Mosunetuzumab for treating relapsed or refractory follicular lymphoma [ID3931]

For public – redacted

Technology appraisal committee C [6 December 2022]

Chair: Stephen O'Brien

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Company: Roche

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

Key changes in new methods:

- There is no separate consideration of 'end of life criteria', this is now considered more broadly as a 'severity modifier'
    - company has not submitted a case for a 'severity modifier' in this appraisal
- Companies are asked to 'present an overall assessment of uncertainty' in their submission

Mosunetuzumab for treating relapsed or refractory follicular lymphoma

- ✓ **Background**
- ❑ Clinical evidence – results and points to consider 1
- ❑ Modelling – overview and points to consider 2
- ❑ Base case assumptions
- ❑ Other considerations: Equality, innovation, uncertainty, severity, managed access proposal incl. Cancer Drugs Fund
- ❑ Summary

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Key issues

ICER impact key: Small  Large  Quadrant change  Unknown 

Key issues	Resolved?	ICER impact
1. Suitability and representativeness of RB as a comparator • Is RB a suitable comparator in 3rd line setting? • Is RB representative of any type of R-Chemo in absence of other data	For discussion *Uncertainty*	Unknown 
2. Generalisability of GO29781 patient cohort to the NHS		
3. Suitability of indirect treatment comparisons • Matching-adjusted indirect comparison (MAIC) of mosunetuzumab vs R2 • Propensity score analysis (PSA) of mosunetuzumab vs RB	For discussion *Uncertainty*	Unknown 
4. Plausibility of survival modelling – do results align with expectations?	For discussion	Differs 
5. Subsequent therapy assumptions in all arms		Small 

Resolved key issues	Resolved?	ICER impact
6. Immature data to model post-progression utilities [clarified this includes beyond end of treatment]	Yes *Uncertainty*	Unknown 
7. Inconsistent application of adjusted and unadjusted survival data in model [now corrected]	Yes	Small 
8. Unnecessary half-cycle correction applied in model [EAG now agrees]		
9. Removal of OB as a comparator [agreement it is rarely used 3rd line]		

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; R2, rituximab + lenalidomide; TE, technical engagement

Background on follicular lymphoma

Disease

- Indolent, low grade (1 to 3A) non-Hodgkin lymphoma affecting B-cells
- Symptoms include enlarged lymph nodes, fatigue, fevers, night sweats, weight loss, increased risk of infection and bone marrow failure
- Chronic course with disease relapses

Epidemiology

- ~2,470 new cases in 2019

Aim of treatment

- Extend remission and control symptoms, but survival and remission duration worsen with more lines of therapy
    - ~75% of patients have 1st-line chemotherapy or radiotherapy, of these ~27% relapse and receive 2nd line treatment
    - ~34% patients on 2nd line treatment relapse and move to 3rd line

<20% of NHLs are follicular lymphoma

Most common in aged >60 years

~200 people eligible for 3rd line treatment per year

5-year survival rate at 3rd line ~65%

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Abbreviations: NHL, non-Hodgkin lymphoma

Patient perspectives

Fear of relapse, need for more and better treatment options

Submissions from Lymphoma Action and the Follicular Lymphoma Foundation

Unmet need:

- Incurable cancer that will return and need subsequent treatments for life
- Some people do not need treatment initially but have active monitoring. Patients find this psychologically challenging and emotionally draining
- Lack of durable response and need for repeated treatment. Side effects
- Limited treatment options and more options needed for patients who relapse or become refractory to current treatments

"…there is always the fear of relapse"

"my husband has been shielding with me and has not been able to resume his hobbies or social life either during the COVID pandemic"

Mosunetuzumab:

- May give patients with relapsed disease an additional treatment option and longer life-expectancy, without debilitating and unpleasant side effects
- Patients interested to learn more about 'bi-specifics' – antibodies targeting 2 different sites
- Disadvantage – given by infusion (slow)

Clinical perspectives

Advanced FL is incurable, mosunetuzumab may offer a new treatment option

Submissions from clinical specialists in FL

Unmet need:

- Treatment resistance, early progression, and poor survival in 20–25%
- Cumulative complications or treatment resistance after multiple therapies
- No current standard of care, which creates difficulties in treatment choice

Mosunetuzumab:

- First in class, may offer a step change in management
- Additional line of therapy effective across all subgroups
- Improvement in progression free survival expected
- Manageable, mostly low-grade toxicity profile. High grade cytokine release syndrome a rare but recognised specific complication (mostly cycle 1 or 2)
- Could be delivered in non-specialist centres after suitable training

"Advanced FL is incurable. Treatment aims to stop disease progression whilst maintaining quality of life"

"Mosunetuzumab is effective in high-risk patients with early relapse or refractory disease – key unmet need"

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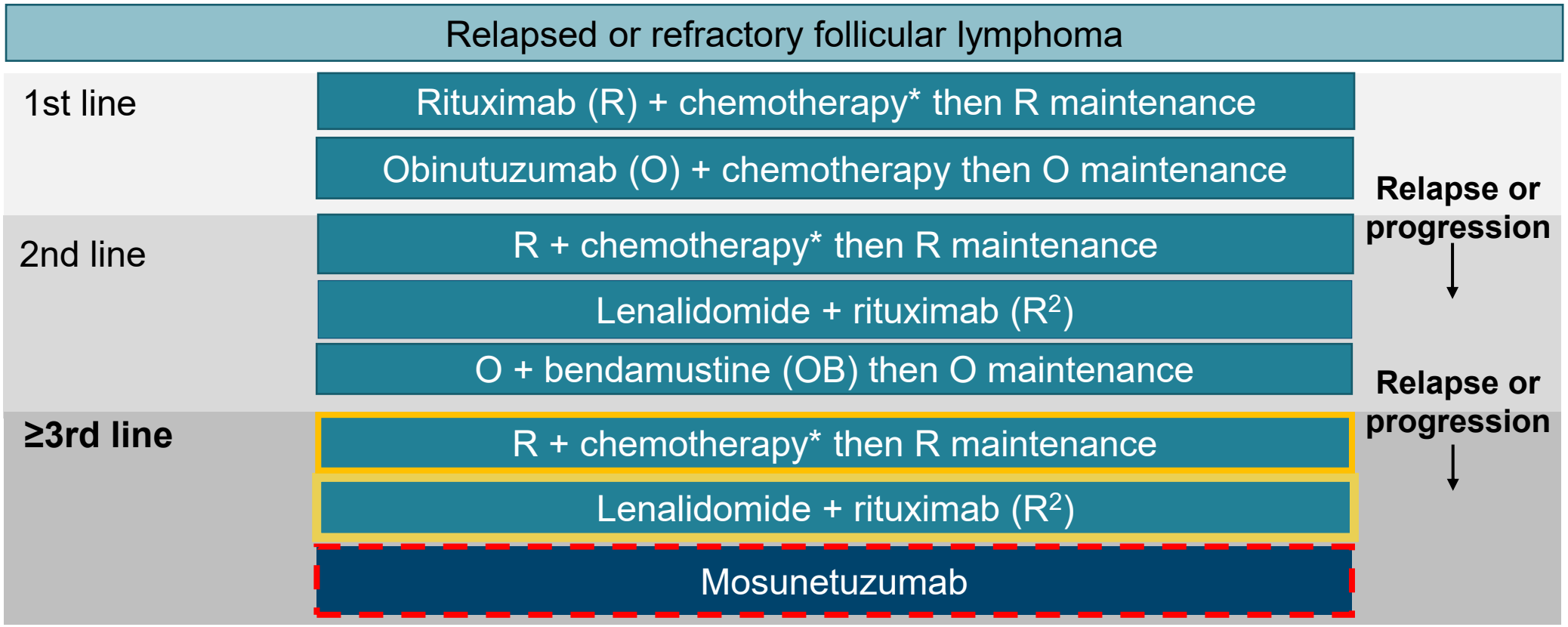
Abbreviations: FL, follicular lymphoma

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

What are the most appropriate comparators at 3rd line+ for the technology?

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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

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 • Patient access scheme available

Drug cost per treatment cycle (list price)

Intervention	Dosing	Drug cost per treatment cycle (list price)	Length
Mosun, 3rd cycle onwards	1 mg for CYCLE 1 DAY 1, 2 mg for CYCLE 1 DAY 8, 60 mg for CYCLE 1 DAY 15 and for CYCLE 2 DAY 1, and 30 mg for each subsequent CYCLE up to and including the last one.	6600.00	
Monthly cost of mosun		9566.07	
Rituximab	375 mg/m^2 every 21 days; R^2: 375 mg/m^2 Day 1, 8, 15 and 22 Cycle 1, Day 1 Cycles 2-5	1,414.50	/4 week R^2; /3 week other
Bendamustine	90 mg/m^2 Days 1 and 2 for RB	279.33	/3 week for RB
Lenalidomide	20 mg Days 1—21 or 10 mg if CrCl >=30 and <60 out of 28 day cycle	1,181.08	/week

Intervention	Cycles	Cycle length	Max number of weeks under treatment
Mosun	17	21	51
RB	6	21	18
R^2 (ritux only)	5	28	20
R^2 (len only)	12	28	48

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Abbreviations: CrCl, creatinine clearance; Mosun, mosunetuzumab; RB, rituximab + bendamustine; R^2, rituximab + lenalidomide; R rituximab; RR, relpased refractory

Decision problem

Population aligned with MA, with fewer comparators

Table: Population, intervention, comparators and outcomes

	Final scope	Company submission
Population	Adults with relapsed or refractory (RR) follicular lymphoma (FL)	Aligned with clinical data and MA • Adults with RR FL who have received ≥2 prior systemic therapies
Intervention	Mosunetuzumab	As per scope
Comparators	• R^2 • R + chemotherapy • OB → obinutuzumab (maint) Best supportive care (BSC)	• R^2 Narrower than scope because: • R + chemotherapy represented by R + B alone • OB (removed at technical engagement, rarely used 3rd line in UK) • BSC excluded (considered palliative)
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	As per scope

Abbreviations: B, bendamustine; BSC, best supportive care; FL, follicular lymphoma; MA, marketing authorisation; maint, maintenance; O, obinutuzumab; R^2, rituximab + lenalidomide; R rituximab; RR, relpased refractory

Key issue 1: Suitability and representativeness of RB as a comparator

Only RB has usable data for a comparison of mosunetuzumab with any type of R+Chemo

Background – no suitable data on R-CHOP or R-CVP

- In TA627, clinical experts acknowledged 'no evidence for R-CHOP and R-CVP in previously treated FL'
  - ITC against R-CHOP using patient-level data from EORTC 20981 trial not feasible

Company – aware of limitations of considering RB as a comparator in 3rd line setting

- Conducts ITC vs RB – a propensity score analysis using individual patient data for RB from 2 clinical trials – best and only option for comparison of mosunetuzumab with any R+Chemo
- Acknowledges RB may not be commonly used 3rd line, but clinical experts confirmed that if a patient was to receive RB 3rd line, the observed data would reflect what they would expect to see in clinical practice

EAG comments – lack of data can't be resolved within current appraisal

- Clinical adviser: RB not a good representative for R+Chemo due to differences in patients receive them

Clinical expert comments – no current standard of care in 3rd line setting

- Lack of data on standard therapy including R-CHOP and no data to challenge whether RB is representative in 3rd line setting
- Differences between RB and R+Chemo seen in 1st line setting may be less evident in 3rd line setting

Given the general lack of data and no current standard of care, is committee satisfied that RB is a suitable and representative comparator treatment in the 3rd line setting?

Abbreviations: B, bendamustine; Chemo, chemotherapy; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CVP, cyclophosphamide, vincristine and prednisolone; EORTC, European research agency for research and treatment of cancer; ITC, indirect treatment comparison; R, rituximab

Mosunetuzumab for treating relapsed or refractory follicular lymphoma

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- ✓ **Clinical evidence**
  - **– Results**
  - **– Points to consider 1**
- ❑ Modelling – overview and points to consider 2
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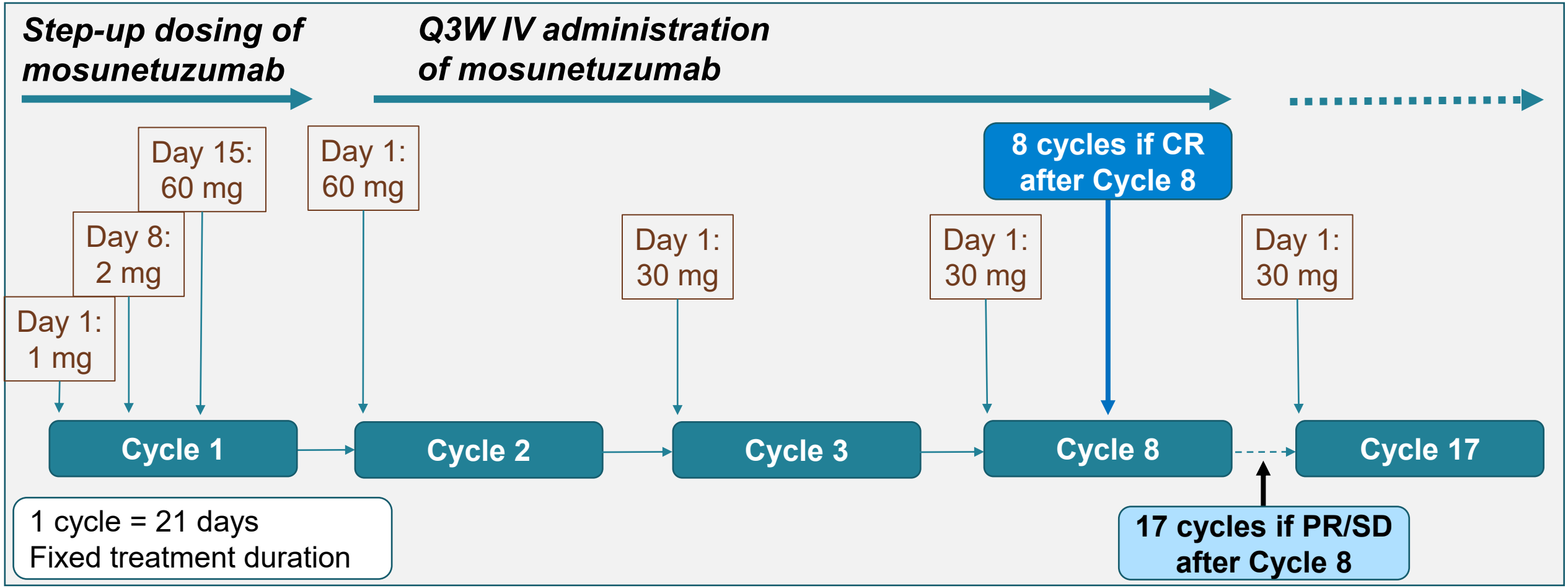
Key clinical study: Phase 1/2, multicentre, singe-arm, open label

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

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

Key issue 2: Generalisability of GO29781 patient cohort to the NHS

>50% patients receiving mosunetuzumab were double-refractory to prior therapy

Table: GO29781 patient and disease characteristics

Characteristic	Mosunetuzumab (n=90)	Compared with UK practice:*
Median age, years	60	~66 years
Male, %	61	
ECOG PS, %		✓ ECOG PS
0	59	
1	41	
Ann Arbor Stage, %		✓ Stage
I-II	23	
III-IV	77	
FLIPI Risk Group, %		✓ FLIPI
Low (0, 1)	29	
Intermediate (2)	27	
High (3–5)	44	

*Company clinical expert feedback in TE where some differences suggested but overall considered representative

Expert view was that cohort broadly representative of UK: 2% from UK vs 44% US → treatments for FL are similar

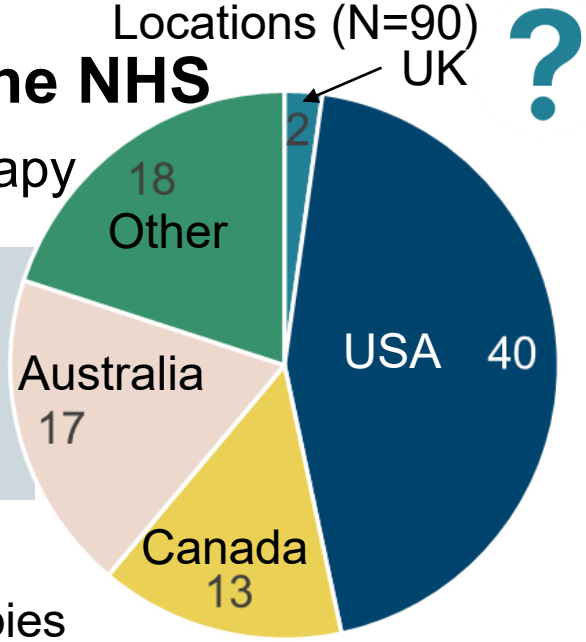


Table: GO29781 prior therapies

Prior therapies	Mosunetuzumab (n=90)
Number, % 2 3 >3	 38 31 31
Double-refractory to prior anti-CD20 and alkylating agent, %	53
POD24 after 1st systemic therapy, %	52

Is the committee satisfied that the mosunetuzumab cohort sufficiently reflects the NHS population?

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; FLIPI, Follicular lymphoma international prognostic index; POD24, progression of disease within 24 months

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

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

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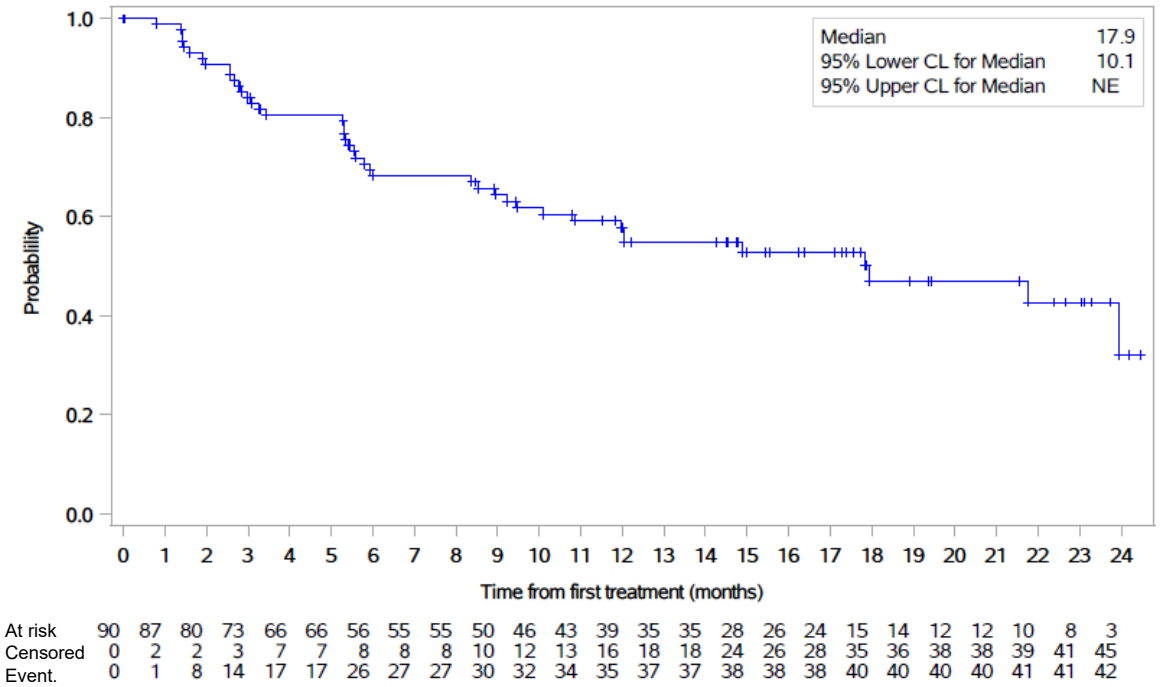
Abbreviations: CR, complete response; IRF, independent review facility; PET, positron emission tomography; PD, progressive disease; PR, partial response; SD, stable disease

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]

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

Adverse events in GO29781 pivotal cohort

Most patients who had cytokine release syndrome (CRS) had grade 1–2 events

Table: Summary of adverse events

	Mosunetuzumab (n=90)
Adverse events (AEs), %	
Any AE	100
Deaths	[redacted]
Discontinuation due to AE or death	4
Most common AEs, %	
CRS by Lee 2014 criteria	[redacted]
CRS by ASTCT 2019 criteria	44
Fatigue	37
Headache	31

CRS events:

- Most patients who had CRS had grade 1–2 events
- Grade 3–4 CRS in [redacted] patients by Lee 2014 criteria, 2 patients by ASTCT 2019 criteria
- 2 patients had mosunetuzumab treatment withdrawn due to CRS
- Highest incidence of CRS was in cycle 1, on Day 15

Company

- With increasing experience of mosunetuzumab use by clinicians, pre-emptive management and treatment of CRS likely to improve, reducing its incidence relative to that seen in early phase trial

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Abbreviations: AE, adverse events; ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome

Used in model

Company indirect treatment comparison: methods (1)

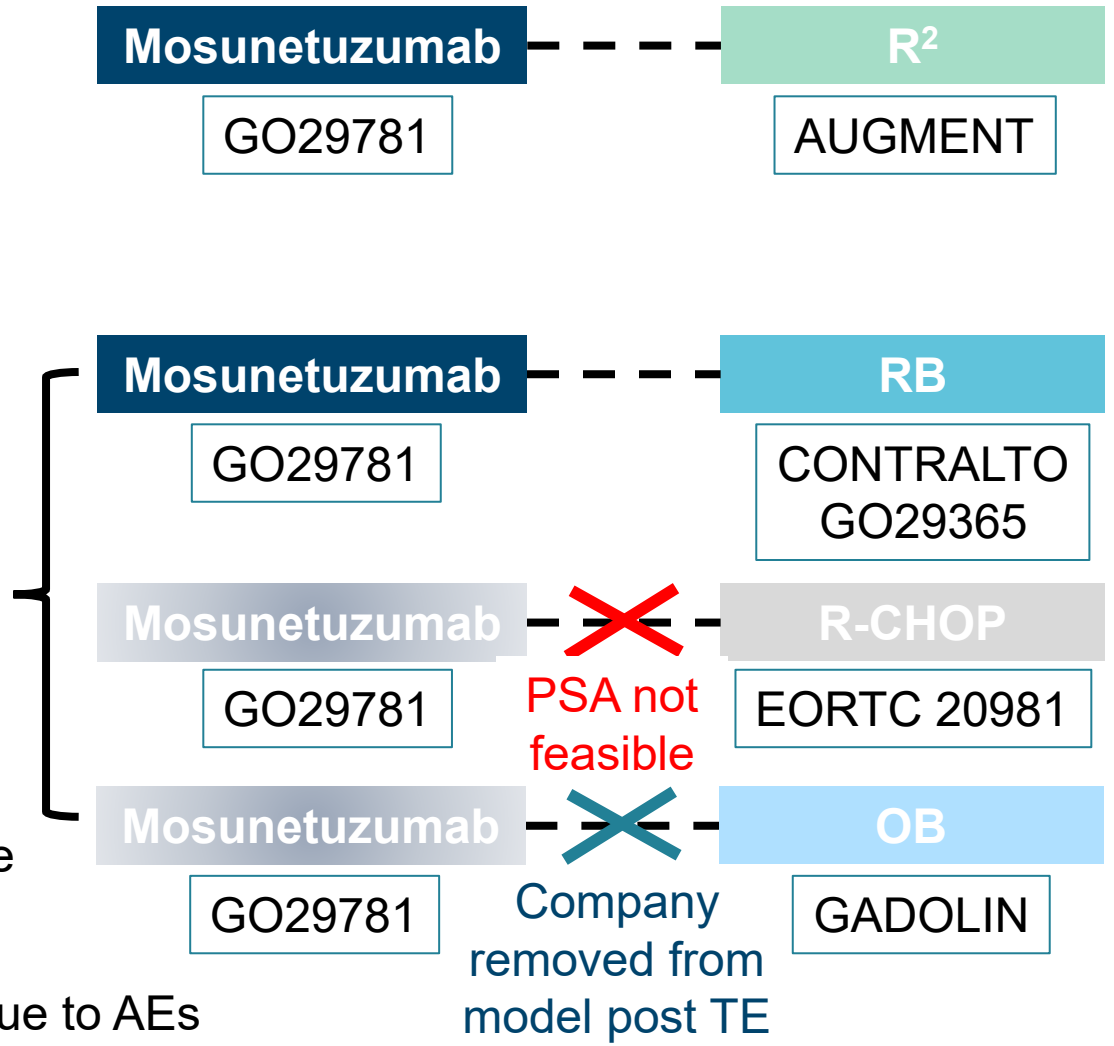
ITC of mosunetuzumab vs R-CHOP attempted but considered not feasible

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
- Inverse probability of treatment weighting (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

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Abbreviations: AE, adverse event; B, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CR, complete response; IPD, individual patient data; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; O, obinutuzumab; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PSA, propensity score analysis; R^2, rituximab + lenalidomide; R, rituximab; TE, technical engagement

Company indirect treatment comparison: methods (2)

Some variables not included in MAIC or imputed

Table: Company high priority prognostic factors and effect modifiers used in ITCs

Variable	Outcome	Mosun. vs R^2 In MAIC?	Mosun. vs RB^2 In PSA?
Number of previous therapies	3 vs >3 or median	**No**	Yes (≥3)
Refractory to previous therapy	Progressed/relapsed vs No	Yes	Yes
Refractory to prior anti-CD20	Yes vs No	**No**	Yes
Early relapse status (POD24)	Yes vs No	Yes	Yes
Prior ASCT	Yes vs No	**No**	Yes
Size of largest LN lesion	Mean	**No**	Yes
Bulky disease	Yes vs No	Yes	**No**
FLIPI	<3 vs >=3	Yes	Yes
Age	Mean	Yes	Yes
Ann Arbor stage	1-2 vs 3-4	Yes	Yes
High lactate dehydrogenase	Yes vs No	Yes	Yes
Bone marrow involvement	Yes vs No	Yes	Yes
Low haemoglobin	Yes vs No	**Yes but imputed**	Yes

Abbreviations: ASCT, autologous stem cell transplant; B, bendamustine; FLIPI, Follicular Lymphoma International Prognostic Index; ITC, indirect treatment comparison; LN, lymph node; MAIC, matching-adjusted indirect comparison; POD24, progression of disease within 24 months; PSA, propensity score analysis; R^2, rituximab + lenalidomide; R, rituximab

Summary of ITC results

EAG notes conflicting results across the ITCs leading to high uncertainty

Table: Company's summary of ITC results

[redacted]

EAG comments – high uncertainty

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

Company – mosunetuzumab data immature relative to comparators

For MAIC of mosunetuzumab vs R^2:

- Eligibility criteria between studies not fully harmonised → introduced bias. In AUGMENT, only 47% were 3rd line+ vs all 3rd line+ in GO29781, and all were non-refractory to R vs 79% refractory to R in GO29781

For PSA of mosunetuzumab vs RB:

- Even after optimal pair matching (not used in base case), notable differences in key prognostic factors [redacted]

Abbreviations: AE, adverse event; B, bendamustine; EAG, external assessment group; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; PSA, propensity score analysis; R^2, rituximab + lenalidomide; R, rituximab

Results of MAIC: mosunetuzumab vs R²

[redacted]

Mosunetuzumab [redacted] compared with R²

Table: EAG's summary of MAIC results (Jan. 2022 data cut) **Used in model**

	Unadjusted estimate (95% CI)	Weighted estimate (95% CI)	Weighted bias corrected bootstrap (95% CI, p-value)
Hazard ratio			
Progression-free survival	[redacted]	[redacted]	[redacted]
Overall survival	[redacted]	[redacted]	[redacted]
Odds ratio			
Complete response	[redacted]	[redacted]	N/A
Overall response	[redacted]	[redacted]	N/A
Discontinuation due to AEs	[redacted]	[redacted]	N/A

EAG comments

- [redacted]
- [redacted]

Abbreviations: AE, adverse event; CI, confidence interval; EAG, external assessment group; HR, hazard ratio; Jan., January; MAIC, matching-adjusted indirect comparison; R², rituximab + lenalidomide

Results of PSA: mosunetuzumab vs RB

Mosunetuzumab [redacted] compared with RB

Table: EAG's summary of PSA results (Jan. 2022 data cut) **Updated in model**

	Unadjusted estimate (95% CI)	IPTW based estimate (95% CI) [post-hoc adjusted]	Optimal pair matching estimate (95% CI) [post-hoc adjusted]
Sample size	81 + 46	81 + 42	46 + 46
Hazard ratio			
Progression-free survival	[redacted]	[redacted]	[redacted]
Overall survival	[redacted]	[redacted]	[redacted]
Odds ratio			
Complete response	[redacted]	[redacted]	[redacted]
Overall response	[redacted]	[redacted]	[redacted]
Discontinuation due to AEs	[redacted]	[redacted]	[redacted]

EAG comments

- [redacted]

Abbreviations: AE, adverse event; B, bendamustine; CI, confidence interval; EAG, external assessment group; Jan., January; IPTW, inverse probability of treatment weighting; PSA, propensity score analysis; R, rituximab

Key issue 3: Suitability of indirect treatment comparisons – MAIC

Residual imbalance produces high uncertainty and possible bias

Background on ITC of mosunetuzumab and R²

- Several variables were unmatched in the MAIC → high uncertainty and potential bias (direction unclear)
- Company imputed value of "Low Hgb level" when value unknown for target population

Company – residual bias is against mosunetuzumab

- To address concerns about unmatched variables, company provided an updated summary table for the MAIC, including all priority baseline characteristics reported, before and after weighting was provided
  - Shows that important residual bias against mosunetuzumab remains for all factors that were not included in the adjustment (ECOG, only 1 prior line of therapy, refractory to prior anti-CD20-containg regimen, time since completion of last therapy >2 years, presence of B-symptoms)

EAG – mosunetuzumab population unhealthier but not possible to quantify impact of this

- Uncertainty surrounding unmatched variables means extent of any bias against mosunetuzumab is unclear
- Excluding variable "Low Hgb level" increases the effective sample size → should have been excluded
- Small effective sample size of analyses → true efficacy of mosunetuzumab unlikely to be well-represented

Clinical expert comments

- "Number of previous therapies" an important prognostic variable not included in MAIC

Taking account of the potential problems, does the committee consider the company's MAIC for the comparison of mosunetuzumab and R² suitable for use in decision making?

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Abbreviations: EAG, external assessment group; ECOG, Eastern Cooperative Oncology Group; MAIC, matching-adjusted indirect comparison; R², rituximab + lenalidomide

Key issue 3: Suitability of indirect treatment comparisons – PSA

Uncertainty in some of interaction terms and confounders included

Background on ITC of mosunetuzumab and RB

- Company used a matching method in it's original base case scenario, but after TE it switched to using an inverse probability of treatment weighting (IPTW) approach with an improved population balance
- EAG critiqued the interaction terms and confounders that were included in the PSA model

Company – double-refractory status an important confounder

- Clarifies that selection of covariates in final propensity score model (IPTW) was based on considerations of improvement in overall covariate balance, not on based on subjectivity or medical recommendation
- Exclusion of double-refractoriness to anti-CD20 and alkylating agents from the propensity score model, as EAG suggests, would lead to increased bias and suboptimal estimates of relative treatment effect

EAG – unclear whether double-refractory status should be included

- Analysis of including double-refractory status had wide standard errors of analysis → unreliability
  - When interaction with treatment arm included, impact seen in mosunetuzumab arm but neutral effect in RB arm → clinical plausibility unclear
- Presence of individuals with potentially outlier weights in IPTW analysis (preferred) → limitation of analysis
- Standard IPTW analyses, without post-hoc covariate adjustment, would be a valuable comparison for decision making purposes, but these have not been provided by the company

Taking account of the potential problems, does the committee consider the company's PSA for the comparison of mosunetuzumab and RB suitable for use in decision making?

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Abbreviations: B, bendamustine; EAG, external assessment group; IPTW, inverse probability of treatment weighting; ITC, indirect treatment comparison; O, obinutuzumab; PSA, propensity score analysis; R, rituximab; TE, technical engagement

Not used in model

Company's additional ITC of mosunetuzumab and US real world data on commonly available 3rd line treatments for FL

[redacted]

Company – supporting evidence provided at TE

[redacted]

EAG comments

- ITC generally well conducted
- But pooled comparator population may not be representative of UK care

[redacted]

*August 2021 data cut of GO29781 pivotal cohort

Abbreviations: Chemo, chemotherapy; CI, confidence interval; CR, complete response; EAG, external assessment group; ESS, effective sample size; FL, follicular lymphoma; HR, hazard ratio; ITC, indirect treatment comparison; OR, odds ratio; R^2, rituximab + lenalidomide; R, rituximab; RWD, real world data; TE, technical engagement

Mosunetuzumab for treating relapsed or refractory follicular lymphoma

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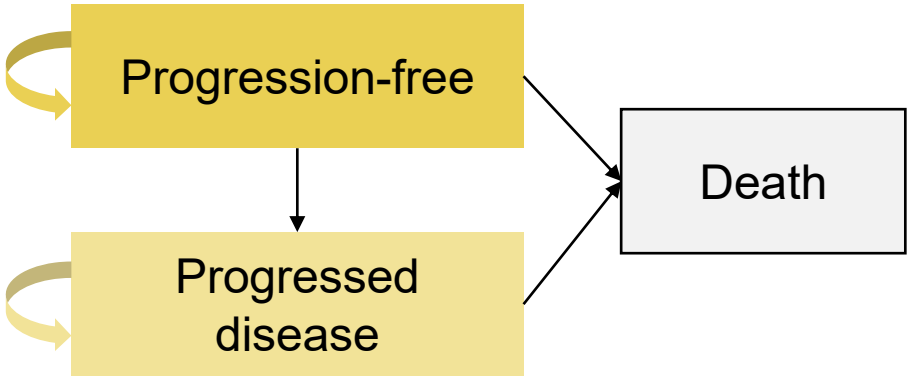
Company's model overview

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:
  - For comparison with R^2: fewer QALYs than comparator in company and EAG base cases
  - For comparison with RB: more QALYs than comparator in company and EAG base cases
- Assumptions with greatest ICER effect:
  - For comparison with R^2: setting PFS equal to R^2 beyond 25 months
  - For comparison with RB: pooling of OS data for the 2 arms

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

Key model features

Company removed comparison with OB from base case at technical engagement

Table: Features of company's model

Model features	Description
Model type	Partitioned survival model (progression-free, post-progression, dead)
Population	Adult patients with relapsed or refractory follicular lymphoma who have received at least two prior systemic therapies
Intervention	Mosunetuzumab
Comparators	Lenalidomide with rituximab (R^2), rituximab plus bendamustine (RB)
Time horizon	40 years time
Treatment waning effect	No
Model cycle	1 week, with half-cycle correction applied
Discount rates	3.5% for both health and costs outcomes
Utility values	PFS and PPS values from GO29781 trial used in base case • Utility data collected beyond end of treatment, with up to 2.5 years follow-up
Costs	BNF, eMIT, NHS References costs 2019/2020
Perspective	NHS and Personal Social Services

Abbreviations: B, bendamustine; BNF, British National Formulary; eMIT, electronic market information tool; O, obinutuzumab; PFS, progression free survival; PPS, post progression survival; R^2, rituximab + lenalidomide; R, rituximab

[redacted]

Model inputs from ITCs

Company updated results for the comparison of mosunetuzumab with RB

Table: ITC results used in model for comparison with R^2

MAIC of mosunetuzumab vs R^2	Weighted estimate (95% CI)
Progression-free survival HR	[redacted]
Overall survival HR	[redacted]
Complete response OR	[redacted]
Overall response OR	[redacted]
Discontinuation due to AEs OR	[redacted]

Table: ITC results used in model for comparison with RB – updated

PSA of mosunetuzumab vs RB	IPTW based estimate (95% CI) [post-hoc adjusted]
Progression-free survival HR	[redacted]
Overall survival HR	[redacted]
Complete response OR	[redacted]
Overall response OR	[redacted]
Discontinuation due to AEs OR	[redacted]

Abbreviations: AE, adverse event; B, bendamustine; HR, hazard ratio; ITC, indirect treatment comparison; IPTW, inverse probability of treatment weighting; MAIC, matching-adjusted indirect comparison; OR, odds ratio; PSA, propensity score analysis; R^2, rituximab + lenalidomide; R, rituximab

Key issue 4: Plausibility of survival modelling (1)

Company and EAG disagree on pooling of OS data due to data immaturity

General comments

Company – updated distributions but without pooling of OS data

- Extrapolations may be a conservative view given the limitations and potential bias against mosunetuzumab in ITC results, may not represent the true benefit of mosunetuzumab
- Considers EAG's OS pooling, which does not account for any survival benefit, overly conservative even in light of the limited follow up
  - Inconsistent with high complete response rate seen in trial [redacted]

EAG – prefers pooled OS data due to immaturity

- For both comparisons, prefers to use pooled estimates to extrapolate OS due to immaturity of mosunetuzumab data, few events occurring [redacted]
  - Company's suggests potential bias against mosunetuzumab, but this has not been quantified and unlikely to be uniform across groups
- Noted: model had a starting age of 60 years when age 67 may be more reflective of UK population. Has little effect on EAG base case due to pooled data but age parameter may become influential if separate modelling of OS is supported

Abbreviations: EAG, external assessment group; ITC, indirect treatment comparison; OS, overall survival; PFS, progression-free survival

PFS extrapolation of mosunetuzumab for comparison with R^2

Company and EAG differ on mosunetuzumab extrapolation

Company's PFS extrapolations after TE

EAG's preferred PFS extrapolation – [redacted]

Probability of progression-free

[redacted]

[redacted]

EAG comments

- For mosunetuzumab, EAG uses log normal switched to R^2 log normal at [redacted]

Abbreviations: EAG, external assessment group; ICER, incremental cost effectiveness ratio; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; R^2, rituximab + lenalidomide; TE, technical engagement

OS extrapolations of mosunetuzumab for comparison with R²

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 R², [redacted]

EAG: Pooled OS → ICER quadrant change

What is the committee's view on the company's approach to modelling survival for mosunetuzumab vs R²? Should OS data be pooled?

Abbreviations: EAG, external assessment group; KM, Kaplan–Meier; ICER, incremental cost effectiveness ratio; OS, overall survival; R², rituximab + lenalidomide; TE, technical engagement

PFS extrapolations of mosunetuzumab for comparison with RB

Company and EAG agree on extrapolations

EAG – agree with company → no ICER impact

Company's and EAG's preferred PFS extrapolations after TE

Abbreviations: B, bendamustine; EAG, external assessment group; ICER, incremental cost effectiveness ratio; PFS, progression-free survival; R, rituximab; TE, technical engagement

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 R^2, [redacted]

EAG: Pooled OS data → large impact on ICER

What is the committee's view on the company's approach to modelling survival for mosunetuzumab vs RB? Should OS data be pooled?

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

Modelling of progression-free survival and overall survival

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

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]				

- Apart from pooling, company and EAG only differ on PFS extrapolation for mosunetuzumab in R^2 comparison

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

Key issue 4: Plausibility of survival modelling (2)

Company's model [redacted]

Key:
- Favours mosun.
- Favours comparator
- No difference

Mosunetuzumab vs R^2

EAG – [redacted]

- [redacted]
- [redacted]
- [redacted]

Modelled LYGs	Total LYGs in deterministic base case	
	Company	EAG
Mosunetuzumab	9.6	10.5
R^2	10.4	10.5

R^2 > Mosun. | Pooled

Tech team note: [redacted]

Mosunetuzumab vs RB

EAG – [redacted]

- [redacted]
- [redacted]

Tech team note: [redacted]

Modelled LYGs	Total LYGs in deterministic base case	
	Company	EAG
Mosunetuzumab	9.9	9.2
RB	8.3	9.2

Mosun. > RB | Pooled

Abbreviations: B, bendamustine; EAG, external assessment group; KM, Kaplan–Meier; LYG, life-years gained; MAIC, matching-adjusted indirect comparison; mosun., mosunetuzumab; OS, overall survival; PFS, progression-free survival; R^2, rituximab + lenalidomide; R, rituximab

Key issue 5: Subsequent therapy assumptions in all arms

Post-TE, company and EAG differ on subsequent therapy proportions after R^2

Company – after technical engagement

- Updated time at which subsequent treatments costs applied, from point of treatment discontinuation to point of disease progression, to be more reflective of clinical practice
- Applies to all treatment arms (Mosun., R^2 and RB)

EAG comments

- Makes modelling more realistic
- But bias in favour of mosunetuzumab (↓ costs) because PFS and time on treatment (ToT) assumed equal for comparators, while for mosunetuzumab ToT is distinguished from PFS before treatment ends

Table: Proportions of patients receiving subsequent therapy by type after TE

Subsequent treatment type	Company – in all arms (M, R^2 and RB)	EAG – revised for base case of R^2 arm only
R + lenalidomide (R^2)	35%	0%
R + chemotherapy	25%	50%
Other (non-R) chemotherapy	10%	20%
Palliative care	10%	10%
Trials	20%	20%

EAG preference

- No patients in R^2 arm would receive R^2 as subsequent treatment on disease progression → ICER quadrant change
- Agrees with company for mosunetuzumab and RB arms

Which subsequent therapy proportions does the committee consider is most reflective of clinical practice?

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Abbreviations: B, bendamustine; EAG, external assessment group; Mosun., mosunetuzumab; PFS, progression-free survival; R^2, rituximab + lenalidomide; R, rituximab; TE, technical engagement; ToT, time on treatment

Key issue 6: Immature data to model post-progression utilities

PPS utility data collected beyond end of treatment but likely small number of patients

Background

- Company submission unclear about whether patient-reported outcome data beyond cycle 8 (when treatment ends for patients with complete response) was analysed, so EAG considered data immature

Utility inputs into model

Health state	Utility value	Source
Progression-free survival	0.80	GO29781 pivotal cohort
Post-progression survival	0.75	GO29781 pivotal cohort

Company – after Technical Engagement

- Confirmed all data up to most recent follow-up (January 2022 data cut) used to estimate utilities
  - 63 observations identified in PPS state were used in regression, of these 19 were made after 1 year
  - Observations that could not be identified due to censoring were treated as a different group

EAG comments – after Technical Engagement

- Accepts data to model PPS utilities were collected beyond treatment completion or discontinuation
- Some uncertainty remains – the 63 observations identified likely to be from smaller number of patients

Is the committee satisfied with data used to inform post-progression utilities in the model?

Abbreviations: EAG, external assessment group; PPS, post progression survival

Mosunetuzumab for treating relapsed or refractory follicular lymphoma

- ❑ Background
- ❑ Clinical evidence – results and points to consider 1
- ❑ Modelling – overview and points to consider 2
- ✓ **Base case assumptions**
- ❑ Other considerations: Equality, innovation, uncertainty, severity, managed access proposal incl. Cancer Drugs Fund
- ❑ Summary

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ICER impact key: small or <£10K  >£100K  quadrant change 

Summary of company and EAG base case assumptions

Differences in survival extrapolations and subsequent therapy types assumed

Table: Assumptions in company and EAG base case

Assumption	Company base case	EAG base case	ICER impact
Comparison of mosun. vs R^2	Included	Included	N/A
Comparison of mosun. vs RB	Included	Included	N/A
PFS extrapolations	Vs R^2: log normal (R^2) and Weibull (mosunetuzumab) Vs RB: log normal (both arms)	Vs R^2 differs with: log normal [redacted] then as R^2 (mosunetuzumab arm)	
OS extrapolations	Vs R^2: Weibull Vs RB: exponential	Same extrapolations but with pooled data for mosunetuzumab and comparators	vs R^2  vs RB 
Subsequent therapy	All arms: 35% R^2, 25% R+Chemo, 10% other (non-R) chemotherapy	Differs in R^2 arm: no R^2, 50% R+Chemo, 10% other (non-R) chemotherapy	
Half-cycle correction	Applied	Applied	

Abbreviations: B, bendamustine; Chemo, chemotherapy; EAG, external assessment group; ICER, incremental cost effectiveness ratio; mosun., mosunetuzumab; OS, overall survival; PFS, progression free survival; R^2, rituximab + lenalidomide; R, rituximab

Company scenario analyses

Note: summary is based on current PAS for mosunetuzumab and CMU discounts (midpoint for rituximab)

Mosunetuzumab vs R^2 comparison
Scenario 1: No half-cycle correction
Scenario 2: Pooled OS
Scenario 3: Alternative OS distributions [(a) mosunetuzumab and R^2 Weibull; (b) mosunetuzumab log logistic, R^2 Weibull]
Scenario 1 and 3a → did not change the overall conclusion of company base case **Scenario 2 and 3b → cost effectiveness estimates are substantially higher than £30k/QALY gained**
Mosunetuzumab vs RB comparison
Scenario 1: No half-cycle correction
Scenario 2: Pooled OS
Scenario 3: Alternative OS distributions [(a) mosunetuzumab and RB exponential; (b) mosunetuzumab log logistic, RB exponential]
Scenario 4: Regression adjustment
Scenario 1, 3a and 3b → cost effectiveness estimates are around £30k/QALY gained **Scenario 2 → cost effectiveness estimate is substantially higher than £30k/QALY gained** **Scenario 4 → cost effectiveness estimate is below £30k/QALY gained**

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Abbreviations: B, bendamustine; OS, overall survival; PAS, patient access scheme; R^2, rituximab + lenalidomide; R, rituximab

EAG scenario analyses

Note: summary is based on current PAS for mosunetuzumab and CMU discounts (midpoint for rituximab)

Mosunetuzumab vs R^2 comparison

- Non-proportional hazard assumed, half cycle correction for TTOT removed and PFS remains same as EAG base case

Scenario 1: Independent OS and a log-normal extrapolation is used for R^2 OS

Scenario 2: Pooled OS with log-logistic extrapolation

Scenario 3: Independent OS and a log-normal extrapolation is used for R^2. Number of people remaining on treatment beyond 6 months increased by 10%, 30% and 50%

Scenario 1 to 3 → did not change the conclusion of EAG base case

Mosunetuzumab vs RB comparison

- Non-proportional hazard assumed and half cycle correction for TTOT removed

Scenario 1: Use exponential distribution for PFS for both arms as it had the lowest BIC and fits well to the KM survival function

Scenario 2: OS and PFS set to company's base case and the number of people who remain on treatment beyond 6 months is increased by 10%, 30% and 50%. TTOT is set to the EAG base case

Scenario 3: Use Log-normal distribution for OS for both arms based on pooled OS data

Scenario 4: Assume exponential independent OS

Scenario 5: Assume log-normal independent OS

Scenario 1, 2, 4 and 5 → cost effectiveness estimates around and above £30k/QALY gained
Scenario 3 → cost effectiveness estimate is substantially higher than £30k/QALY gained

PAS, patient access scheme; PFS, progression-free survival; R^2, rituximab + lenalidomide; R, rituximab; TTOT, time to off treatment

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 company and EAG base case
- Mosunetuzumab vs RB: mosunetuzumab cost effectiveness estimates are around or higher than £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; YG, life years gained; QALY, quality adjusted life years; PAS, patient access scheme; R^2, rituximab + lenalidomide; R, rituximab

Mosunetuzumab for treating relapsed or refractory follicular lymphoma

- ❑ Background
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- ❑ Summary

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Other considerations

Mosunetuzumab has a novel mechanism of action

Equality considerations

- Company & clinical experts: No equality issues expected

Innovation

- Clinical experts: This technology is the first of a new class of drugs for multiply relapsed FL in an area where there is no current standard of care

Uncertainty – summary of overall assessment by company

- Company acknowledges that due to data sparsity and immaturity, some uncertainty in efficacy estimates included within economic model
    - Underlying populations informing the ITC were not perfectly matched. Relaxation of inclusion criteria for patients included in the ITC biased against mosunetuzumab
    - Clinical advisors commented that comparisons from the ITC for R^2 in particular were not what they would expect to see in practice

Abbreviations: FL, follicular lymphoma; ITC, indirect treatment comparison; R^2, rituximab + lenalidomide;

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

Managed access – including Cancer Drugs Fund

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

Additional data collection including [redacted]

Company

Further data collection from GO29781:

- Annual analyses of mosunetuzumab data in GO29781 pivotal cohort planned until at least [redacted] – will inform long term extrapolation and help resolve uncertainty in mosunetuzumab modelled benefit

[redacted]

- [redacted]
- [redacted]

Proposed additional data collection on comparators:

- Sponsored projects and supporting investigator-initiated analyses of real world data would generate more robust comparator data for the control arms of the ITC
- Data collection through SACT could help address issues around lack of suitable clinical effectiveness data for the comparison with R-CHOP and generalisability of the patient cohort to the NHS
- Proposed data collection methods are consistent with evidence package appraised in recent NICE CDF reviews in haematological indications: daratumumab (TA783) and venetoclax (TA796) were recommended following additional data collected in SACT

Abbreviations: CDF, Cancer Drugs Fund; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; ITC, indirect treatment comparison; R, rituximab; 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	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	Unlikely to be resolved with data collection	Low, no further data collection possible / proposed, patient numbers uncertain
Lack of suitable clinical effectiveness data for the comparison with R-CHOP	SACT, but data unlikely to be mature at exit Committee judgement needed on length of data collection	Low*
Generalisability of the patient cohort to the NHS	SACT for UK-based data	High

*Also some potential for interrogating retrospective SACT data but managed access not needed for this

The committee need to make a judgement on whether data collection until [redacted] would sufficiently resolve uncertainty?

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

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Key issues

ICER impact key: Small  Large  Quadrant change  Unknown 

Key issues	Resolved?	ICER impact
1. Suitability and representativeness of RB as a comparator • Is RB a suitable comparator in 3rd line setting? • Is RB representative of any type of R-Chemo in absence of other data	For discussion *Uncertainty*	Unknown 
2. Generalisability of GO29781 patient cohort to the NHS		
3. Suitability of indirect treatment comparisons • Matching-adjusted indirect comparison (MAIC) of mosunetuzumab vs R2 • Propensity score analysis (PSA) of mosunetuzumab vs RB	For discussion *Uncertainty*	Unknown 
4. Plausibility of survival modelling – do results align with expectations?	For discussion	Differs 
5. Subsequent therapy assumptions in all arms		Small 

Resolved key issues	Resolved?	ICER impact
6. Immature data to model post-progression utilities [clarified this includes beyond end of treatment]	Yes *Uncertainty*	Unknown 
7. Inconsistent application of adjusted and unadjusted survival data in model [now corrected]	Yes	Small 
8. Unnecessary half-cycle correction applied in model [EAG now agrees]		
9. Removal of OB as a comparator [agreement it is rarely used 3rd line]		

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; R2, rituximab + lenalidomide; TE, technical engagement

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Thank you.