Zanubrutinib for treating relapsed or refractory marginal zone lymphoma [ID5085]

PART 1: For PROJECTOR – contains noCON information

Technology appraisal committee C [7 May 2024]

Chair: Stephen O'Brien

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Company: BeiGene

Zanubrutinib for treating marginal zone lymphoma

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on marginal zone lymphoma*

Rare, slow-growing, B-cell lymphoma commonly found at edges of lymph nodes

Causes: genetic and environmental factors including infectious agents

Epidemiology

- More common in men and elderly (average age at diagnosis 60-70 years); median age of 69 years for advanced MZL needing systemic therapy
- Annual UK incidence: 4.1 per 100,000 persons

Diagnosis and classification

- 3 subtypes based on tissue of origin: extranodal or MALT, nodal, splenic
- Lugano staging system: common in clinical practice
- Advanced MZL: relapsing and remitting pattern

Symptoms

- Few people have symptoms at diagnosis
- Common symptoms: fever, weight loss, night sweats, fatigue, lymphadenopathy, splenomegaly, cytopenia, site-specific complications

*See appendix – Slide 29

Abbreviations: MALT, mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma

Patient and clinical perspectives*

Limited treatment options that are well tolerated and convenient

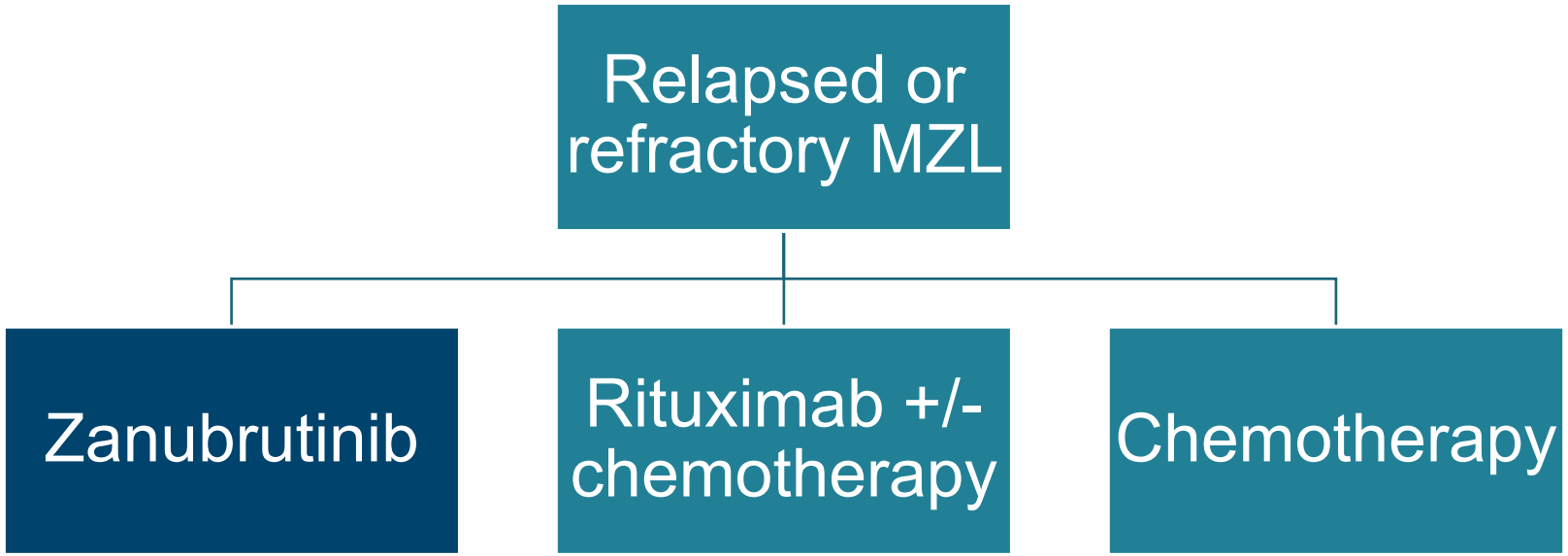
- Diagnosis can have a significant impact on people with MZL and their families affecting all aspects and their quality of life, which is as important as living longer
- Delayed diagnosis is common, affecting start of treatment
- Anxious period for people on active monitoring (watch and wait), and their families, waiting for when symptoms warrant treatment
- Coordinated multidisciplinary care needed from range of specialities including haematology, respiratory and urology
- Significant unmet need for treatments in rarer MZL, especially after relapse on first-line treatment for people who cannot have chemotherapy (frailer or older)
- Relapse is common and pathway of care not well defined
- Treatment choice depends on disease stage, MZL subtype, previous therapies, age, fitness, tolerance of previous treatment, availability of trials and clinician experience
- Tolerability and convenience are important factors when choosing treatments
- Zanubrutinib can be used by full range of R/R MZL and improve quality of life (not having treatment in hospital which can be stressful, time consuming and a financial burden)

Abbreviations: MZL, marginal zone lymphoma; R/R, relapsed or refractory

*See appendix – Slide 31

Treatment pathway and positioning of zanubrutinib

Zanubrutinib licensed for use after at least 1 prior anti-CD20-based therapy



What are the most appropriate comparators for zanubrutinib?

Abbreviations: MZL, marginal zone lymphoma; Rituximab is an anti-CD20 monoclonal antibody

Zanubrutinib (Brukinsa, BeiGene)

First licensed treatment option for relapsed or refractory MZL in UK

Marketing authorisation	• Treatment of adults with MZL who have had at least 1 prior anti-CD20-based therapy (Jan 2023)
Mechanism of action	• Irreversible inhibitor of Bruton's tyrosine kinase (BTK), a signalling molecule of B-cell and cytokine receptor pathways • Inhibits B-cell proliferation, trafficking, chemotaxis and adhesion
Administration	• Oral • Recommended total daily dose: 320 mg (either 4 x 80mg capsules once daily or 2 x 80mg capsules twice daily)
Price	• List price for 120 x 80mg capsules: £4,928.65 • Annual cost of treatment: £59,965 • Patient access scheme applicable

Abbreviations: MZL, marginal zone lymphoma

Key issues

Company has accepted EAG base case including updated costs and assumptions on adverse events

Issue	Resolved?	ICER impact
1. Clinical evidence: zanubrutinib single-arm trials and immature PFS and OS data	No	Unknown
2. Indirect treatment comparison: unanchored MAIC	No	Unknown
3. Use of partitioned survival model	No	Unknown
4. Parametric survival curves for extrapolations of PFS and OS	Partially	Medium
5. Utility values for PF and PD health states^	Yes	Small

^Not included in slides for discussion

Abbreviations: ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival

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Key issue 1: Clinical evidence for zanubrutinib*

Single arm trials with immature PFS and OS data

Company

- Pooled data from 2 single-arm phase 1/2 trials, MAGNOLIA and AU-003 (total n=88)
- Primary endpoint: ORR assessed by IRC (not used in economic model)
- Secondary endpoints in model: PFS (assessed by IRC or INV), OS, AEs, EQ5D-5L

EAG comments

- Well-designed and conducted trials with measures to minimise risk of bias
- Trials' population representative of people likely to have zanubrutinib in NHS
- Acknowledging rarity of MZL, methodological limitations of single-arm trials and in using external historical control group (HMRN registry) to assess comparative effectiveness
- Immature PFS and OS data increase uncertainty of extrapolations: median PFS and OS not reached at median 27.4 and 28.7 months follow-up in MAGNOLIA or in AU-003

Is the clinical trial evidence for zanubrutinib suitable for decision making?

Abbreviations: AE, adverse event; EQ5D, EuroQol-5 dimensions; HMRN, Haematological Malignancy Research Network; INV, investigator; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

*See appendix – Slide 32

MAGNOLIA and AU-003 results

	MAGNOLIA (n=66)		AU-003 (n=20)	
	IRC-assessed	INV-assessed	IRC-assessed (2 October 2020)	INV-assessed (31 March 2021)
PFS				
Events, n (%)	[redacted]	[redacted]	NR	NR
Median, months (95% CI)	[redacted]	[redacted]	NE (20.3, NE)	[redacted]
OS				
Events, n (%)	[redacted]		NR	[redacted]
Median, months (95% CI)	[redacted]		NR	NR
ORR (%) (95% CI)	68.2 (55.6, 79.1)	75.8 (63.6, 85.5)	16 (56.3, 94.3)	[redacted]
Median DOR, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Median TTR, months (range)	[redacted]	[redacted]	2.8	[redacted]
Median TTF, months (95% CI)	[redacted]		NR	NR

Abbreviations: CI, confidence interval; DOR, duration of response; INV, investigator; IRC, independent review committee; NE, not estimable; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure; TTR, time to treatment response

Key issue 2: Indirect treatment comparison – unanchored MAIC*

Results highly uncertain because of limited data on potential confounders

Company

- To assess comparative effectiveness of zanubrutinib, company used data from HMRN registry and pooled MAGNOLIA-003 to conduct an unanchored MAIC
  - HMRN treatments: bendamustine-rituximab, rituximab monotherapy, cyclophoshamide-rituximab +/- steroids, R-CVP, chlorambucil, R-CHOP, FCR, other rituximab, other non-rituximab
- Conducted sensitivity analyses on MAIC: MAGNOLIA data only, excluding chemotherapy alone regimens from HMRN treatments, leave-out-1 approach on 5 covariates

EAG comments

- Concerns about pooling of immunotherapy, CIT and chemotherapy regimens into 1 comparator and applicability of some treatments to current NHS practice
- Unanchored MAIC with only 5 covariates is uncertain and lack of epidemiological data mean unable to quantify impact of unknown confounders and effect modifiers

Is the unanchored MAIC appropriate for decision making?

Abbreviations: CIT, chemoimmunotherapy; FCR, fludarabine, cyclophosphamide, rituximab; HMRN, Haematological Malignancy Research Network; MAIC, matching-adjusted indirect comparison; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CVP, rituximab, cyclophosphamide, vincristine, prednisolone

*See appendix – Slide 38

MAIC results

Analysis	PFS (IRC)		OS	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Base case – MAGNOLIA-003 (n=86) vs HMRN treatments (n=[redacted])				
Pre-matching (n=86)	[redacted]	[redacted]	[redacted]	[redacted]
Model (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analyses – MAGNOLIA only (n=68)				
Pre-matching (n=68)	[redacted]	[redacted]	[redacted]	[redacted]
Model (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analyses – MAGNOLIA-003 vs HMRN treatments with chemotherapy alone excluded (n=[redacted])				
Pre-matching (n=[redacted])^	[redacted]	[redacted]	[redacted]	[redacted]
Model (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis – leave-1-out approach from base-case analysis				
Age omitted (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Response to last prior systemic therapy omitted (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
POD24 omitted (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior lines of therapy omitted (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Time since diagnosis omitted (ESS=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
^changed to match subheading data				

Is zanubrutinib clinically effective?

Abbreviations: CI, confidence interval; ESS, effective sample size; HMRN, Haematological Malignancy Research Network; HR, hazard ratio; IRC, independent review committee; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; POD24, disease progression within 2 years

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Key issue 3: Use of partitioned survival model*

State transition model may be an alternative to partitioned survival model

Company

- Used partitioned survival model in line with recommendations from NICE DSU TSD 19

EAG comments

- PSMs have a key methodological limitation such that health state occupancy is based on a set of non-mutually exclusive survival curves, where extrapolations from these survival curves may not be appropriate
- Suggested state transition model may be more appropriate but acknowledge data limitations to parameterise the model

Is the partitioned survival model appropriate for decision making?

*See appendix – Slide 40

NICE Abbreviations: DSU, Decision Support Unit; PSM, partitioned survival model; TSD, technical support document

Key issue 4: Parametric survival curves for extrapolations of PFS and OS*

Company and EAG base cases use log-logistic distribution for PFS and OS for zanubrutinib and HMRN treatments

Company

- Used Kaplan-Meier data from MAGNOLIA-003 and HMRN to extrapolate long-term PFS and OS
- Distribution chosen based on statistical goodness of fit (AIC, BIC), visual inspection and clinical plausibility
- Provided scenario analyses using different distributions

EAG comments

- Immature zanubrutinib PFS and OS data mean extrapolations are highly uncertain
- Significant heterogeneity in extrapolations from different parametric survival curves with almost identical statistical fit for MAGNOLIA-003 and HMRN data
- Lack of concurrence between estimates from different parametric survival curves and clinical expert opinion from company and EAG

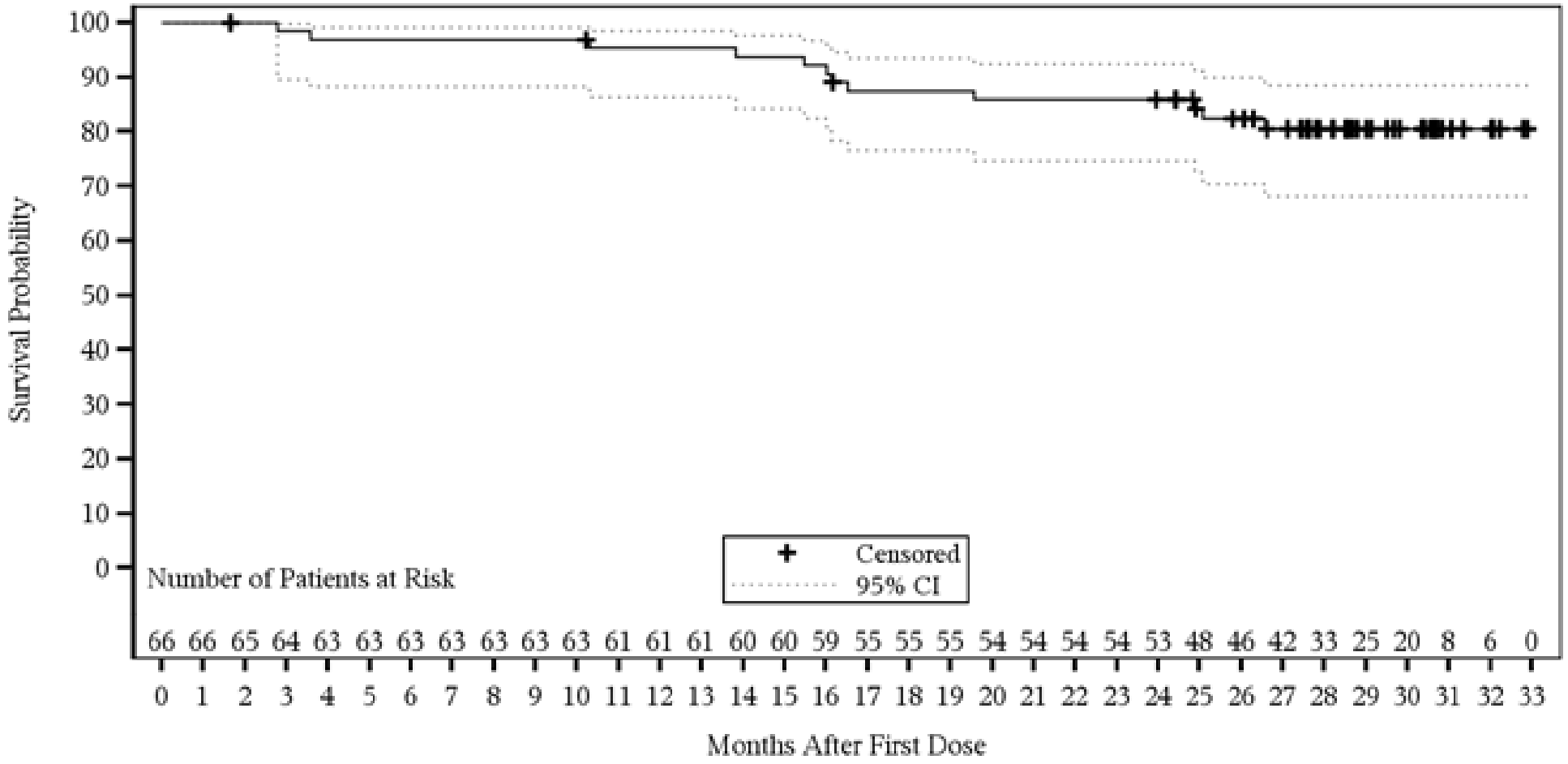
Are the log-logistic extrapolations of PFS and OS for zanubrutinib and HMRN treatments plausible?

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; HMRN, Haematological Malignancy Research Network; OS, overall survival; PFS, progression-free survival

*See appendix – Slides 41-44

MAGNOLIA overall survival: Kaplan-Meier curve

Overall survival for MAGNOLIA (n=66)

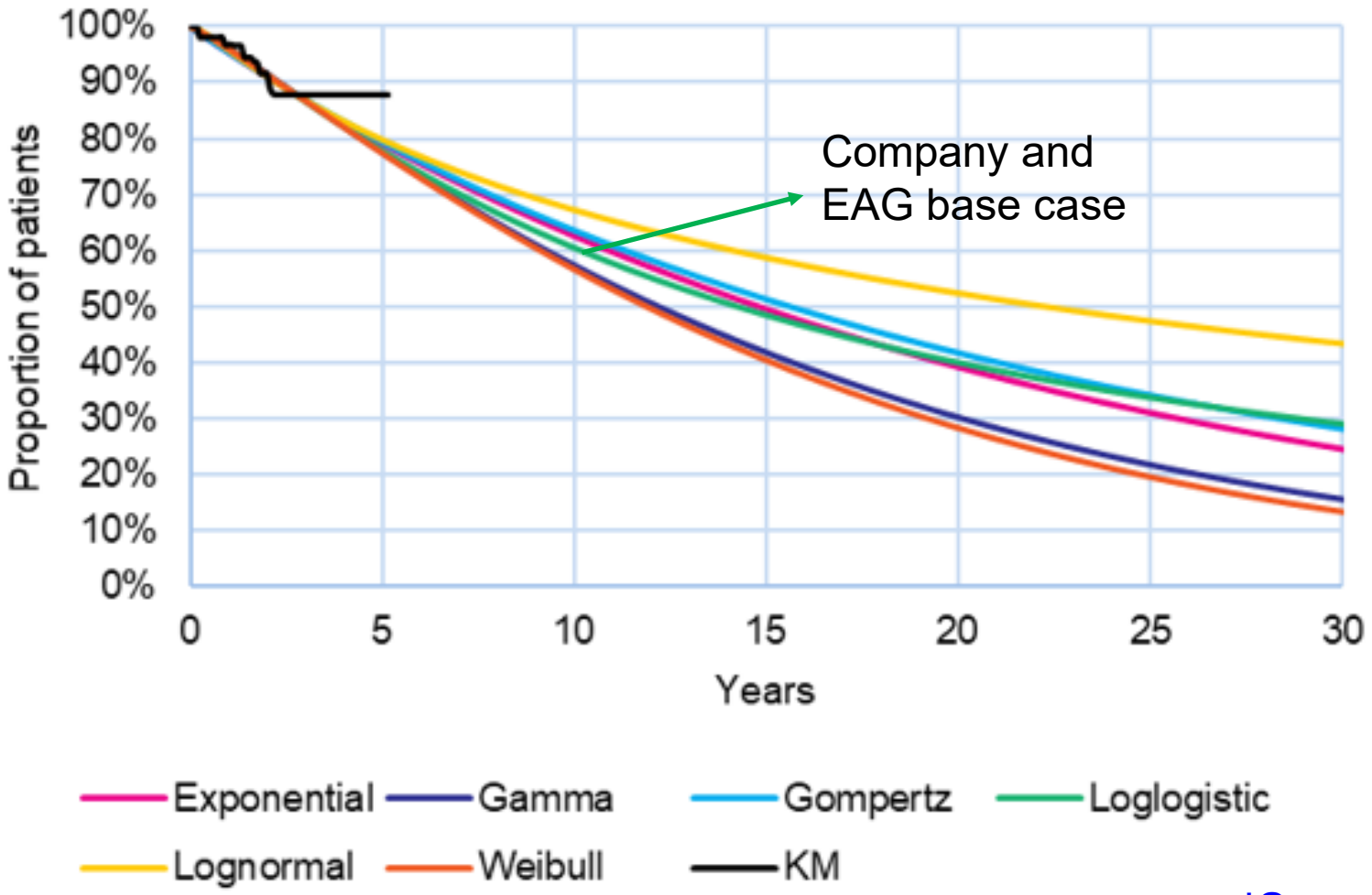


*See appendix – Slides 41-44

Extrapolations for zanubrutinib: OS

Company and EAG base cases use log-logistic distribution

KM for OS overlaid with extrapolated parametric survival curves – zanubrutinib (pooled MAGNOLIA and AU-003, weighted to HMRN treatments, n=[redacted])



Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; HMRN, Haematological Malignancy Research Network; IKM, Kaplan Meier; OS, overall survival

*See appendix – Slides 41-44

Extrapolations for HMRN treatments: OS

Company and EAG base cases use log-logistic distribution

KM for OS overlaid with extrapolated parametric survival curves – HMRN treatments n=[redacted])

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; HMRN, Haematological Malignancy Research Network; KM, Kaplan Meier; OS, overall survival

*See appendix – Slides 41-44

Summary of company and EAG base case assumptions

Company now accepts EAG base case assumptions

Assumption	Company original base case	EAG base case
Comparator	HMRN treatments: bendamustine-rituximab, rituximab monotherapy, cyclophoshamide-rituximab +/- steroids, R-CVP, chlorambucil, R-CHOP, FCR, other rituximab, other non-rituximab	Consider HMRN treatments may include therapies not used in NHS practice but accepts for base case
Treatment effectiveness and extrapolations	• PFS and OS HMRN treatments and zanubrutinib: log-logisitic • TTD zanubrutinib: log-logisitic	Consider company reasoning for choosing log-logistic over log-normal is questionable but accepts log-logistic given inherent uncertainty from immature data
Treatment waning	No waning	No waning
Health state utilities	• PF: MAGNOLIA (capped by general population utility) • PD: CADTH pCODR	• PF: as company base case • PD: adjusted for utility decrement from PF to PD states (as in TA627)
AE disutilities and durations	Same for all AEs	Use disutilities and durations specific to AE
Drug costs	BNF prices	eMIT prices

Abbreviations: AE, adverse event; FCR, fludarabine, cyclophosphamide, rituximab; HMRN, Haematological Malignancy Research Network; OS, overall survival; pCODR, pan-Canadian Oncology Drug Review; PD, progressed disease; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CVP, rituximab, cyclophosphamide, vincristine, prednisolone; TTD, time to treatment discontinuation

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

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Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme

Cost-effectiveness deterministic results*

Scenarios generally have a small impact on the ICER

No.	Scenario (applied to company and EAG base case)	Incremental costs (£) vs HMRN	Incremental QALYs vs HMRN	ICER (£/QALY) vs HMRN + / - £30,000
1	**Company and EAG base case**	See part 2	See part 2	-
2	PFS distribution (most conservative): zanubrutinib (exponential), HMRN treatments (log-normal)	↑	↓	+
3	OS distribution (most conservative analysis): zanubrutinib (Weibull) and HMRN treatments (log-normal)	↓	↓	-
4	Scenarios 2 and 3 combined	↑	↓	+
5	MAGNOLIA-003 weighted to HMRN excluding chemotherapy alone (n=[redacted])	↓	↓	-
6	CHRONOS-3 trial data (rituximab monotherapy; n=29)	↓	↓	+
7	Treatment waning: [redacted]	↓	↓	+
8	Treatment waning: [redacted]	↔	↓	-

Abbreviations: HMRN, Haematological Malignancy Research Network; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year

*See appendix – Slide 45-46

Zanubrutinib for treating marginal zone lymphoma

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- ✓ **Other considerations**
- ❑ Summary

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Other considerations

- **Innovation**
  - Zanubrutinib: innovative, novel, oral, first licensed treatment option for R/R MZL in UK
  - 'Step-change' in a treatment pathway addressing unmet need for people with no available options and can help to standardise care and pathways in R/R MZL
  - Company state that model underestimates:
    - improvement in safety profile with zanubrutinib due to limitations of HMRN data
    - reduction in resource use from oral administration
- **Equality**: No equality issues raised
- **Severity**: Company considered severity modifier not relevant for appraisal
- **Managed access**: Company has not submitted a managed access proposal

Are there any equality issues to be considered?
Are there any uncaptured benefits?

Abbreviations: HMRN, Haematological Malignancy Research Network; MZL, marginal zone lymphoma; R/R, relapsed or refractory

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Abbreviations: ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival

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Thank you

End of Part 1

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Zanubrutinib for treating marginal zone lymphoma [ID5085]

Supplementary appendix

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Marginal zone lymphoma: staging

Lugano staging commonly used in clinical practice

- **Extranodal:** arises in organs typically without lymphoid tissue (stomach, thyroid, skin, lungs, salivary glands). Associated with chronic inflammation and infections. 30% advanced at diagnosis
- **Nodal:** occurs in lymph nodes (head and neck). Presents with painless abnormal lymph nodes. 60% advanced at diagnosis
- **Splenic:** marginal zone growth pattern in spleen. May present with lymphocytosis or cytopenia. Associated with enlarged spleen. Diagnosed via blood tests, scans and bone marrow samples
- **Advanced:** disease extending beyond tissue of origin to different nodal or extranodal sites. Characterised by relapse and remission

Lymphoma extent	Ann Arbor Stage	Paris Staging	Lugano Staging
Mucosa and submucosal layer	I1E	T1N0M0	I
Muscularis propria, serosal layer	I2E	T2N0M0	I
Penetration beyond serosa	I2E	T3N0M0	I
Direct infiltration of adjacent organs	I2E	T4N0M0	IIE
Locoregional lymph nodes	II1E	T1-T4N1M0	II1
Abdominal lymph nodes (beyond local)	II2E	T1-T4N2M0	II2
Extra-abdominal lymph node spread	IIIE	T1-T4N3M0	IV
Dissemination to distant/non-GI organs	IV	T1-T4N0-N3M1	IV

Decision problem

Population, intervention and outcomes in line with final scope

Comparators from final scope

Final scope	Company	EAG comments
• Rituximab +/- chemotherapy • Chemotherapy • Best supportive care (BSC) • Splenectomy (for splenic MZL)	• Rituximab +/- chemotherapy • Chemotherapy Other options not considered appropriate for people with MZL after ≥ 1 anti-CD20-based therapy • **BSC**: Management for R/R MZL involves active monitoring or systemic treatment. BSC is only considered after all viable treatment options, including clinical trials are exhausted, and people are too frail to tolerate any active therapy. BSC considered to be end-of-life care and not relevant comparator for people having active treatment • **Splenectomy:** not recognised as option for R/R MZL (ESMO guidelines)	Consider company included comparators are those most typically seen in UK clinical practice but: • EAG clinical advice: rituximab monotherapy may have only limited use in patient population (very elderly who cannot tolerate chemotherapy) • Agree company's exclusion of BSC and splenectomy is appropriate

NICE Abbreviations: MZL, marginal zone lymphoma; R/R, relapsed or refractory

Patient and clinical perspectives

Zanubrutinib can be used by most people and is well tolerated

Submissions from Lymphoma Action, patient and clinical experts

- Uncertainty and anxiety of a diagnosis can impact on the person and their families
- MZL is rare making it more difficult to determine which treatment should be given
- Pathway of care is not well defined leading to differences in opinion between professionals
- Perceived lack of options, toxicity of current treatments with enduring fatigue, often exacerbated by need for regular hospital visits
- Zanubrutinib is well tolerated with low rates of stopping because of adverse events
- Zanubrutinib is suitable to use across full range of people presenting with R/R MZL

"*Any treatment that has lower toxicity and offers the strong possibility of good quality of life would be amazing*"

"*The toxicity of chemotherapy is a concern as it may have contributed to the impairment of my kidney function. I do worry whether I will be able to tolerate further treatment of this sort should my disease relapse*"

Link to Patient and clinical perspectives

 Abbreviations: MZL, marginal zone lymphoma; R/R, relapsed or refractory

Zanubrutinib clinical trials used in model

	MAGNOLIA (Phase 2) – median 28 mnths FUP	AU-003 Part 2 – median 39 mnths FUP
Design	International, multi-centre, single arm, open-label	
Population: adults (≥18 years)	• 68 histologically confirmed MZL (splenic, nodal, extranodal) • ≥1 prior line of therapy (inc. anti-CD20 therapy) • Documented failure to achieve PR or documented progressive disease after most recent systemic treatment	• 20 R/R MZL • ≥1 prior line of therapy
Intervention: Zanubrutinib	2 x 80mg oral capsules 2x/day in 28-day cycles (until progression, toxicity, death, study discontinuation or termination)	320mg 1x/day or 160mg 2x/day
Primary outcome: ORR by IRC	% with best overall response of CR or PR using Lugano classification from start of treatment to data cut off	% best overall response of CR, PR, stable disease, progressive disease or not evaluable
Key secondary outcomes	ORR (INV), PFS, OS, DOR, QOL, AEs	ORR (INV), DOR, PFS, TTR, OS, AEs
Locations	UK, Australia, China, Czech Republic, France, Italy, New Zealand, South Korea, USA	Australia, Italy, New Zealand, South Korea, USA

Link to Key issue 1

Abbreviations: AE, adverse event; CR, complete response; DOR, duration of response; FUP, follow up; INV, investigator; mnth, month; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; QOL, quality of life; R/R, relapsed or refractory; TTR, time to treatment response

Baseline characteristics: zanubrutinib trials and HMRN registry (1)

Characteristic	MAGNOLIA (n=68)	AU-003 (n=20)	HMRN (n=[redacted])
Mean (SD) age (years)	[redacted]	69.5 (7.47)	[redacted]
Male, n (%)	36 (52.9)	10 (50)	NR
UK, n (%)	[redacted]	0	100
ECOG PS 0, n (%)	39 (57.4)	7 (35)	NR
Mean (SD) time diagnosis to entry or first dose^ (months)	[redacted]	[redacted]	NR
Extranodal, n (%)	26 (38.2)	9 (45)	NR
Nodal, n (%)	26 (38.2)	5 (25)	NR
Splenic, n (%)	12 (17.6)	6 (30)	NR
Refractory, n (%)	22 (32.4)	4 (20)	[redacted]
1 prior therapy, n (%)	[redacted]	8 (40)	NR
2 prior therapies, n (%)	[redacted]	8 (40)	[redacted]
Mean (SD) time from last therapy to entry or first dose^^ (assumed months)	[redacted]	[redacted]	NR

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Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; HMRN, Haematological Malignancy Research Network; NR, not reported; SD, standard deviation

Link to Key issue 1

Baseline characteristics: zanubrutinib trials and HMRN registry (2)

Characteristic	MAGNOLIA (n=68)	AU-003 (n=20)	HMRN (n=[redacted])
Any prior radiation therapies, n (%)	15 (22.1)	1 (5)	NR
Prior stem cell transplant, n (%)	4 (5.9)	0	NR
Prior systemic regimens, n (%)			
Rituximab-based chemoimmunotherapy	60 (88.2)	19 (95)	NR
Alkylating agents	58 (85.3)	19 (95)	NR
R-CVP	25 (36.8)	13 (65)	[redacted]
BR	22 (32.4)	4 (20)	[redacted]
R-CHOP	17 (25)	5 (25)	[redacted]
Rituximab monotherapy	7 (10.3)	4 (20)	[redacted]
Prior anti-CD20-based therapy, %	[redacted]		[redacted]

Abbreviations: BR, bendamustine, rituximab; HMRN, Haematological Malignancy Research Network; NR, not reported; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CVP, rituximab, cyclophosphamide, vincristine, prednisolone

Link to Key issue 1

HMRN cohorts: treatment regimens

Characteristic	Immunotherapy only (n=[redacted])	Chemotherapy and chemoimmunotherapy (n=[redacted])	**Base case:** rituximab +/- chemotherapy and chemotherapy alone (n=[redacted])	Rituximab +/- chemotherapy (n=[redacted])
Bendamustine plus rituximab (%)	-	[redacted]	[redacted]	[redacted]
Rituximab monotherapy (%)	[redacted]	-	[redacted]	[redacted]
R-CVP (%)	-	[redacted]	[redacted]	[redacted]
Chlorambucil (%)	-	[redacted]	[redacted]	-
Cyclophosphamide / rituximab +/- steroid (%)	-	[redacted]	[redacted]	[redacted]
R-CHOP (%)	-	[redacted]	[redacted]	[redacted]
FCR (%)	-	[redacted]	[redacted]	[redacted]
Other rituximab (%)	-	[redacted]	[redacted]	[redacted]
Other non-rituximab (%)	-	[redacted]	[redacted]	-

Link to Key issue 1

Abbreviations: FCR, fludarabine, cyclophosphamide, rituximab; HMRN, Haematological Malignancy Research Network; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CVP, rituximab, cyclophosphamide, vincristine, prednisolone

HMRN cohorts: baseline characteristics

Characteristic	Immunotherapy only (n=[redacted])	Chemotherapy and chemoimmunotherapy (n=[redacted])	**Base case:** rituximab +/- chemotherapy and chemotherapy alone (n=[redacted])	Rituximab +/- chemotherapy (n=[redacted])
Prior therapies (%)				
2	[redacted]	[redacted]	[redacted]	[redacted]
3+	[redacted]	[redacted]	[redacted]	[redacted]
Response to last systemic therapy (%)				
Refractory	[redacted]	[redacted]	[redacted]	[redacted]
POD24	[redacted]	[redacted]	[redacted]	[redacted]
Age				
Mean age (years)	[redacted]	[redacted]	[redacted]	[redacted]
Prior therapy				
Prior anti-CD20-based therapy (%)	[redacted]	[redacted]	[redacted]	[redacted]
Time since diagnosis – mean (months)	[redacted]	[redacted]	[redacted]	[redacted]
Time since last therapy (months)	[redacted]	[redacted]	[redacted]	[redacted]

Link to Key issue 1

Abbreviations: HMRN, Haematological Malignancy Research Network; POD24, disease progression within 2 years

HMRN cohorts: Outcomes

Characteristic	Immunotherapy only (n=[redacted])	Chemotherapy and chemoimmunotherapy (n=[redacted])	**Base case:** rituximab +/- chemotherapy and chemotherapy alone (n=[redacted])	Rituximab +/- chemotherapy (n=[redacted])
PFS (%)				
at 1 year	[redacted]	[redacted]	[redacted]	[redacted]
at 3 years	[redacted]	[redacted]	[redacted]	[redacted]
at 5 years	[redacted]	[redacted]	[redacted]	[redacted]
at 6 years	[redacted]	[redacted]	[redacted]	[redacted]
OS (%)				
at 1 year	[redacted]	[redacted]	[redacted]	[redacted]
at 3 years	[redacted]	[redacted]	[redacted]	[redacted]
at 5 years	[redacted]	[redacted]	[redacted]	[redacted]
at 6 years	[redacted]	[redacted]	[redacted]	[redacted]

Link to Key issue 1

Abbreviations: HMRN, Haematological Malignancy Research Network; OS, overall survival; PFS, progression-free survival

ITC methodology: unanchored MAIC

HMRN: used to inform outcomes (PFS and OS) for comparator treatments and is largest registry dataset from 14 UK hospitals containing ~4 million people with a similar age and sex profile to rest of UK, and a comparable socioeconomic and urban/rural distribution to England. In the HMRN, clinical practice follows national guidelines, and all haematological cancers and their precursor conditions are diagnosed and coded using latest WHO ICD-O-3 classification at a single integrated laboratory, Haematological Malignancy Diagnostic Service (HMDS)

Unanchored MAIC: Patient characteristics were available from HMRN to accurately select cohort aligned with eligibility criteria of MAGNOLIA-003. IPD for baseline characteristics not available from HMRN. Used MAIC and HMRN treatments that reflect standard of care in UK

5 covariates available: prior lines of therapy (1 vs 2 vs ≥3), refractory to last therapy (yes vs no), age (mean and variance), POD24 (yes or no), median time since diagnosis (< median vs ≥ median)

HMRN treatments: bendamustine-rituximab, rituximab monotherapy, cyclophoshamide-rituximab +/- steroids, R-CVP, chlorambucil, R-CHOP, FCR, other rituximab, other non-rituximab

Abbreviations: FCR, fludarabine, cyclophosphamide, rituximab; HMRN, Haematological Malignancy Research Network; IPD, individual patient data; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; POD24, disease progression within 2 years; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CVP, rituximab, cyclophosphamide, vincristine, prednisolone

Link to Key issue 2

MAGNOLIA-003 characteristics matched to HMRN

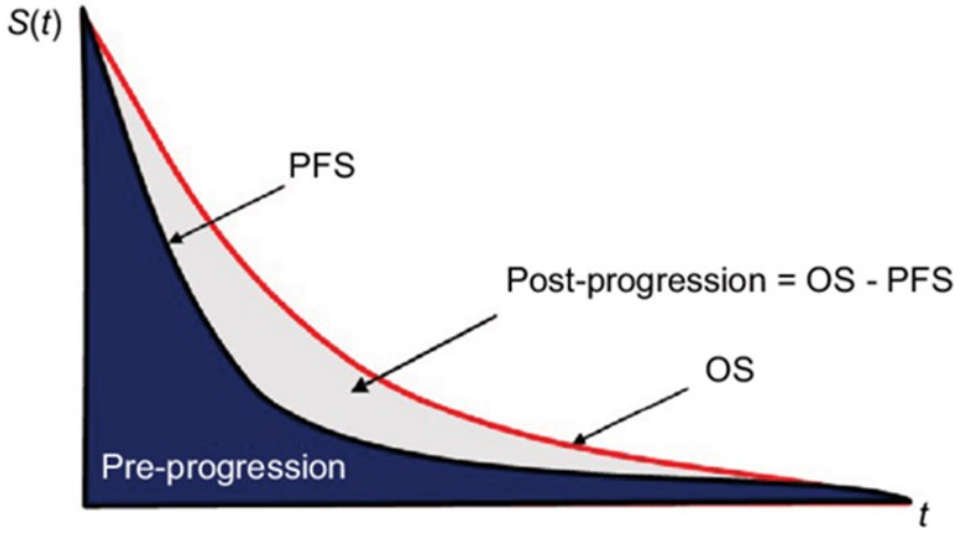
Characteristics	MAGNOLIA-003 (n=86), unweighted	MAGNOLIA-003 (ESS=[redacted]), weighted	HMRN (n=[redacted])
2 lines of prior therapy (%)	[redacted]	[redacted]	[redacted]
3+ lines of prior therapy (%)	[redacted]	[redacted]	[redacted]
Refractory response to last systemic therapy (%)	[redacted]	[redacted]	[redacted]
POD24 (%)	[redacted]	[redacted]	[redacted]
Mean age (years)	[redacted]	[redacted]	[redacted]
Time since diagnosis ≥ median (%)	[redacted]	[redacted]	[redacted]

Link to Key issue 2

NICE Abbreviations: ESS, effective sample size; HMRN, Haematological Malignancy Research Network; POD24, disease progression within 24 months of initiation of systemic therapy

Company's model overview

Model structure



- Technology affects **costs** by:
  - Higher unit price than current treatments
- Technology affects **QALYs** by:
  - Increasing PFS and OS
- Assumptions with greatest ICER effect:
  - use of MAGNOLIA trial data only for zanubrutinib rather than pooled MAGNOLIA-003 dataset
  - inclusion of age-sex matched background mortality restriction
  - implementing most conservative PFS parametric survival curve

- Partitioned survival model: 4-week cycle length, half cycle correction, lifetime horizon (27 years), NHS/PSS perspective, 3.5% discount
- Baseline characteristics: 73 years, [redacted] female, [redacted] BSA
- Base case extrapolations PFS, OS, TTD for zanubrutinib and HMRN treatments: log-logistic

Link to Key issue 3

Abbreviations: BSA, body surface area; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation

Extrapolations for zanubrutinib: PFS

Company and EAG base cases use log-logistic distribution

KM for IRC-assessed PFS overlaid with extrapolated parametric survival curves – zanubrutinib (pooled MAGNOLIA and AU-003, weighted to HMRN treatments, n=)

Distribution	Median (years)	PFS (%) at landmark timepoints in years					
		1	2	5	10	20	30
KM data	Not reached			-	-	-	-
Exponential							
Weibull							
Gompertz							
Log-normal							
Log-logistic							
Gamma							

Distribution	Zanubrutinib	
	AIC	BIC
Exponential		
Weibull		
Gompertz		
Log-normal		
Log-logistic		
Gamma		

NICE

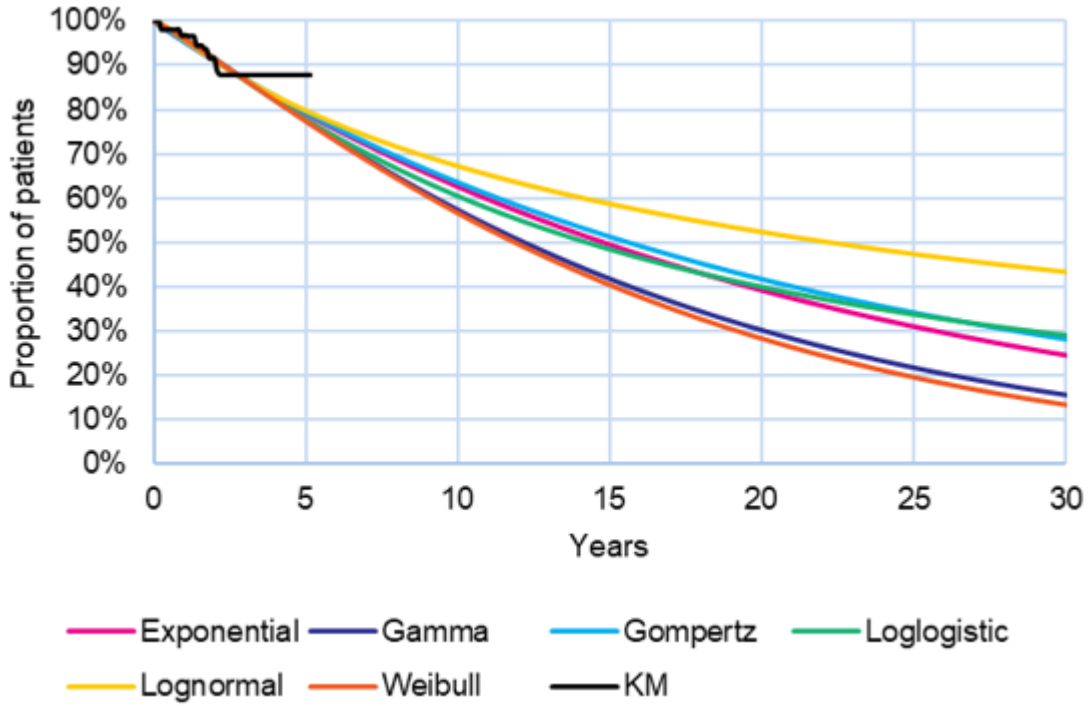
Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; HMRN, Haematological Malignancy Research Network; IRC, independent review committee; KM, Kaplan Meier; PFS, progression-free survival

Link to Key issue 4

Extrapolations for zanubrutinib: OS

Company and EAG base cases use log-logistic distribution

KM for OS overlaid with extrapolated parametric survival curves – zanubrutinib (pooled MAGNOLIA and AU-003, weighted to HMRN treatments, n=[redacted])



Distribution	Median (years)	OS (%) at landmark timepoints in years					
		1	2	5	10	20	30
KM data	Not reached	[redacted]	[redacted]	-	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Distribution	Zanubrutinib	
	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

NICE

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; HMRN, Haematological Malignancy Research Network; IKM, Kaplan Meier; OS, overall survival

Link to Key issue 4

Extrapolations for HMRN treatments: PFS

Company and EAG base cases use log-logistic distribution

KM for PFS overlaid with extrapolated parametric survival curves – HMRN treatments n=[redacted])

Distribution	Median (years)	PFS (%) at landmark timepoints in years					
		1	2	5	10	20	30
KM data	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Distribution	HMRN treatments	
	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

NICE

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; HMRN, Haematological Malignancy Research Network; KM, Kaplan Meier; PFS, progression-free survival

Link to Key issue 4

Extrapolations for HMRN treatments: OS

Company and EAG base cases use log-logistic distribution

KM for OS overlaid with extrapolated parametric survival curves – HMRN treatments n=[redacted])

Distribution	Median (years)	OS (%) at landmark timepoints in years					
		1	2	5	10	20	30
KM data	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Distribution	HMRN treatments	
	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; HMRN, Haematological Malignancy Research Network; KM, Kaplan Meier; OS, overall survival

Link to Key issue 4

Cost-effectiveness deterministic results (1)

Scenarios generally have a small impact on the ICER

No.	Scenario (applied to company and EAG base case)	Incremental costs (£) vs HMRN	Incremental QALYs vs HMRN	ICER (£/QALY) vs HMRN + / - £30,000
1	**Company and EAG base case**	See part 2	See part 2	**-**
2	PFS distribution same for zanubrutinib and HMRN treatments: Weibull	↔	↔	**-**
3	PFS distribution: zanubrutinib and HMRN treatments (exponential)	↔	↔	**-**
4	OS distribution: zanubrutinib and HMRN treatments (exponential)	↑	↑	**-**
5	TTD distribution for zanubrutinib (exponential)	↓	↔	**-**
6^	CHRONOS-3 trial data (rituximab monotherapy; n=29) and most conservative extrapolations for PFS and OS PFS: zanubrutinib (exponential), CHRONOS (log-logistic) OS: zanubrutinib (Gompertz), CHRONOS (exponential)	↓	↓	**Dominated**

^EAG comment: OS curve for zanubrutinib crosses below OS curve for comparator after about 5 years

Link to Cost-effectiveness results

NICE Abbreviations: HMRN, Haematological Malignancy Research Network; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TTD, time to treatment discontinuation

Cost-effectiveness deterministic results (2)

Scenarios generally have a small impact on the ICER

No.	Scenario (applied to company and EAG base case)	Incremental costs (£) vs HMRN	Incremental QALYs vs HMRN	ICER (£/QALY) vs HMRN + / - £30,000
1	**Company and EAG base case**	See part 2	See part 2	-
7	Adjusted (by standardised mortality ratio = 1.41) age-gender matched background mortality restriction applied	↓	↓	+
8	Time horizon: 20 years	↓	↓	-
9	Patient history/physical exam in progression-free (PF) health state: 0.149	↓	↔	-
10	Patient history/physical exam in PF health state: 0.329	↑	↔	-
11	Haematologist visits in PF health state: 0.149	↓	↔	-
12	Haematologist visits in PF health state: 0.329	↑	↔	-
13	Relaxing assumption: 1-off subsequent treatment cost (zanubrutinib and HMRN treatments)	↔	↔	-

Link to Cost-effectiveness results

NICE

Abbreviations: HMRN, Haematological Malignancy Research Network; ICER, incremental cost-effectiveness ratio; PF, progression free; QALY, quality-adjusted life year