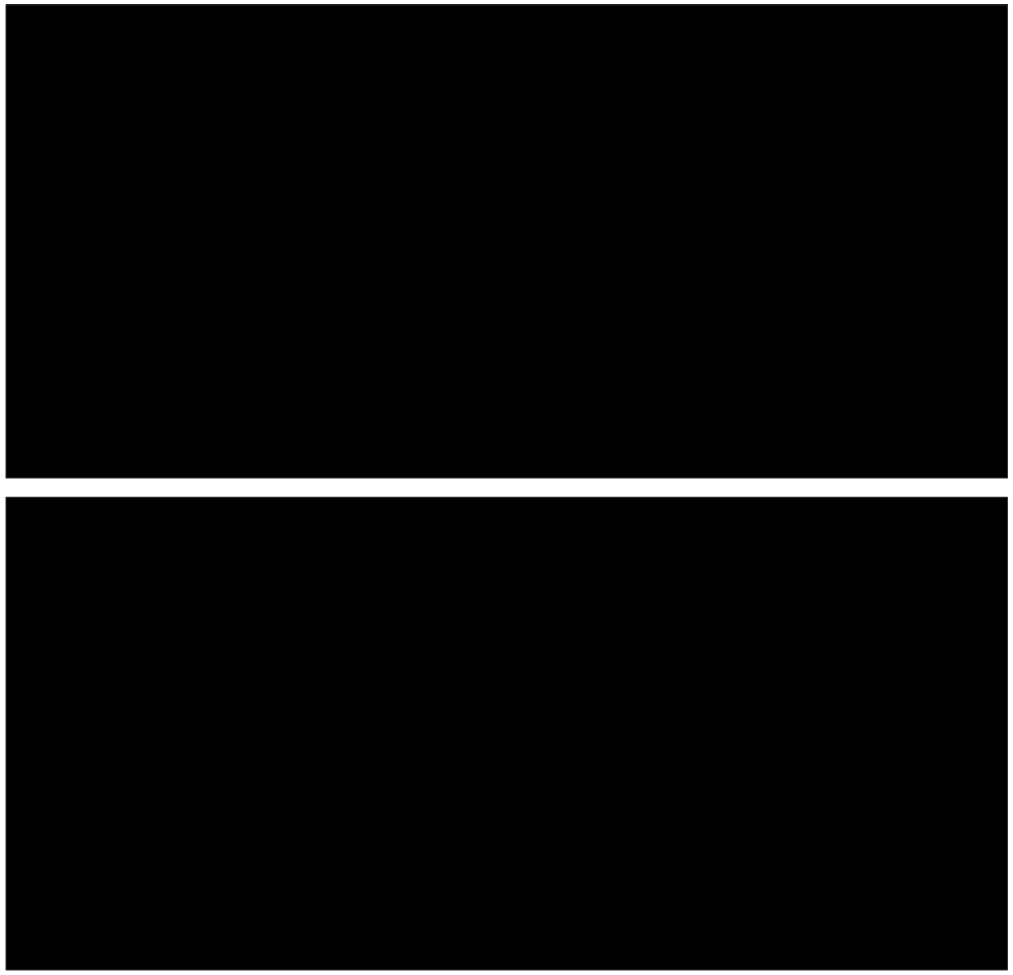
	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Zanubrutinib (match BR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BR	[redacted]	[redacted]			
Zanubrutinib (match DRC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DRC	[redacted]	[redacted]			

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

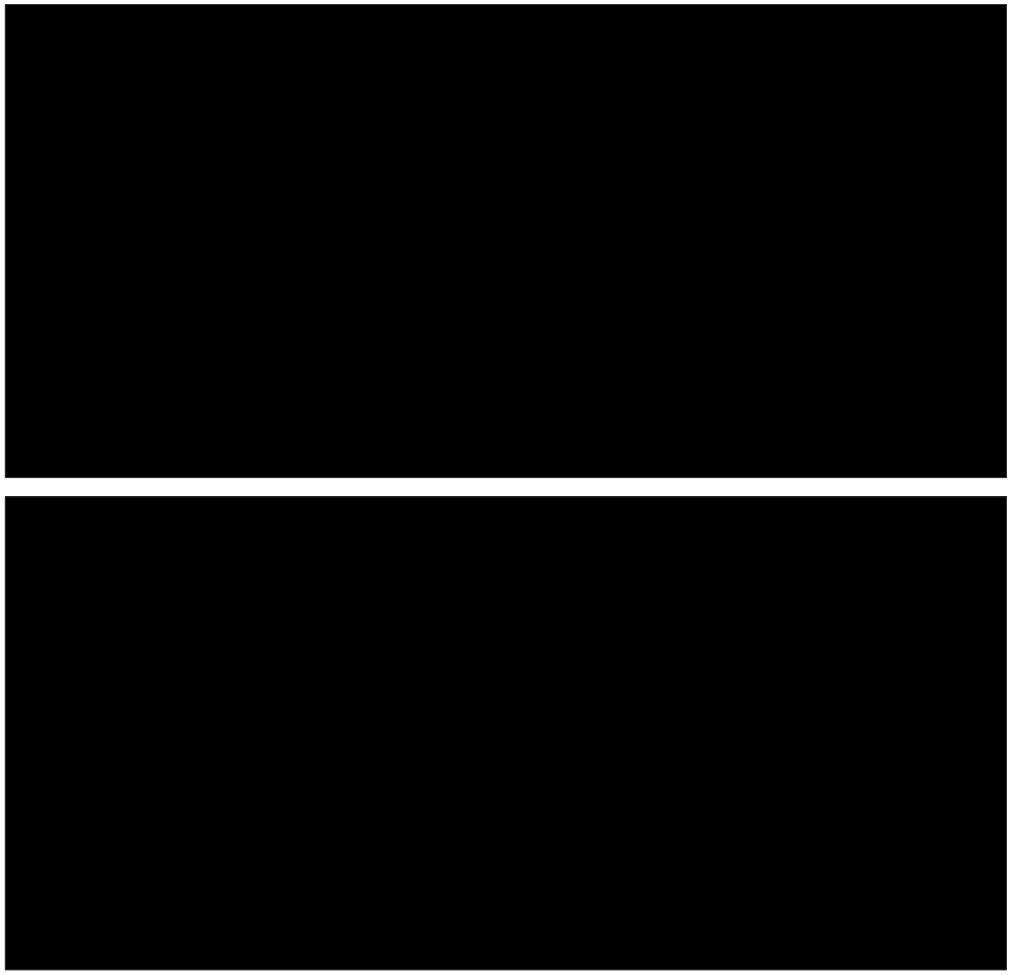
Progression free survival

Zanubrutinib [redacted] vs BR and DRC, regardless of comparison method

ERG base case: MAIC



Company base case: STC



BR = bendamustine rituximab; MAIC = matching adjusted indirect comparisons; PFS = progression-free survival; STC = simulated treatment comparisons

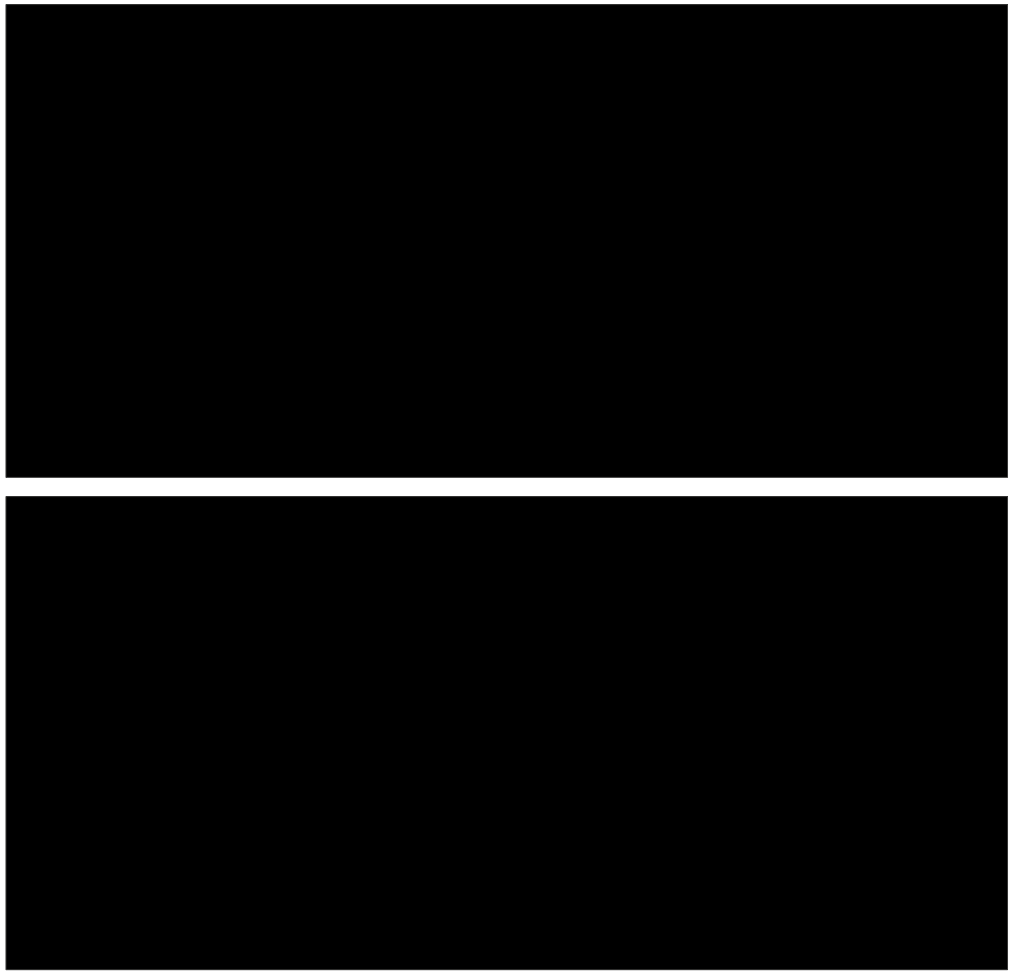
Overall Survival

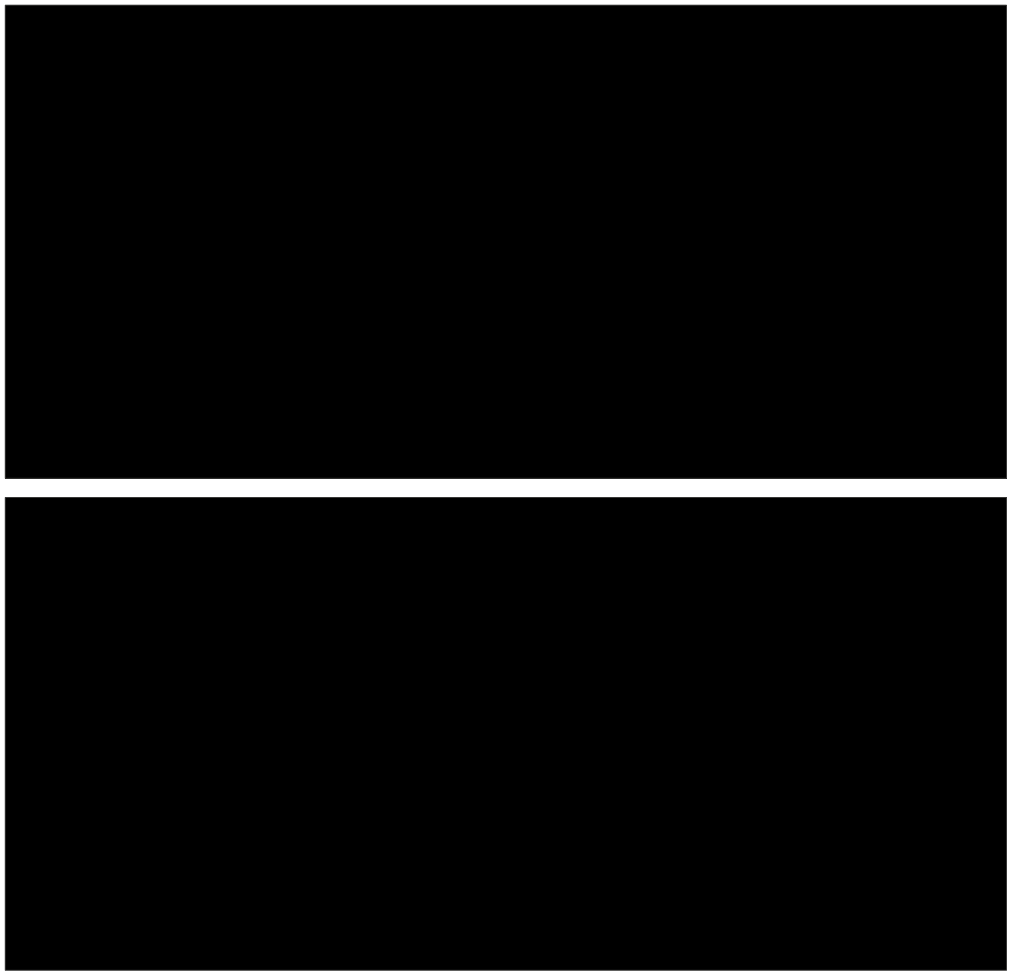
Zanubrutinib [redacted] vs BR and DRC, regardless of comparison method

[redacted]

ERG base case: MAIC

Company base case: STC





BR = bendamustine rituximab; MAIC = matching adjusted indirect comparisons; OS = overall survival; STC = simulated treatment comparisons