Mosunetuzumab for treating relapsed or refractory follicular lymphoma [ID3931]

Public – redacted

Technology appraisal committee C [14 March 2023]

Chair: Stephen O'Brien

Evidence assessment group: Warwick Evidence

Technical team: Catherine Spanswick, Louise Crathorne, Christian Griffiths, Ross Dent

Company: Roche

Mosunetuzumab for treating relapsed or refractory follicular lymphoma

- ✓ **Background**
- ❑ ACM1 conclusions overview
- ❑ Clinical evidence
- ❑ Modelling
- ❑ Points to consider
- ❑ Base case assumptions and results summary
- ❑ Other considerations: Equality, severity, managed access proposal incl. Cancer Drugs Fund
- ❑ Summary

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Abbreviations: ACM1, 1st appraisal committee meeting

RECAP

Mosunetuzumab (Lunsumio, Roche)

Table: Technology details

Marketing authorisation	Indicated as monotherapy for the treatment of adult patients with relapsed or refractory follicular lymphoma who have received at least 2 prior systemic therapies
Mechanism of action	• Bi-specific antibody targeting CD20 on B-cells and CD3 on T-cells. When both arms of mosunetuzumab are bound, T-cell activation and toxin release (perforin and granzyme) lead to B-cell lysis and cell death
Administration	• Intravenous infusion • Up to 8 cycles in people who achieve a complete response after Cycle 8 • Additional 9 cycles (17 cycles in total) can be given in people who achieve a partial response or stable disease, unless unacceptable toxicity or disease progression • Prophylactic premedication recommended for cytokine release syndrome and infusion related reactions
Price	• List price per dose: £220 for 1 mg, £440 for 2 mg, £6,600 for 30 mg, £13,200 for 60 mg • Total at list price: £66,660 for 8 cycles, £126,060 for 17 cycles • Confidential patient access scheme available

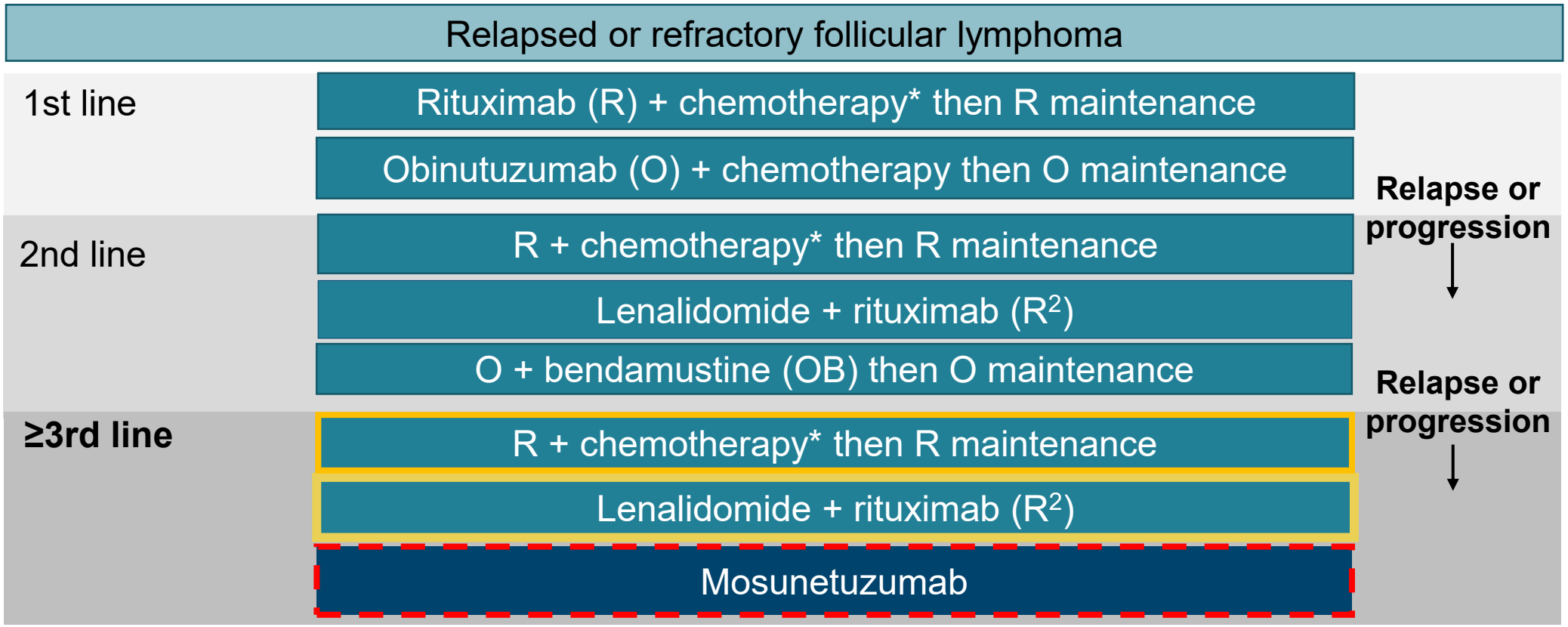
RECAP

Treatment pathway

Technology being evaluated

Comparator in model

Mosunetuzumab positioned after at least 2 lines of systemic therapy



*Chemotherapy with R includes R-CHOP, R-CVP and RB, and is represented by RB only in the model

Note: ASCT an option if remission after 2nd or 3rd line treatment and patient fit enough. If relapse or progression post-ASCT, then 3rd line+ treatment

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Abbreviations: ASCT, autologous stem cell transplant; B, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CVP, cyclophosphamide, vincristine and prednisolone; O, Obinutuzumab; R, rituximab; R2, rituximab + lenalidomide

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Mosunetuzumab is not recommended

Committee conclusions at ACM1

Clinical effectiveness

- Clinical evidence suggests that follicular lymphoma responds to treatment with mosunetuzumab, so the cancer may not get worse as quickly. But these results are from a single arm open label study, **GO29781.**
    - Study included people with a poor prognosis and was broadly generalisable to UK clinical practice
- Indirect comparisons of mosunetuzumab with other treatment options very uncertain with inconsistent results

Cost effectiveness

- Most likely cost-effectiveness estimates for mosunetuzumab highly uncertain and do not represent a cost-effective use of NHS resources

Managed access

- More data would not sufficiently resolve the high level of uncertainty
    - Unclear how much longer-term data can be collected from GO29781 single arm study
    - Timeframe for data collection may not be long enough to demonstrate OS benefit, a key uncertainty
    - Unlikely SACT data would sufficiently resolve the high uncertainty associated with the ITCs
- Mosunetuzumab is not likely to be cost effective

Abbreviations: ACM1, 1st appraisal committee meeting

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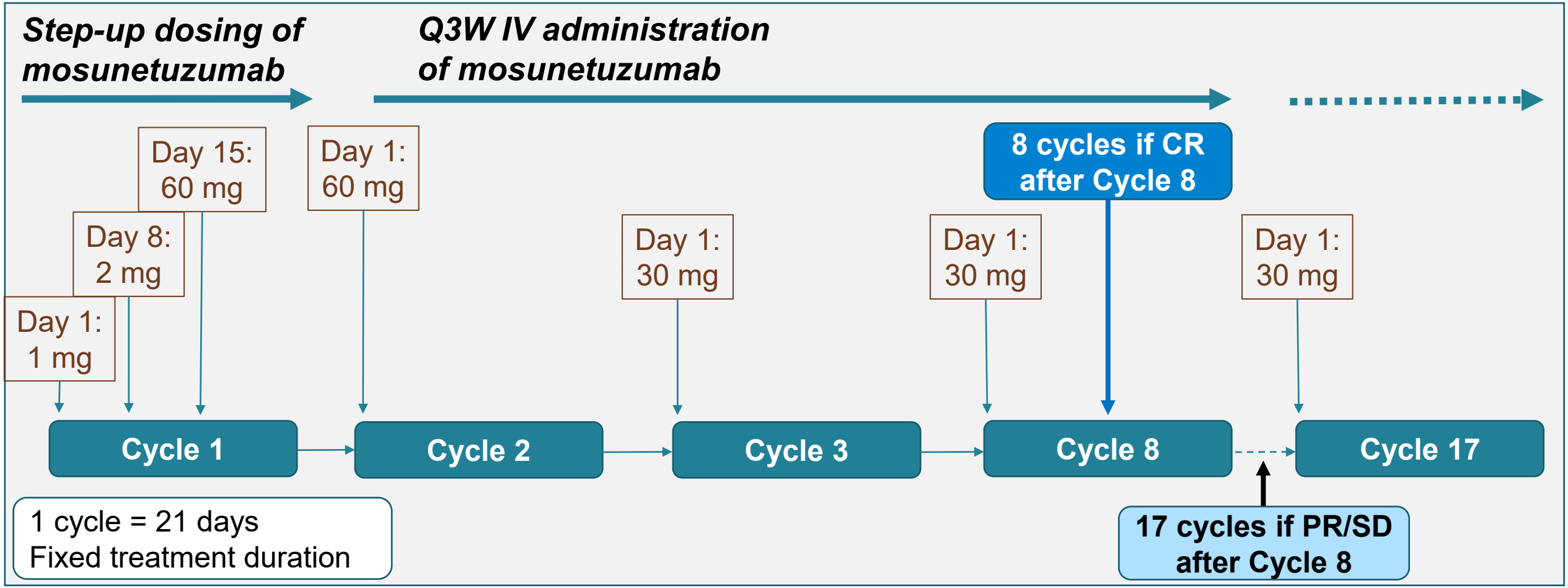
Key clinical study: Phase 1/2, multicentre, singe-arm, open label

GO29781 pivotal cohort (N=90): relapsed/refractory follicular lymphoma (Grade 1–3a) treated with ≥2 prior therapies including both anti-CD20 and alkylating agent

- Primary outcome: % patients with best overall response of complete response (CR; IRF assessed)



Response assessed by CT and PET-CT using Cheson 2007 criteria

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Abbreviations: CR, complete response; CT, computed tomography; IRF, independent review facility; IV, intravenous; PET positron emission tomography; PR, partial response; Q3W, every 3 weeks; SD, stable disease

GO29781 pivotal cohort results for tumour response

60% of patients had a complete response to mosunetuzumab

Primary efficacy endpoint (data cut off 15 March 2021):
Complete response rate (IRF assessed) of 58%, significantly greater than in historical controls (14%, p<0.0001)

Table: Tumour response data at 27 August 2021 data cut off:

	Mosunetuzumab (n=90)
Response classification by IRF with or without PET scan, %	
Complete response (CR)	60
Partial response (PR)	[redacted]
Stable disease (SD)	[redacted]
Progressive disease (PD)	[redacted]
Missing	[redacted]

- Median follow-up of 18 months
- At latest data cut ([redacted], median follow-up [redacted] months), [redacted]

Duration of response (IRF):

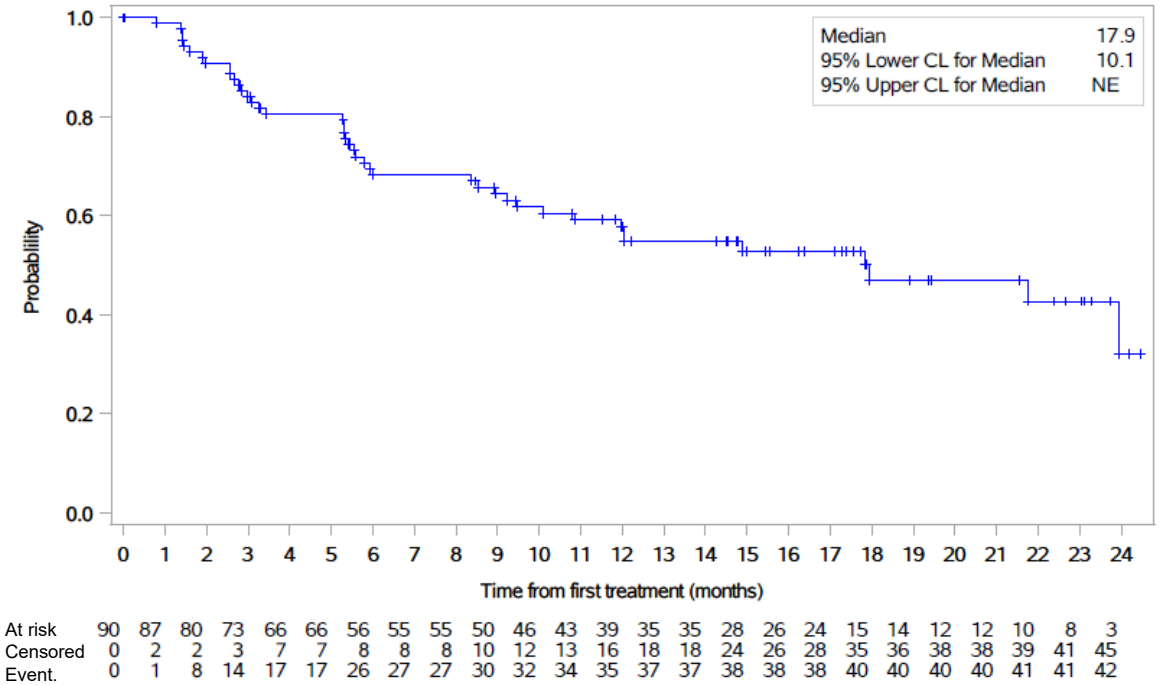
- From time of response, median follow-up was 15 months
- 40% of patients who had CR or PR subsequently had disease progression or died
- At 12 and 18 months, 62% and 57% of patients, respectively, remained in response

Abbreviations: CR, complete response; IRF, independent review facility; PET, positron emission tomography; PD, progressive disease; PR, partial response; SD, stable disease

GO29781 pivotal cohort results for survival endpoints

Median progression-free survival 17.9 months, overall survival data is immature

Kaplan–Meier plot of progression-free survival:



Kaplan–Meier plot of overall survival:

Table: Survival outcomes at 27 August 2021 data cut off

Mosunetuzumab (N=90)	PFS (IRF assessed)	OS (IRF assessed)
Events, n	42	8
Median survival	17.9 months	Not reached
Rate at 12 months	58%	93% [6/90]
Rate at 18 months	46%	91% [8/90]

- At latest data cut ([redacted], median follow-up [redacted] months), [redacted]

Abbreviations: CL, confidence limit; IRF, independent review facility; n, number; NE, not evaluable; OS, overall survival; PFS, progression free survival

RECAP

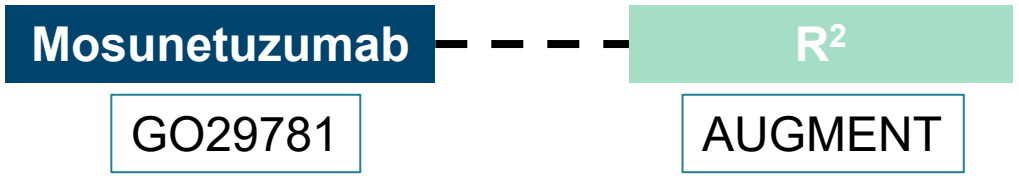
Used in model

Company's indirect treatment comparison methods

ITCs of mosunetuzumab vs R^2 and vs RB were conducted

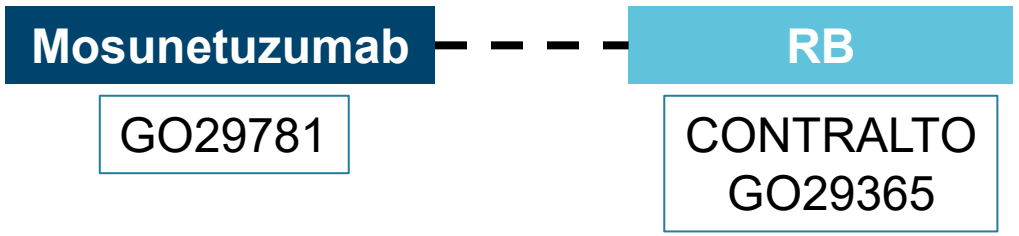
Unanchored matching-adjusted indirect comparison (MAIC)

- GO29781 pivotal cohort population was matched and statistically adjusted to resemble that of comparator study (AUGMENT), to predict treatment effect if mosunetuzumab had been evaluated in this population



Propensity score analyses (PSA)

- Possible with IPD from RB study (and mosunetuzumab study)
- Estimate of treatment effect after accounting for differences in covariates believed to be prognostic factors or treatment-effect modifiers across treatment groups with IPD



- IPTW approach, which uses weighting based on propensity score, used in base case post-TE

ITC outcomes: OS, PFS, ORR, CR, treatment discontinuation due to AEs

Abbreviations: AE, adverse event; B, bendamustine; CR, complete response; IPD, individual patient data; inverse probability of treatment weighting, IPTW; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PSA, propensity score analysis; R^2, rituximab + lenalidomide; R, rituximab

[redacted]

Summary of ITC results

EAG notes conflicting results across the ITCs leading to high uncertainty

Table: Company's summary of ITC results

[redacted]

Company comments on MAIC

Eligibility criteria of studies not fully harmonised → introduced bias

In AUGMENT (R^2)

- only 47% patients were 3rd line+ vs all 3rd line+ in GO29781
- all were non-refractory to R vs 79% refractory to R in GO29781

- MAIC of mosunetuzumab vs R^2: mosunetuzumab [redacted]
  - HR (95% CI) weighted estimates for tumour response: CR, [redacted]; OR [redacted]
- PSA of mosunetuzumab vs RB: mosunetuzumab [redacted]
  - HR (95% CI) weighted estimates for survival: PFS, [redacted]; OS [redacted]

EAG comments – high uncertainty

- Conflicting results across ITCs where the effect of mosunetuzumab varies in direction and magnitude
- [redacted]

Abbreviations: AE, adverse event; B, bendamustine; CR, complete response; EAG, external assessment group; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; OR, overall response; OS, overall survival; PFS, progression-free survival; PSA, propensity score analysis; R^2, rituximab + lenalidomide; R, rituximab

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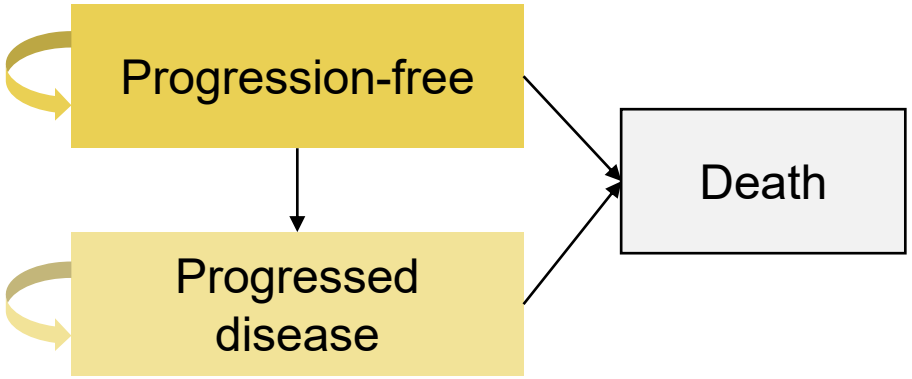
Company's model overview

3 state partitioned survival model

Model structure



Background: The NICE TA627 committee found this model structure acceptable for decision making

EAG comments: Partitioned survival model appropriate for modelling the decision problem

- Technology affects **costs** by:
  - Higher costs than either comparator (R^2, RB) in company and EAG base cases
- Technology affects **QALYs** by:
  - Comparison with R^2: fewer QALYs than comparator in company and EAG base cases
  - Comparison with RB: more QALYs than comparator in company and EAG base cases
- Assumptions with greatest ICER effect:
  - Comparison with R^2: setting PFS equal to R^2 beyond [redacted]
  - Comparison with RB: pooling OS data for both arms
  - Both comparisons: source of utility values → explored in EAG scenario analysis for ACM2

Abbreviations: B, bendamustine; EAG, external assessment group; ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression free survival; QALY, quality adjusted life year; R^2, rituximab + lenalidomide; R, rituximab

Modelling of progression-free survival and overall survival

Company and EAG agree on most curve choices used and but not on pooling

Background

- EAG prefers to use pooled estimates to extrapolate OS due to immaturity of mosunetuzumab data, few events occurring and because no significant differences seen in ITC results
- Company and EAG also differ on PFS extrapolation used for mosunetuzumab in R^2 comparison

Table: Base case survival extrapolations used after technical engagement

	PFS		OS	
	Company	**EAG**	**Company**	**EAG**
For comparison with R^2				
Mosunetuzumab	Weibull	Log normal [redacted], then same as R^2	Weibull	Weibull (pooled)
R^2	Log normal	Log normal		
For comparison with RB				
Mosunetuzumab	Log normal	Log normal	Exponential	Exponential (pooled)
RB				
[redacted]				

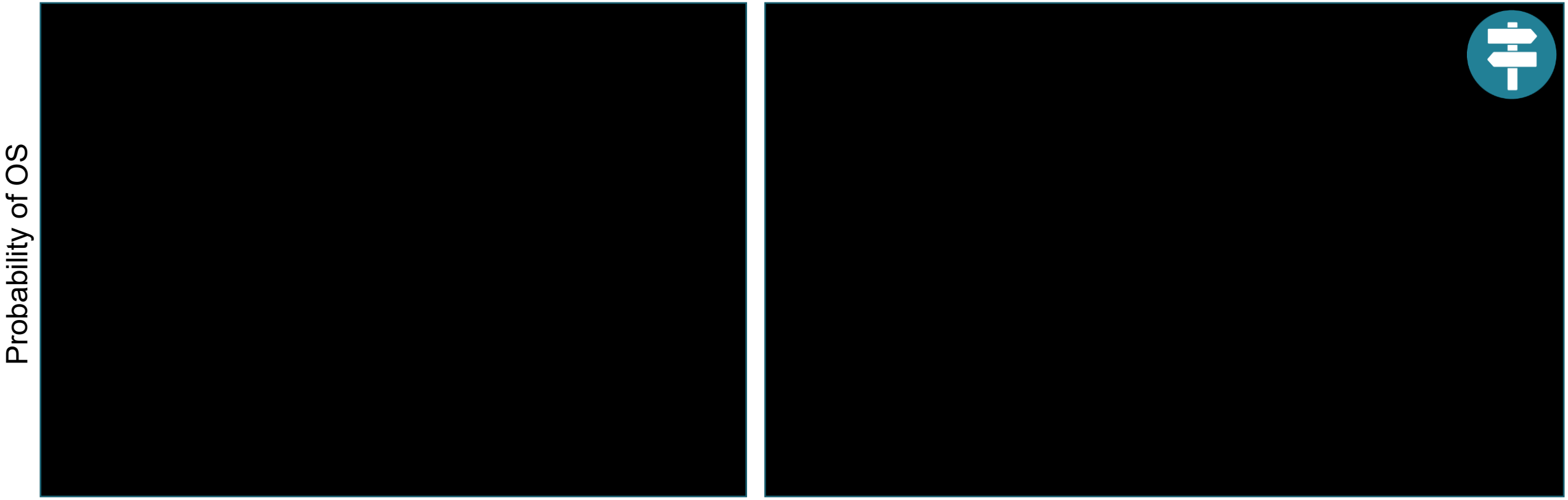
Abbreviations: B, bendamustine; EAG, external assessment group; ITC, indirect treatment comparison; mo, months; OS, overall survival; PFS, progression-free survival; R^2, rituximab + lenalidomide; R, rituximab

OS extrapolations of mosunetuzumab for comparison with R^2

Company and EAG agree on choice of curve but EAG prefers to pool OS data

Company's OS extrapolations after TE

EAG's preferred OS extrapolation – pooled*



Company – patients alive at 20 years:

- Mosunetuzumab, [redacted] vs R^2, [redacted]

*KM data in EAG model may contain an error but extrapolation is accurate

EAG: Pooled OS → ICER quadrant change

Abbreviations: EAG, external assessment group; KM, Kaplan–Meier; ICER, incremental cost effectiveness ratio; OS, overall survival; R^2, rituximab + lenalidomide; TE, technical engagement

ICER impact: Large

OS extrapolations of mosunetuzumab for comparison with RB

Company and EAG agree on choice of curve but EAG prefers to pool OS data

Company's OS extrapolations after TE

EAG's preferred OS extrapolation – pooled*

*KM data in EAG model may contain an error but extrapolation is accurate

Company – patients alive at 20 years:

- Mosunetuzumab, [redacted] vs RB, [redacted]

EAG: Pooled OS data → large impact on ICER

Abbreviations: B, bendamustine; EAG, external assessment group; KM, Kaplan–Meier; ICER, incremental cost effectiveness ratio; OS, overall survival; R, rituximab; TE, technical engagement

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  - **–DG consultation responses and outstanding issues**
  - – Representativeness of RB for R-Chemo
  - – ITC comparison of mosunetuzumab versus R^2
  - – Subsequent therapy assumptions
  - – Utility values
- ❑ Base case assumptions and results summary
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Abbreviations: ACM1, 1st appraisal committee meeting; B, bendamustine; DG, draft guidance; R, rituximab; R2, rituximab + lenalidomide

Draft guidance consultation responses

Summary of consultation responses

Received from:

- 1 professional organisation consultee: Association of Cancer Physicians
- 1 web comment: on behalf of NCRI Lymphoma Group
- Company: Roche
    1. Representativeness of RB for R-Chemo at 3rd line+
    2. ITC comparison of mosunetuzumab versus R^2
        i. Challenge of single arm evidence – not cost-effective at zero cost?
    3. Subsequent therapy assumptions
    4. Utility values
    5. Managed access proposal

Company base case

Other considerations

Abbreviations: B, bendamustine; ITC, indirect treatment comparison; NCRI, National Cancer Research Institute; R^2, rituximab + lenalidomide; R, rituximab

Association of Cancer Physicians & NCRI Lymphoma Group perspectives (1/2)

Recommendation does not address unmet need

- Lack of treatment options at 3rd or 4th line
  - Many people have had 1 line of immunochemotherapy (ICT) followed by R^2, or 2 lines of ICT
  - Same treatment rarely re-used on relapse due to cumulative toxicities / prior refractoriness
  - More intensive therapy typically contraindicated after non-intensive 1st line therapy
- Does not consider early treatment failure, which leads to inferior outcomes
- Mosunetuzumab an extra line of therapy in critical area

Limitations with comparators / comparator data considered

- R-CHOP rarely used → number of suitable alternative treatments overestimated
- HMRN registry data available for R-CHOP and R-CVP, and real world data on '3rd line treatment' (3 datasets completed[a])

[a]SCHOLAR-5 dataset (Ghione P et al, Blood. 2022); US multi-centre cohort (Casulo et al, 2022); single centre UK dataset (Linton K et al, Blood 2021)

Abbreviations: B, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CVP, cyclophosphamide, vincristine and prednisolone; HMRN, Haematological Malignancy Research Network; ICT, immunochemotherapy; R^2, rituximab + lenalidomide; R, rituximab

Association of Cancer Physicians & NCRI Lymphoma Group perspectives (2/2)

Too much emphasis on overall survival

- EAG base cases do not include any potential overall survival benefit for mosunetuzumab → conservative
- PFS benefit (seen in modelled comparison of mosunetuzumab and RB) seldom translates into improved survival for FL due to long natural history and heterogenous population having a range of treatments
- Previous studies have failed to show overall survival benefit for one treatment over another

Other DG comments included on later slides consider:

- Value of comparing cost effectiveness against RB and R^2
- Unbalanced study populations in ITC of mosunetuzumab vs R^2
- 3 studies of R^2 in relapsed or refractory FL underway,[a] other upcoming data on standard care including FOUNDATION UK study[b]
- Equalities

[a]NCT01996865 (primary completion April 2023); NCT04680052 (primary completion February 2024); NCT04712097 (primary completion August 2025), Roche trial
[b]REFRACT UK-NCRI (reporting August 2025); NCT04745832 (primary completion April 2026); NCT02626455; FOUNDATION UK

Abbreviations: B, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CVP, cyclophosphamide, vincristine and prednisolone; FL, follicular lymphoma; HMRN, Haematological Malignancy Research Network; ICT, immunochemotherapy; R^2, rituximab + lenalidomide; R, rituximab

ICER impact key: Large  Unknown 

Key issues for ACM2

Key issues	Resolved?	ICER impact
Representativeness of RB for all type of R-chemotherapy	No. *Uncertainty*	
Indirect treatment comparison of mosunetuzumab and R^2 • Challenge of single arm evidence – not cost-effective at zero cost?	No. *Uncertainty*	
Subsequent therapy assumptions in R^2 arm – company and EAG now agree	Yes	None
Utility values – company and EAG now take different approach, EAG explores in scenario analysis	No. To discuss *Uncertainty*	
Other consideration • Potential equality issue for people who can't access standard treatment due to frailty or age?	To discuss	N/A

Abbreviations: B, bendamustine; Chemo, chemotherapy; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusted indirect comparison; O, Obinutuzumab; PSA, propensity score analysis; R, rituximab; R^2, rituximab + lenalidomide; TE, technical engagement

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Abbreviations: ACM1, 1st appraisal committee meeting; B, bendamustine; DG, draft guidance; R, rituximab; R2, rituximab + lenalidomide

No updates to model

Representativeness of RB for all type of R-chemotherapy

No changes to the modelling. Future studies may provide relevant data

ACM1 conclusion

- RB is a reasonable comparator in itself, but whether it is representative of other types of R plus chemotherapy is highly uncertain

DG consultation comments – Association of Cancer Physicians & NCRI Lymphoma Group

- Suitability of using RB / R-chemo as a comparator at 3rd line and beyond is limited
- Upcoming data from 3 studies including standard care comparators (R-CHOP, R-CVP, RB, R^2) could be used to inform assumptions about comparators

Company DG response

- Lack of trial evidence for R-chemo in later treatment lines for follicular lymphoma → no evidence available to demonstrate whether RB is representative of R-chemo regimens as a whole
- Clinical experts: patients receiving RB would typically be *"younger and fitter"* (DG section 3.5) than patients receiving other R-chemo regimens → committee should take this into consideration when reviewing cost-effectiveness estimate for mosunetuzumab vs RB

EAG comments

- Company has not responded to EAG's concerns about the selection of variables included in propensity score analysis, and has not presented alternative analyses to alleviate these concerns

Abbreviations: B, bendamustine; chemo, chemotherapy; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CVP, cyclophosphamide, vincristine, prednisolone; DG, draft guidance; EAG, external assessment group; NCRI, National Cancer Research Institute; R^2, rituximab + lenalidomide; R, rituximab

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No updates to model

Indirect treatment comparison of mosunetuzumab and R^2

No changes to the modelling. Future studies may provide relevant data

ACM1 conclusion

- [ITC]… excluded some important variables, making it highly uncertain with a potential for bias

DG consultation comments – Association of Cancer Physicians & NCRI Lymphoma Group

- Suitability of using R^2 as a comparator at 3rd line and beyond is limited
- Lack of cost-effectiveness not a fair interpretation of evidence given differences in ITC study populations
- Upcoming evidence on R^2 should be considered in re-appraising mosunetuzumab for managed access

Company DG response

- Several variables could not be matched: number of previous therapies, refractory status to previous anti-CD20 inhibitor, previous stem cell transplant, size of largest lymph node
- "Low Hgb level" imputed on clinical advice that it was an importance prognostic variable to control for
- Before/after weighting analysis presented at ACM1 showed residual bias was against mosunetuzumab
- Noted underlying challenges of appraisals based on single arm evidence packages: in the comparison with R^2, mosunetuzumab has potential to be not cost effective at zero cost

EAG comments

- Accepts justification for variables being unmatched, but this remains a limitation of the analysis
- Unclear why "Low Hgb level" imputed and data not provided to explore this in sensitivity analysis

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Abbreviations: ACM1, 1st appraisal committee meeting; DG, draft guidance; EAG, external assessment group; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NCRI, National Cancer Research Institute; R^2, rituximab + lenalidomide

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Company updated subsequent therapy assumptions in R^2 arm

Company and EAG agree on subsequent therapy proportions after R^2

Background

- Original company model assumed people in R^2 arm could be treated with R^2 as a subsequent therapy
- EAG assumed no patients in R^2 arm would have R^2 as subsequent therapy on disease progression

ACM1 conclusion

- Company's subsequent treatment assumptions may not all reflect clinical practice

Company DG response

- R^2 removed from subsequent therapy types in R^2 arm only

Table: Proportions of patients receiving subsequent therapy by type

	Updated in model
Subsequent treatment type	**R^2 arm only**
R + chemotherapy	50%
Other (non-R) chemotherapy	20%
Palliative care	10%
Trials	20%

EAG comments

- Company's updated model now matches EAG preference

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Company updated utility values used in model

EAG: both trial and Wild et al. utility values have weaknesses

Background

- Original company model used GO29781 pivotal cohort as source of utility values
- EAG noted for anyone in the study in early post-progression, corresponding utility value is extrapolated forwards for many years

ACM1 conclusion: Company's approach acceptable but associated with some uncertainty

Company DG response

- Updated utility values using Wild et al. abstract (N=222 UK patients), as reported in TA604*

Table: Utility inputs into model

Health state	GO29781 pivotal cohort value	Updated in model: Wild et al. value
Progression-free survival	0.80	0.81
Post-progression survival	0.75	0.62

EAG comments

- Unable to validate Wild et al. data (abstract) and it has much larger difference between utility values of pre- and post-progression than trial data
- Both sources have weaknesses → EAG base case unchanged (trial data), presents scenario using Wild et al.

*TA604: Idelalisib for treating refractory follicular lymphoma

Does committee have a preferred approach?

Abbreviations: ACM1, 1st appraisal committee meeting DG, draft guidance; EAG, external assessment group

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ICER impact key: Large  Quadrant change 

Summary of company and EAG base case assumptions

Subsequent therapy assumptions and utility values updated

Table: Assumptions in company and EAG base case after DG response

Assumption	Committee comments at ACM1	Company updated base case?	EAG critique	ICER impact
Mosun. vs R^2	ITC results highly uncertain and very unreliable	No	No update	N/A
Mosun. vs RB		No	No update	N/A
OS modelling	Highly uncertain EAG's approach – conservative	No – mosun. and comparator arms modelled separately	No update – assumes no difference in OS between arms	vs R^2  vs RB 
Subsequent therapy	May not all reflect clinical practice	**Yes** for R^2 arm: includes no R^2, 50% R+chemo, 10% other (non-R) chemo	Agrees – matches EAG preference at ACM1	None
Utility values based on trial values	Approach acceptable with some uncertainty	**Yes**: updated for both PFS and PPS using Wild	No update –trial values, scenario using Wild	

Abbreviations: ACM1, 1st appraisal committee meeting; B, bendamustine; chemo, chemotherapy; DG, draft guidance; EAG, external assessment group; ICER, incremental cost effectiveness ratio; mosun. mosunetuzumab; OS, overall survival; PFS, progression free survival; PPS, post-progression survival; R^2, rituximab + lenalidomide; R, rituximab

Cost-effectiveness results

Example results table:

	Total			Incremental			ICER (£/QALY)	INMB at £20K	INMB at £30K
Technology	**Costs (£)**	**LYG**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**			
Mosunetuzumab									
Comparator									

All ICERs are reported in PART 2 slides because they include confidential discounts for:

- lenalidomide and rituximab (Commercial Medicines Unit prices)
- mosunetuzumab (Patient Access Scheme discount)

Results accounting for all of these discounts:

- Mosunetuzumab vs R^2: mosunetuzumab is more costly and less effective in both company and EAG base cases
- Mosunetuzumab vs RB: mosunetuzumab cost effectiveness estimates are around or above £30k/QALY gained in company base case (across range of rituximab prices) and substantially higher than £30k/QALY gained in the EAG base case

Abbreviations: B, bendamustine; EAG, external assessment group; ICER, incremental cost effectiveness ratio; INMB, incremental net monetary benefit; LYG, life years gained; QALY, quality adjusted life years; R^2, rituximab + lenalidomide; R, rituximab

EAG scenario and additional analyses

Note: summaries below include mosunetuzumab PAS and all comparator discounts

Scenario analysis using alternative health state utility value from Wild et al:

EAG base case for both comparisons (mosunetuzumab vs R^2 and mosunetuzumab vs RB)

→ Using Wild utility values did not change conclusion of EAG base case for either comparison

Additional analysis assuming median age matches UK follicular lymphoma population:

ACM1 comments and conclusion

- UK median age around 66 years… Study population [median age 60]… was broadly generalisable to UK

Updated company base case for mosunetuzumab vs RB comparison (not explored for mosunetuzumab vs R^2)

→ Increasing median population age to 65.6 years (HMRN data) partly changed conclusion of updated company base case for mosunetuzumab vs RB, moving all ICERs above £30k/QALY gained

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Abbreviations: ACM1, 1st appraisal committee meeting; B, bendamustine; EAG, external assessment group; HMRN, Haematological Malignancy Research Network; ICER, incremental cost effectiveness ratio; PAS, patient access scheme; R^2, rituximab + lenalidomide; R, rituximab

Mosunetuzumab for treating relapsed or refractory follicular lymphoma

- ❑ Background
- ❑ Clinical evidence – recap
- ❑ Modelling – recap
- ❑ Points to consider
- ❑ Base case assumptions and results summary
- ✓ **Other considerations: Equality, severity, managed access proposal incl. Cancer Drugs Fund**
- ❑ Summary

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Abbreviations: ACM1, 1st appraisal committee meeting

Other considerations – equality

Consultation comments suggest equality consideration needed

DG consultation comments – NCRI Lymphoma Group

- DG decision will discriminate against older/frailer patients who do not have equal access to full range of standard immunochemotherapy options, and have even greater need for novel therapies earlier in disease course

Abbreviations: DG, draft guidance; ITC, indirect treatment comparison; NCRI, National Cancer Research Institute

RECAP

Note: This topic uses NICE's updated methods for health technology evaluations, 2022: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation

- The company has not submitted a case for a 'severity modifier' to be applied

Severity – company submission

- None of the analyses expected to meet the threshold for adjustment to the QALY value for severity:

Expected total QALYs for general population	Assumed current treatment	Total QALYs expected for people living with the condition, under current treatment	Absolute QALY shortfall	Proportional QALY shortfall
12.34	R^2	7.63	4.71	0.38
	RB	6.27	6.07	0.49

- Therefore, no severity modifier to be applied (QALY weight = 1)

Values are less than 12 so no adjustment for severity

Values are less than 0.85 so no adjustment for severity

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Abbreviations: : B, bendamustine; R^2, rituximab + lenalidomide; R, rituximab QALY, quality-adjusted life years

RECAP

Managed access – including Cancer Drugs Fund (1/2)

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

Company's proposals to support managed access (1/2)

Additional data collection planned for mosunetuzumab and standard care

Company DG response – recap with new information on [redacted]

Treatment type	Data source	Design	Notes
Mosunetuzumab	GO29781 pivotal cohort of clinical study	Prospective	Annual analyses until at least 2024 ➢ Extra 2 to 3 years follow up
Mosunetuzumab	Real world evidence (CDF)	Prospective, non-interventional, multi-national	*If mosunetuzumab in CDF* [redacted] data cut ➢ PFS data
[redacted]	[redacted]	[redacted]	[redacted]

- Consistent with evidence appraised in NICE CDF reviews in haematological indications that were recommended after data collection through SACT (TA783 and TA796)

DG consultation comments – NCRI Lymphoma Group

- Clinical studies with completion dates during 2023–2026 and real world evidence may provide further data on standard care / comparators that could be incorporated into company's indirect treatment comparisons

Abbreviations: CDF, Cancer Drugs Fund; DG, draft guidance; FL, follicular lymphoma; ITC, indirect treatment comparison; NCRI, national cancer research institute; OS, overall survival; PFS, progression-free survival; Q, quarter; SACT, Systemic Anti-Cancer Therapy

Company's proposals to support managed access (2/2)

EAG notes current appraisal relies on ITCs that were highly uncertain

EAG comments

- With new evidence, there will still be a reliance on indirect treatment comparisons
  - Small effect size seen in current appraisal may persist into any new analyses
  - Extended follow up of existing data may not meaningfully reduce uncertainty
  - Real-world data on mosunetuzumab use unlikely to observe sufficient OS events to produce reliable extrapolation, as experienced with current follow-up of GO29781
- Use of single arm trial data has resulted in positive recommendations in many other appraisals
- In this appraisal, results of ITCs appeared inconsistent, so there is a very high degree of uncertainty over effect and potential benefit of mosunetuzumab which needs to be considered

Background on TA783 and TA796 – cited by company as recommended after time in CDF

- TA783: daratumumab in relapsed and refractory multiple myeloma after 3 previous treatments
  - single arm study (n=106) followed up for a further 16 months, providing updated PFS and OS data
  - SACT data collected on daratumumab use and on subsequent therapies
- TA796: venetoclax in chronic lymphocytic leukaemia
  - SACT data collected on venetoclax use
  - further data on best supportive care had been expected from SACT but could not be collected

Abbreviations: CDF, Cancer Drugs Fund; EAG, evidence assessment group; ITC, indirect treatment comparison; OS, overall survival; PFS, progression-free survival; SACT, Systemic Anti-Cancer Therapy

Cancer Drugs Fund

Further data collection would resolve some uncertainty, but significant uncertainties are likely to remain

Table: Areas of uncertainty

Uncertainty	How uncertainty could be addressed	Likelihood uncertainty resolved
Suitability of ITCs	SACT, more data points for population matching ITCs. Comparator trials would mature (info for context only).	Medium to low, key uncertainty
Plausibility of mosunetuzumab survival modelling	GO29781 for longer term data (ongoing until [redacted]) or head-to-head trial (no trial proposed by company)	Medium
Immature data to model post-progression utilities	GO29781 for longer term data	Medium to high, depends how much data can be collected
Representativeness of RB comparator for other R-chemo including R-CHOP	[redacted]– analysis ongoing (info for context only).	Medium to low, no national coverage
Generalisability of the patient cohort to the NHS	SACT for UK-based data	High

Would data collection until [redacted] sufficiently resolve uncertainty?

Abbreviations: B, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; ITC, indirect treatment comparison; R, rituximab; SACT, Systemic Anti-Cancer Therapy

Managed access – including Cancer Drugs Fund (2/2)

Criteria for a managed access recommendation

The committee is asked to specify:

- What clinical uncertainties would be resolved with further data collection
- What data source(s) could be used to address these uncertainties
- How these data will address the remaining uncertainties
- How long data collection should be (aim for the shortest period possible that would reduce uncertainties enough to allow committee to make a decision at CDF exit)

Real-world evidence on comparators cannot be collected as part of a Managed Access Agreement (MAA)

- A company can collect real-world evidence during managed access, but it would not be a part of the MAA
- The committee should not make a recommendation for the CDF based on comparator data because it cannot be part of the MAA

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ICER impact key: Large  Unknown 

Key issues for ACM2

Key issues	Resolved?	ICER impact
Representativeness of RB for all type of R-chemotherapy	No. *Uncertainty*	
Indirect treatment comparison of mosunetuzumab and R^2 • Challenge of single arm evidence – not cost-effective at zero cost?	No. *Uncertainty*	
Subsequent therapy assumptions in R^2 arm – company and EAG now agree	Yes	None
Utility values – company and EAG now take different approach, EAG explores in scenario analysis	No. To discuss *Uncertainty*	
Other consideration • Potential equality issue for people who can't access standard treatment due to frailty or age?	To discuss	N/A

Abbreviations: B, bendamustine; Chemo, chemotherapy; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusted indirect comparison; O, Obinutuzumab; PSA, propensity score analysis; R, rituximab; R^2, rituximab + lenalidomide; TE, technical engagement

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Thank you.