PART 1

Public observer handout

NICE National Institute for Health and Care Excellence

Lenalidomide for previously treated follicular lymphoma [ID1374]

Lead team presentation

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Company: Celgene

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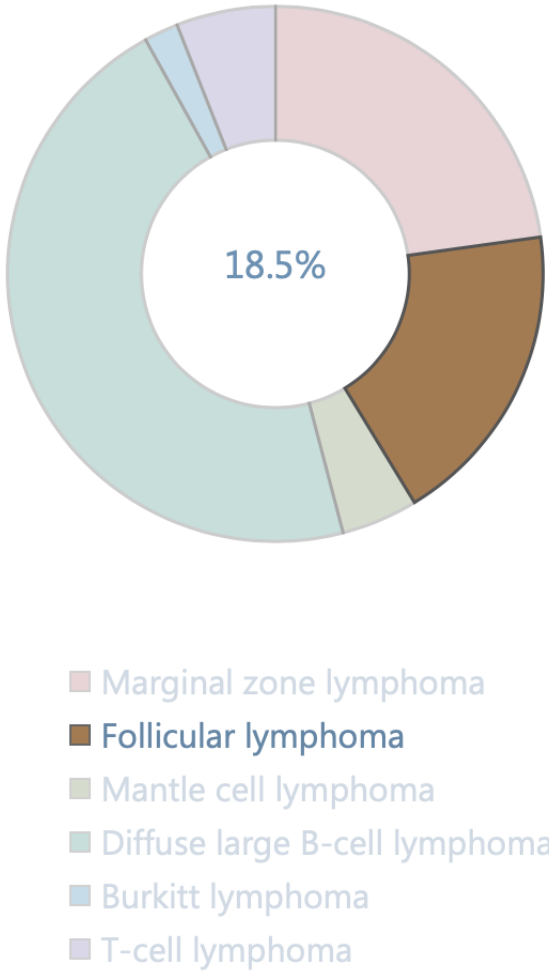
Follicular lymphoma (FL): a type of NHL

- The lymphatic (white blood cell) system is responsible for fighting infection or disease in the body.
- Slow-growing malignant disease of lymph glands.
- Symptoms: lymph node enlargement, fatigue, fevers, night sweats, weight loss, increased risk of infection and bone marrow failure.
- ~2,200 new cases FL per year.
- Average incidence in individuals aged >60.
- Usually considered treatable but incurable.
- **1 in 5** don't need treatment; **4 in 5** treated and usually relapse after a variable period of time.



Non-Hodgkin lymphoma (NHL)[1]

[redacted]

[1]www.hmrn.org
Expected cases per year based on 2010-2016 data

Lenalidomide (Revlimid, Celgene)

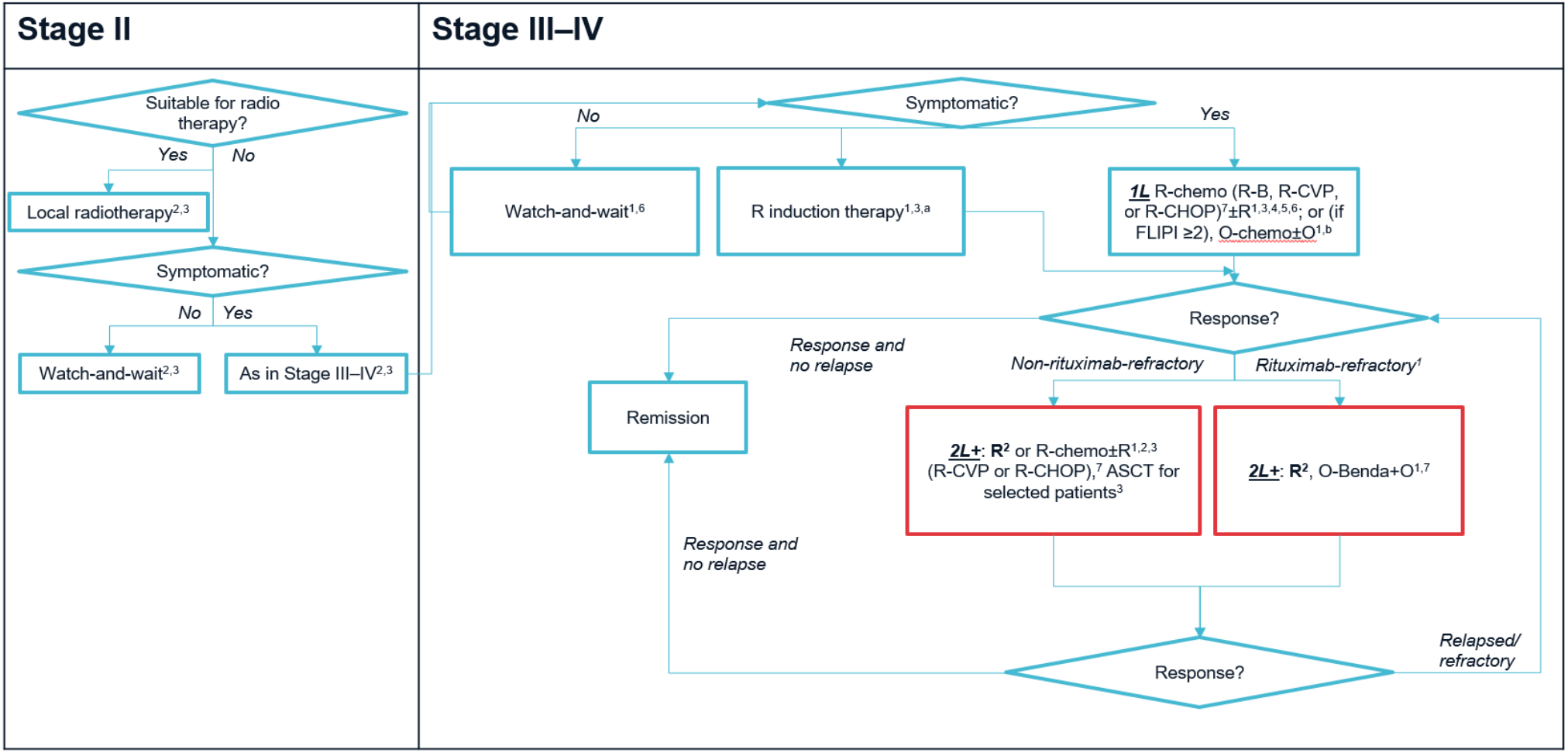
Marketing authorisation (granted 20.12.2019)	Lenalidomide in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated follicular lymphoma (grades 1-3A).
Mechanism of action	Multiple mechanisms including: i) direct effect on tumour; ii) inhibition of blood vessel formation in tumour; iii) modification of immune response.
Administration *	• Recommended starting dose of lenalidomide is 20 mg, orally once daily on days 1 to 21 of repeated 28-day cycles for up to 12 cycles of treatment. • Recommended starting dose of rituximab is 375 mg/m^2 IV every week in cycle 1 (days 1, 8, 15, and 22) and day 1 of every 28-day cycle for cycles 2 through 5.
Price*	• Assuming the starting dose of 20 mg lenalidomide and the AUGMENT mean patient body surface area of 1.85 m^2, the per 28-day cycle costs are £4,168.50 (list price). Based on the median treatment durations for lenalidomide with rituximab patients in AUGMENT ([redacted] months for lenalidomide and [redacted] months for rituximab), the average cost of a course of lenalidomide with rituximab treatment is £60,438. • There is a confidential simple discount PAS.

*Company evidence submission section B.1.2

[redacted]

A new option for patients

Clinical pathway with proposed positioning of lenalidomide with rituximab: figure 1 of company evidence submission



Key: **R**, rituximab; **R-B**, rituximab with bendamustine; **R²**, lenalidomide with rituximab; **O**, obinutuzumab; **benda**, bendamustine; **ASCT**, autologous stem cell transplant; **FLIPI**, follicular lymphoma international prognostic index; **CHOP**, combination chemotherapy; **CVP**, combination chemotherapy; **1L**, first line; **2L**, second line.

[redacted]

Patient perspectives and professional views

Innovation of proposed new treatment option

- Lenalidomide represents a breakthrough for indolent NHL: no approved targeted therapies other than anti-CD-20 antibodies.
- It addresses important an unmet need: overcoming treatment resistance in patients with early relapse or heavily pre-treated chemotherapy-refractory disease.
- Lenalidomide is suitable for older, less fit patients who would not tolerate further chemoimmunotherapy.

Suitability for the NHS setting

- Lenalidomide plus rituximab is generally well tolerated with a toxicity profile that seems fully justified by its clinical efficacy.
- The NHS is set-up to deliver the new technology with no significant resource implications.

[redacted]

Patient perspectives and professional views

- Patients care about living longer and living better
- Relapse is common
- Health-related anxiety
- Family and carers
- Chemotherapy-free treatment options

“It’s an emotional roller coaster, where we’re riding in a fog, never knowing where the highs and drops are or when it will end.”

“Before my next scan, I wake in the night with a panic attack. I dread relapsing and finding there are no more treatment options.”

“I’ve relapsed many times and there’s always been a new treatment when I needed it. But I’m a lot older now and so’s my husband. Neither of us could cope with me going through chemotherapy again. I need a new option.”

AUGMENT: Phase III, multicentre RCT

Population	Patients with non-rituximab-refractory follicular lymphoma (FL, n=295, 82%) and marginal zone lymphoma (grades 1-3A, n=63, 18%). **Information below corresponds to only the 295 patients with FL.**
Treatment / comparator	Lenalidomide with rituximab (n=147) / rituximab monotherapy (n=148).
Key inclusion criteria	≥18 years old; FL between grades 1-3A; previous treatment with one or more prior systemic chemotherapy, immunotherapy, or chemoimmunotherapy and two or more previous doses of rituximab; documented relapsed, refractory, or progressive disease after prior systemic therapy; not rituximab refractory; ECOG performance status ≤2.
Key exclusion criteria	Histology other than FL or clinical evidence of transformed lymphoma, grade 3b FL, systemic therapy within 28 days before cycle 1 day 1 dosing, prior use of lenalidomide, neuropathy grade greater than one, presence or history of CNS involvement by lymphoma, or unwillingness to take venous thromboembolism prophylaxis if considered at risk for a thromboembolic event.
Follow-up	Median: 28.3 months (2.4 years); maximum: 46.7 months (3.9 years).
PFS/OS (95% confidence interval)	Median PFS: Lenalidomide with rituximab: [redacted] months ([redacted], [redacted]); Rituximab monotherapy: [redacted] months ([redacted], [redacted]). PFS HR [redacted] ([redacted], [redacted]). Median OS: not reached in either group. OS HR [redacted] ([redacted], [redacted]).

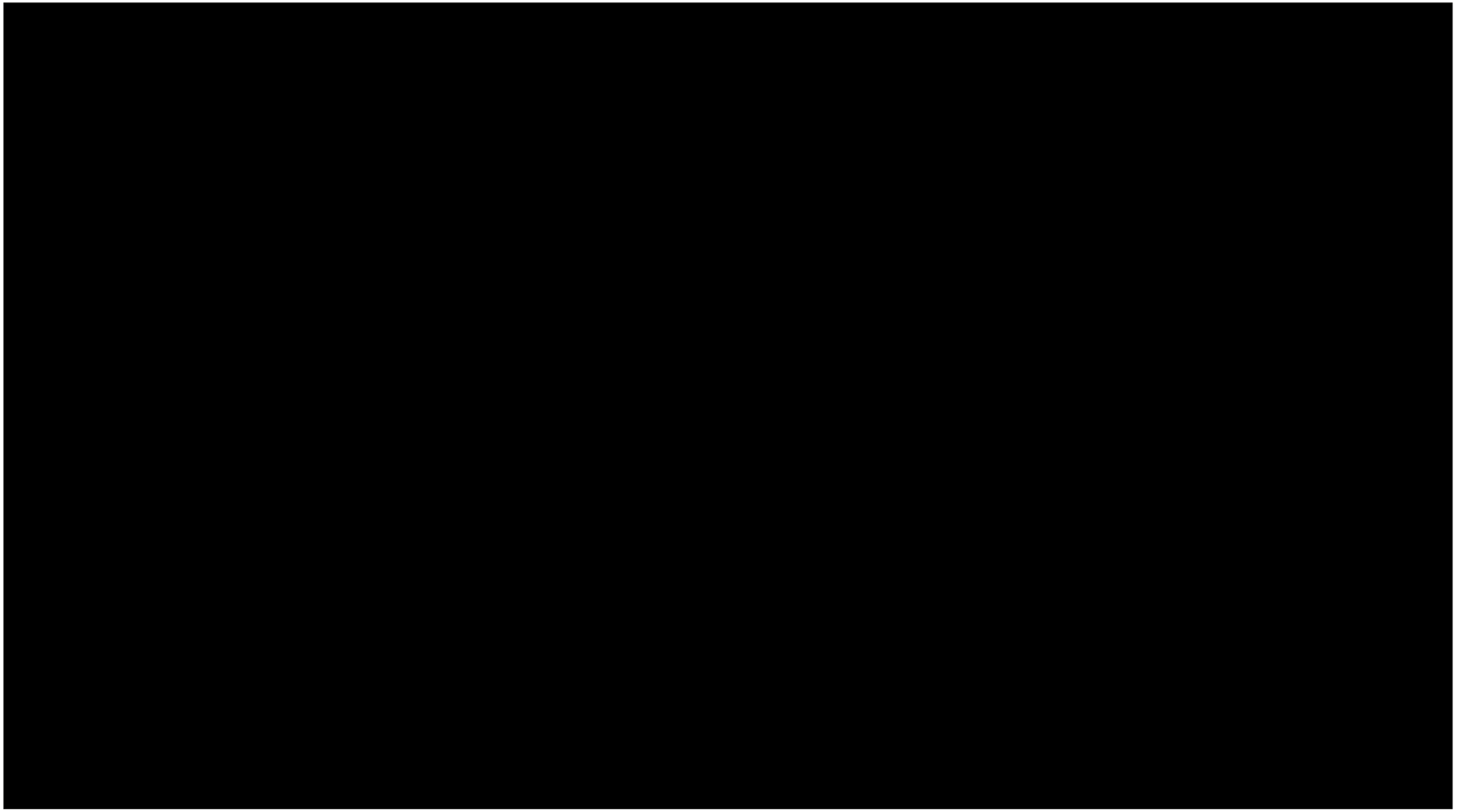
[redacted]

AUGMENT trial OS: MZ and FL population

[redacted]

Figure 8 of company submission

AUGMENT trial OS: FL-only population



[redacted]

Figure 2 of company FL-only addendum

AUGMENT trial PFS: FL-only population

[redacted]

Figure 1 of company FL-only addendum

Key economic information

Model	Partitioned survival model - based on three health states: Progression free, progressed disease (on/off treatment) and death.
Company base-case ICER (R-CVP[1])	£20,156
Technical team preferred ICER (R-CVP[1])	£26,444
Company base-case ICER (R-monotherapy)	£17,233
Technical team preferred ICER (R-monotherapy)	£14,466

Note: ICERs include the confidential discount price for lenalidomide.

1. Since R-CHOP and R-CVP are assumed equally effective [issue 1], and CVP is cheaper than CHOP, CHOP is strictly dominated by CVP. ICERs are therefore provided for lenalidomide with rituximab vs. R-CVP.

[redacted]

Key issues:	Status
1 – Matched adjusted indirect comparison ◇	
R-CHOP and R-CVP: same efficacy?	For discussion
Can the matched-adjusted indirect comparison be improved?	Resolved
Is the matched-adjusted indirect comparison good enough?	For discussion
6 – Early relapse status ◇	
Is it suitable to replace rituximab refractory status with early relapse status?	For discussion
2 – Model structure ◇	
Is a state transition model for R-CHOP/R-CVP required?	For discussion
3 – Long term survival ★	
Which distributions are most suitable for extrapolation of overall survival and progression-free survival?	For discussion
5 – Treatment effect duration ★	
How long is the treatment effect of lenalidomide with rituximab expected to last?	For discussion
4 – Health-related quality of life values	
Should utility values be capped at the general population with or without decrements?	For discussion

[redacted]

Key: high ICER impact: ★ , structural uncertainty: ◇

Issue 1: Matched adjusted indirect comparison (MAIC) (1)

R-CHOP, R-CVP are the most relevant comparators for lenalidomide with rituximab.

- **Data:**
  - 1) UK Haematological Malignancy Research Network [HMRN] registry
  - 2) Van Oers data
  - **ERG and technical team**: Van Oers data not relevant to the UK.
- **Company:** HMRN Kaplan-Meier data for R-CHOP (n=34) and R-CVP (n=33) for OS, PFS and time to next anti-lymphoma treatment are sufficiently similar to assume equivalence.
  - Two regimens pooled (n=63) in the model.
  - Cox proportional hazards model for pooled population shows treatment choice (R-CHOP or R-CVP) is not statistically significant in predicting differences in time to death, progression, or next anti-lymphoma treatment.
- **ERG:** used in different populations (R-CVP: older, R-CHOP younger).
  - Effectiveness therefore difficult to compare.
- **Clinical experts** do not think it appropriate to combine. R-CHOP has longer time to treatment failure than R-CVP (despite similar response rates); PFS is longer with R-CHOP.

[redacted]

R-CHOP and R-CVP: same efficacy?

Overall survival for R-CHOP/R-CVP

[redacted]

Co proportional hazards model output

Variable	Coefficient	Standard error	P-value
Treatment	[redacted]		
Age			
Prior lines of therapy			
Early relapse from diagnosis			
Stage			
Nodal sites			
Prior rituximab			

Key: PH, proportional hazards; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CVP, rituximab plus cyclophosphamide vincristine prednisolone

[redacted]

Source data from HMRN

Progression-free survival for R-CHOP/R-CVP

[redacted]

Cox proportional hazards model output

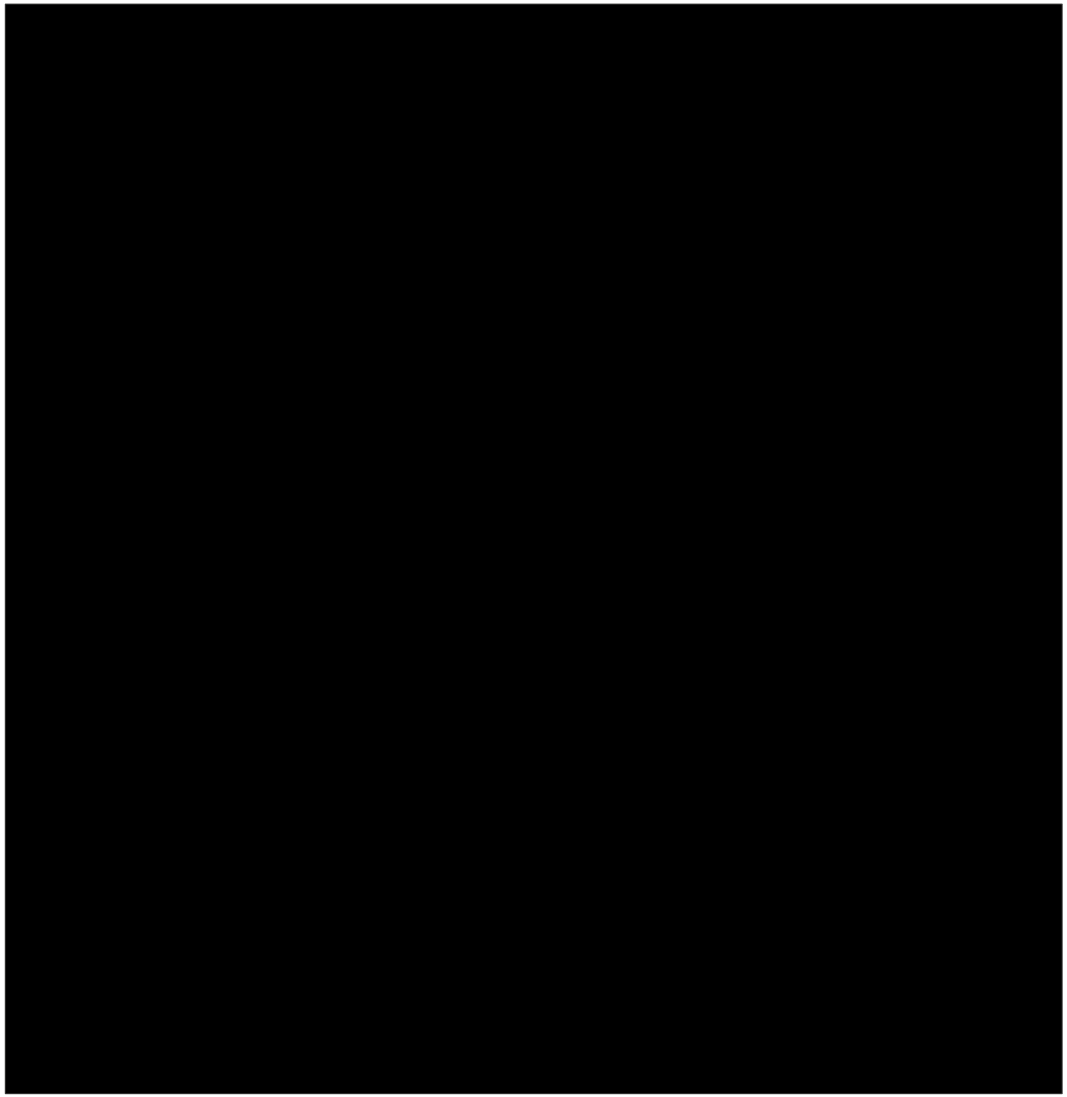
Variable	Coefficient	Standard error	P-value
Treatment	[redacted]		
Age			
Prior lines of therapy			
Early relapse from diagnosis			
Stage			
Nodal sites			
Prior rituximab			

Key: PH, proportional hazards; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CVP, rituximab plus cyclophosphamide vincristine prednisolone.

[redacted]

Source data from HMRN

Time to next anti-lymphoma treatment for R-CHOP/R-CVP



Cox proportional hazards model output

Variable	Coefficient	Standard error	P-value
Treatment			
Age			
Prior lines of therapy			
Early relapse from diagnosis			
Stage			
Nodal sites			
Prior rituximab			

Key: PH, proportional hazards; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CVP, rituximab plus cyclophosphamide vincristine prednisolone.

[redacted]

Source data from HMRN

Issue 1: Matched Indirect treatment comparison (MAIC)

A MAIC is required to compare lenalidomide with rituximab (AUGMENT trial) to R-CHOP/R-CVP (HMRN registry)

- **Company:** MAIC has been improved since technical engagement by including refractory to last therapy. AUGMENT data is now matched to all available covariates from HMRN. Several variables remain unmatched due to lack of data collection by HMRN.
- **ERG:** Results of the MAIC should be interpreted with a high degree of caution due to i) the omission of potentially important covariates ii) small sample sizes, iii) assumed equivalence of R-CHOP/R-CVP, iv) differences in progression-free survival definitions and length of follow-up between AUGMENT and HMRN
- **Technical team:** all available matching criteria from HMRN have now been utilised. It remains uncertain whether the MAIC is reliable given the concerns set out by the ERG.

Is the MAIC good enough?

[redacted]

MAIC matching criteria and reasons for exclusion

Characteristic identified as prognostic and/or a treatment effect modifier	Included in the MAIC?	Reasons for exclusion
Previous exposure to rituximab	✓	
Age	✓	
Refractory to last therapy	✓	
Prior lines of therapy	✓	
Ann Arbor stage (III-IV)	✓	
Nodal sites (>4)	✓	
Bone marrow involvement	✓	
Progression of disease within 24 months	✓	
High LDH	✗	Not collected at baseline by HMRN.
Setum beta-2 microglobulin high	✗	Not collected at baseline by HMRN.
FLIPI risk group (low/intermediate/high)	✗	High LDH (only missing FLIPI variable) is not collected at baseline by HMRN.
Diameter of largest node	✗	Not recorded by HMRN.
Haemoglobin <12 dL/L	✗	Not collected at baseline by HMRN.
FLIPI2 risk group (low/intermediate/high)	✗	Not collected at baseline by HMRN, other than bone marrow involvement.
Time from last treatment	✗	Captured through progression of disease within 24 months (POD24).

Note: Bold characteristics identified as high importance for inclusion

Matched-adjusted indirect comparison (MAIC) before and after technical engagement

Lenalidomide with rituximab (AUGMENT) vs. R-CHOP/R-CVP (HMRN)	HR (95% CI) from MAIC before technical engagement[A] (ESS = 58.88)	HR (95% CI) from MAIC after technical engagement[B] (ESS = 58.91)
OS	[redacted]	
PFS		
TTNLT		
A. Variables included in the adjustment were: age, prior lines of therapy, prior rituximab therapy, POD24, Ann Arbor stage, number of nodal sites and bone marrow involvement.		
B. Variables included in the adjustment were: same as A. Also included refractory to last therapy.		
Key: CI, confidence interval; **ESS**, explained sum of squares; **HMRN**, Haematological Malignancy Research Network; **HR**, hazard ratio; **OS**, overall survival; **PFS**, progression-free survival; **TTNLT**, time to next anti-lymphoma treatment		

[redacted]

Issue 6: relevance of early relapse status

The type of subgroups in the model has changed.

- **Company:** initially provided two subgroups: patients refractory to first-line rituximab ('r-refractory') and patients not refractory to first-line rituximab ('non-r-refractory').
- **Clinical experts (during technical engagement)**: splitting treatment choices based on r-refractory status is 'clinically artificial'.
- **Company (in response to technical engagement):** R-refractory status has been replaced with early relapse ('POD24') to initial chemo-immunotherapy status.
  - Early relapse (POD24) is defined as progression of disease within 24 months of initial chemo-immunotherapy.
  - Early relapse data is provided in both the AUGMENT trial and HMRN registry.
  - Company position is that patients that relapse early from lenalidomide with rituximab have the same outcomes as patients that do not relapse early.
- **ERG and technical team**: assumption of equivalence in outcomes might not hold.
  - KM plots may indicate considerable differences (despite similar hazard ratios).
  - data says nothing about the r-refractory population (follicular lymphoma that did not respond, or progressed, during or up to 6 months after treatment with rituximab or a rituximab-containing regimen).

1. Do both subgroups (early relapse/ no early relapse) respond equally well to lenalidomide with rituximab?

2. If yes, should the results be applicable to all individuals with relapsed FL, considering that r-refractory individuals were not included?

Data for early relapse (POD24)

POD24: progression of disease within 24 months of initial chemo-immunotherapy.

Median PFS, months (95% CI)	All FL patients (n=147/148)	POD24 (n=56/57)	No POD24 (n=89/89)
Lenalidomide with rituximab	39.4 (23.1 - not reported)	30.4 (16.8 - not reported)	39.4 (22.9 - not reported)
R-placebo	13.9 (11.2 - 16.0)	13.8 (6.7 - 16.9)	13.9 (11.2 - 16.6)
HR (95% CI)	0.40 (0.29-0.56)	0.41 (0.24 - 0.68)	0.43 (0.28 - 0.65)
P value	< 0.0001	0.0004	< 0.0001

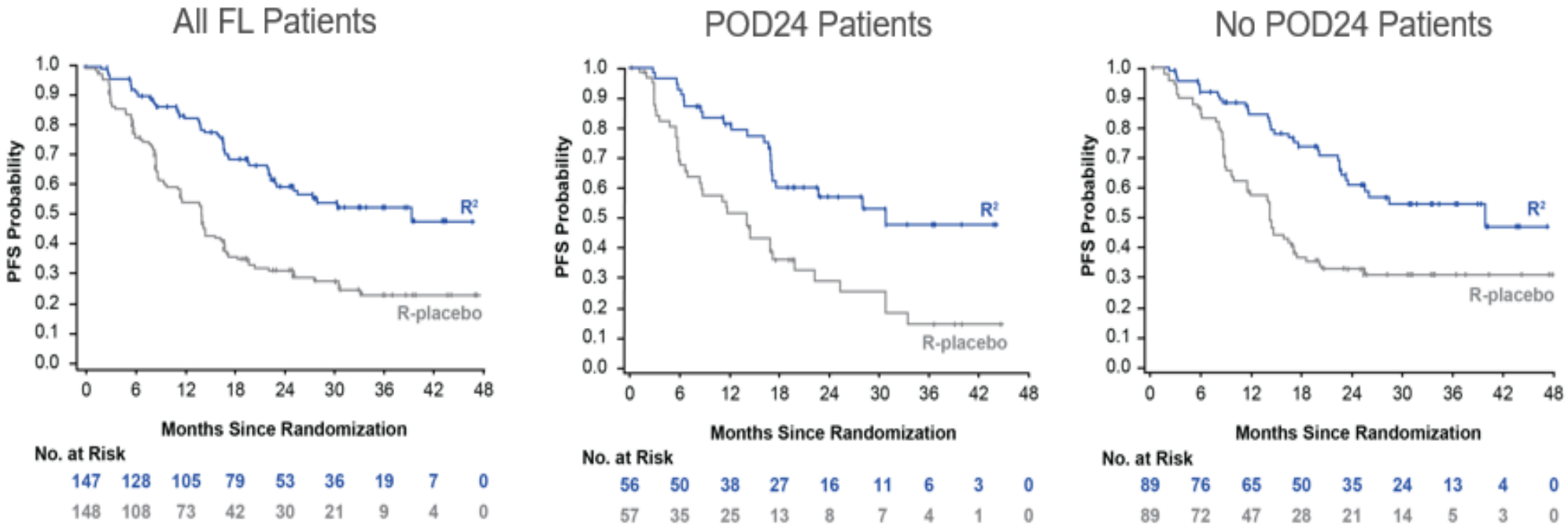


Table and figures from company response to technical engagement

[redacted]

Issue 2: Model structure may be inappropriate (1)

Background

Prior to technical engagement:

- **ERG and technical team:** company should have produced a state transition model to verify the partitioned survival model outputs (especially the plausibility of the extrapolations in the partitioned survival model [issue 3]).
  - Request is in accordance with NICE Decision Support Unit technical support document 19 (recommendation 11).
- **Company:** refused to provide the state transition model for several reasons:
  - A state transition model uses unrandomised end points to model health state transitions.
  - AUGMENT data is immature, leading to inaccurate data to inform transitions.
  - R-CHOP/R-CVP has a small sample size, and reflects less regular disease progression measurement, making it harder to inform transitions between intermediate health states.

Following technical engagement:

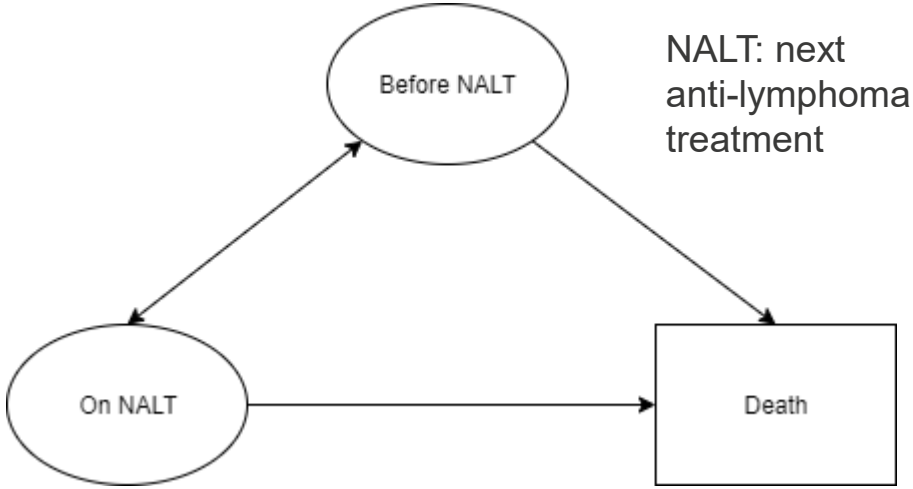
- **Company:** provided a state transition model for lenalidomide with rituximab vs. R-monotherapy only (not R-CHOP/R-CVP).

[redacted]

Overall survival STM and PSM for lenalidomide with rituximab vs. R-monotherapy

[redacted]

STM model structure



NALT: next anti-lymphoma treatment

[redacted]

[redacted]

Issue 2: Model structure may be inappropriate (2)

- **The ERG and technical team:** state transition model is of limited suitability for the following reasons:
  - The absence of a state transition model for the most relevant comparators (R-CHOP/R-CVP).
  - State transition model and partitioned state model for R-mono are only comparable when time to next anti-lymphoma treatment (TTNLT) is assumed equal to progression-free survival (PFS) in the partitioned state model.
    - This was not previously assumed in the base-case or scenarios for the partitioned state model.
    - By assuming that PFS=TTNLT, costs of lenalidomide with rituximab are reduced, and the ICER improves as a result. In the standard partitioned state model, when PFS=TTNLT the ICER for lenalidomide with rituximab reduces by ~£2,000. It is unclear what the results would be if PFS≠TTNLT.

Technology	Incremental			ICER (£/QALYs)
	Costs	Life years gained	Quality-adjusted life years (QALYs)	
Partitioned state model	[redacted]	[redacted]	[redacted]	£17,300
State transition model	[redacted]	[redacted]	[redacted]	£16,160

[redacted]

Is a state transition model for R-CHOP/R-CVP required?

Issue 3: Extrapolations are highly uncertain

Extrapolations are required to calculate expected time to event data (PFS, OS).

- **NICE TSD 14:** Hazard functions should be stratified if independent patient data is available, even if proportional hazard assumption holds.
  - Same extrapolation distribution should be applied to the treatment and comparator arms.

- **Company:** extrapolations are primarily based on consulted clinical expert opinion.

- **ERG:** since the MAIC is uncertain [issue 1] and a state transition model has not been produced for R-CHOP/R-CVP [issue 2], the choice of extrapolation is uncertain and relatively arbitrary:
  - six base cases for lenalidomide with rituximab vs. R-CHOP/R-CVP have been presented, each using a different distribution (exponential, Weibull, etc.).
  - Extrapolations for rituximab vs R-mono are primarily based on best statistical fit of the available KM data.

- **Janssen (commentator):** a state transition model may not be required if the underlying hazard functions for the extrapolations can be assessed.
  - hazard functions for each extrapolation are displayed on the following slides.

- **Technical team**: most decisions are based on clinical expert opinion.

[redacted]

Issue 3: Extrapolations are highly uncertain (1)

Overall survival:

Lenalidomide with rituximab vs. R-CHOP/R-CVP

- **Company:** the Weibull or exponential distribution are the most suitable distributions
- **ERG:** the Weibull curve for FL-only predicts worse survival than the FL+MZL Weibull curve for lenalidomide with rituximab. This is counterintuitive as individuals with FL are relatively younger and fitter than the FL-MZL population. This adds to existing uncertainty.
  - 10 year:
    - FL-MZL: 55%; FL-only: [redacted]
  - 20 year
    - FL-MZL: 28%; FL-only: [redacted]
- **Technical team:** the Weibull distribution is most suitable. Given the extent of the uncertainty, the Weibull produces the most conservative ICER.

Lenalidomide with rituximab vs. R-monotherapy

- **Company:** the log-logistic distribution is the most clinically plausible at 20 years ([redacted] survival). Generalised-gamma time to event data is too optimistic at 20 years ([redacted] survival).
- **ERG:** The generalised gamma distribution provides the best statistical fit of the data.
- **Technical team:** log-logistic is most suitable given i) expert opinion, ii) under the extend of the uncertainty, the log-logistic curve produces the most conservative ICER.

[redacted]

Which extrapolations should be used in the model?

All extrapolation distributions (R-CHOP/R-CVP)

[redacted]

[redacted]

Note: the chosen distribution will also apply to the lenalidomide with rituximab arm (as recommended in NICE TSD 14).

Company OS base case (1): Lenalidomide with rituximab vs R-CHOP/R-CVP **(Weibull)**

Reason for selection: clinical expert opinion

[redacted]

[redacted]

Note: assumes treatment effect of 5 years (company/ERG base case) [issue 5] (grey dashed line).

Company OS base case (2): Lenalidomide with rituximab vs R-CHOP/R-CVP **(exponential)**

Reason for selection: clinical expert opinion

[redacted]

[redacted]

Note: assumes treatment effect of 5 years (company/ERG base case) [issue 5] (grey dashed line).

Company OS base case: Lenalidomide with rituximab vs R-mono **(log-logistic)**

Reason for selection: clinical expert opinion

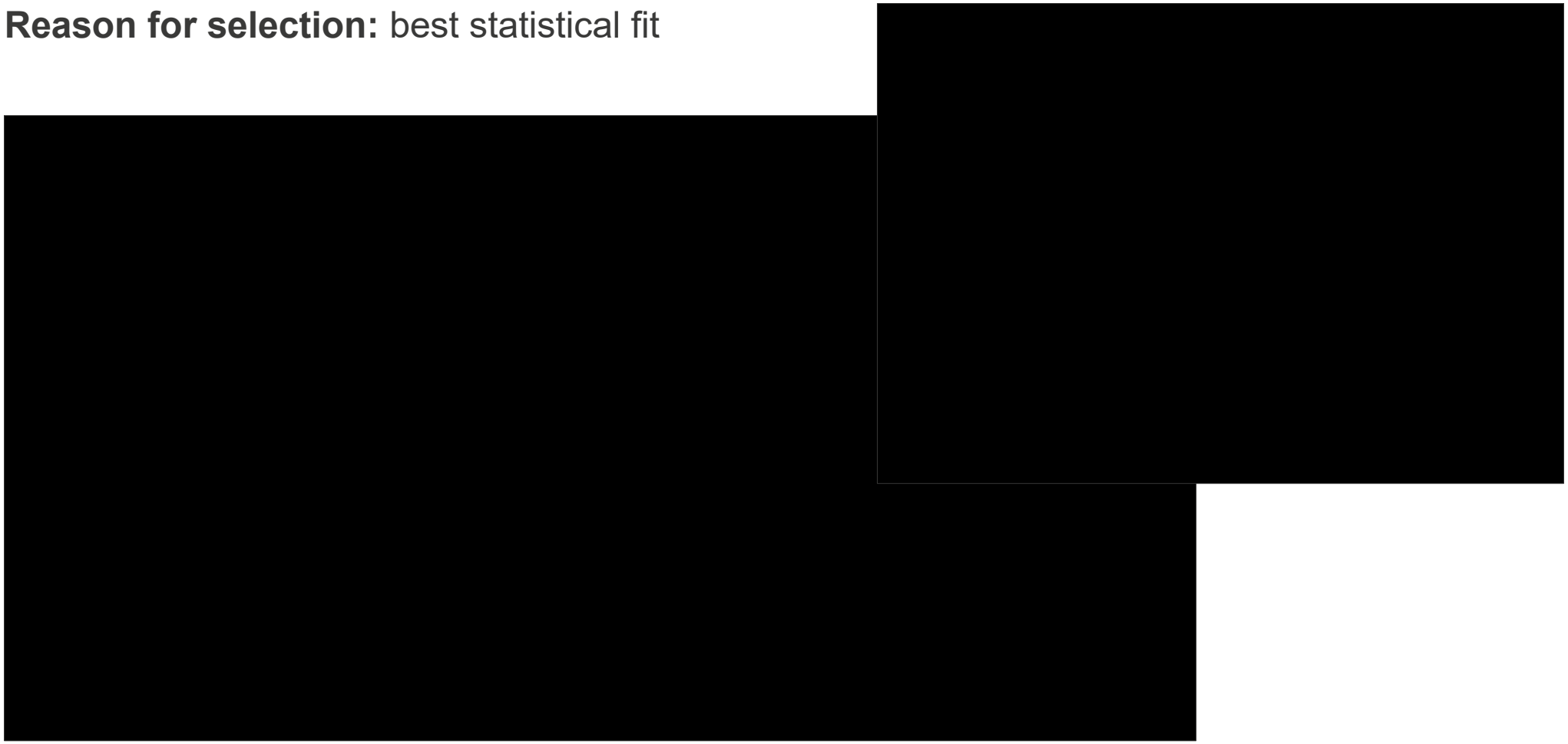
[redacted]

[redacted]

Note: assumes treatment effect of 5 years (company/ERG base case) [issue 5] (grey dashed line).

ERG OS base case:
Lenalidomide with rituximab vs R-mono **(generalised-gamma)**

Reason for selection: best statistical fit



Note: assumes treatment effect of 5 years (company/ERG base case) [issue 5] (grey dashed line).

Issue 3: Extrapolations are highly uncertain (2)

Progression-free survival:

Lenalidomide with rituximab vs. R-CHOP/R-CVP

- **Company:** KM data from AUGMENT should be used for PFS until maximum follow-up (46.7 months). Beyond this time point, the comparator hazard (Weibull) should be applied to extrapolate.
  - prevents the crossing of the OS curves (which clinical experts state would be implausible).
  - the standard parametric distributions for lenalidomide with rituximab are based on immature data.
- **The ERG:** company approach generates a higher PFS for lenalidomide with rituximab compared to standard parametric extrapolations. Log-logistic curve for lenalidomide with rituximab is most appropriate, and the Weibull curve should be used for R-CHOP/R-CVP.
- **The technical team:** the KM+comparator hazard approach should be used if it is most clinically plausible.

Lenalidomide with rituximab vs. R-monotherapy

- **The company:** the log-logistic curve should be used as this is most clinically plausible.
- **The ERG:** the generalised gamma curve should be used as this provides the best statistical fit for the data.
- **The technical team:** log-logistic should be used if it is most clinically plausible.

[redacted]

Which extrapolations should be used in the model?

Company PFS base case: Lenalidomide with rituximab vs R-CHOP/R-CVP **(KM + comparator hazard [Weibull])**

[redacted] **Reason for selection:** crossing of PFS curves is implausible

ERG PFS base case:
lenalidomide with rituximab vs R-CHOP/R-CVP **(log-logistic [lenalidomide+R] / Weibull [R-mono])**

[redacted]

[redacted]

Reason for selection: best statistical fit

Company PFS base case: lenalidomide with rituximab vs R-mono **(log-logistic)**

[redacted]

Reason for selection: clinical expert opinion

ERG PFS base case:
Lenalidomide with rituximab vs R-mono **(generalised-gamma)**

[redacted]

Reason for selection: best statistical fit

Issue 5: Treatment effect duration

When the treatment effectiveness for lenalidomide with rituximab expires, the comparator hazard function will be applied to calculate expected time to event (progression / death).

- **The company:** treatment effect will start to reduce between 5-10 years, and KM curves will eventually begin to merge.
  - used a base-case of 5 years for the treatment effect.

- **Clinical experts:** merging of the curves is likely, crossing of OS and PFS curves is not clinically plausible. Some data suggest the possibility of longer lasting immune-modulated effects following lenalidomide with rituximab treatment (Tuscano et al, BJH 2014).

- **The technical team:** a 5 year treatment effect is the most conservative treatment effect estimate, and given a lack of follow-up data may be most appropriate.

- If using the Weibull distribution for OS, increasing the treatment effect for lenalidomide with rituximab does not improve the ICER. This is due to the nature of the hazard curves.
  - **The technical team** believes that this relationship is possibly due to immature AUGMENT trial follow-up (maximum follow-up of 46.7 months).
  - **The ERG** note that this relationship is observed for most distributions, excluding the exponential distribution (which cannot feature crossing hazard curves). Ultimately the cause of the relationship is unknown.

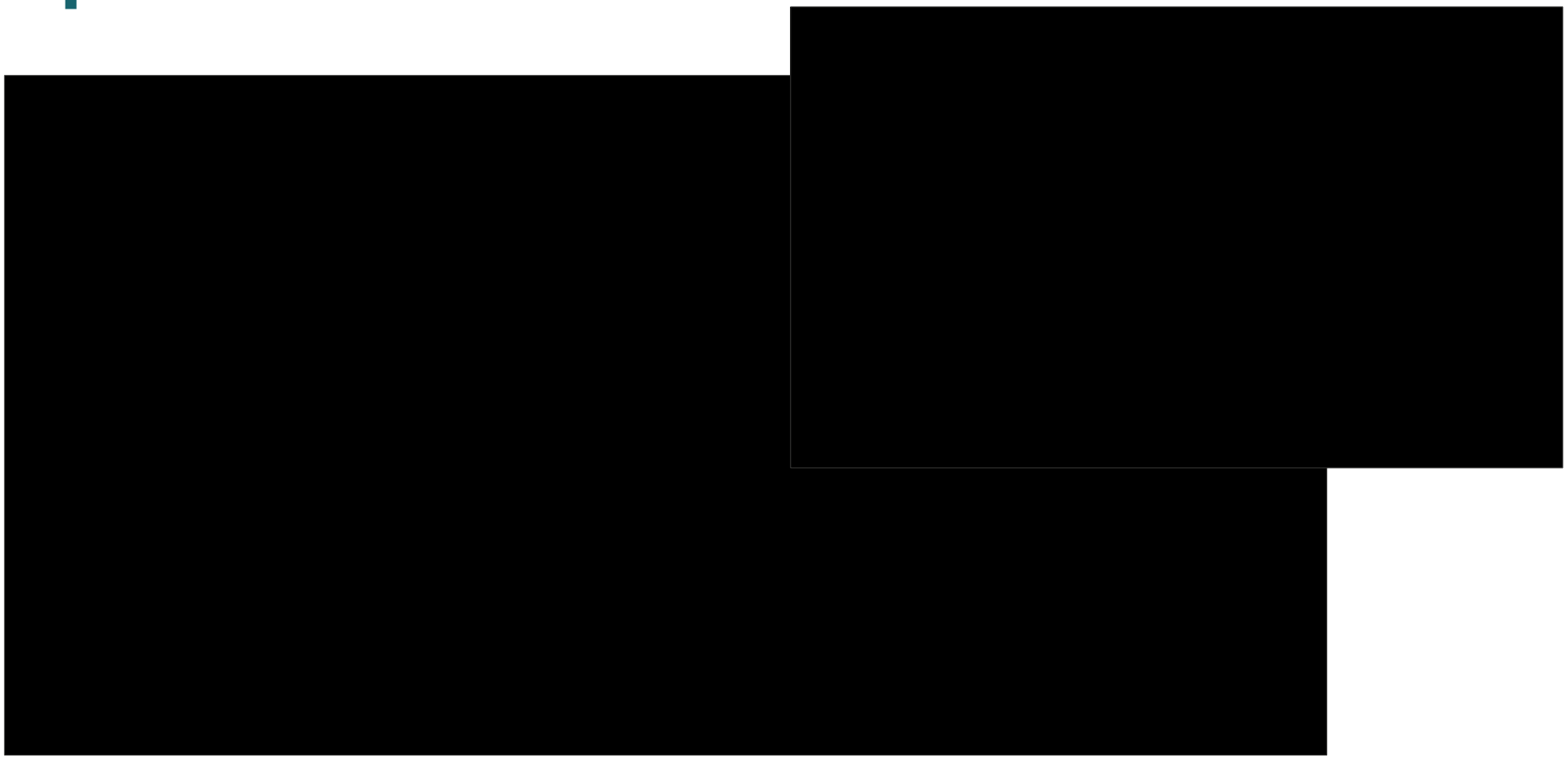
[redacted]

What is the most plausible treatment effect duration?

OS hazard plot (Weibull) for lenalidomide with rituximab vs R-CHOP/R-CVP (base case [5 years])

[redacted]

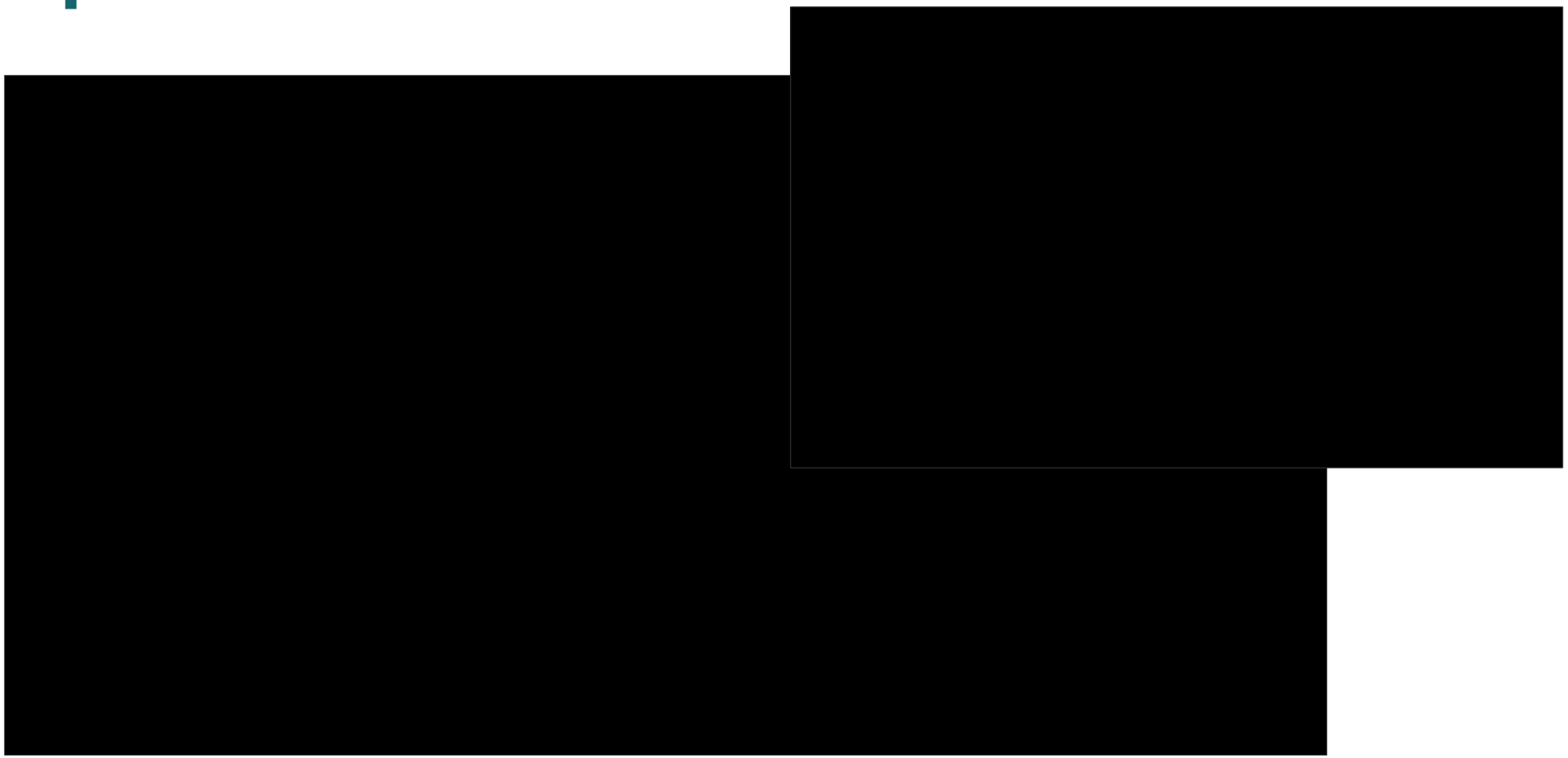
OS 5 years (Weibull) with tech team assumptions



	5 years
Life years (lenalidomide+R)	[redacted]
Incremental life years	[redacted]
ICER	£26,444

[redacted]

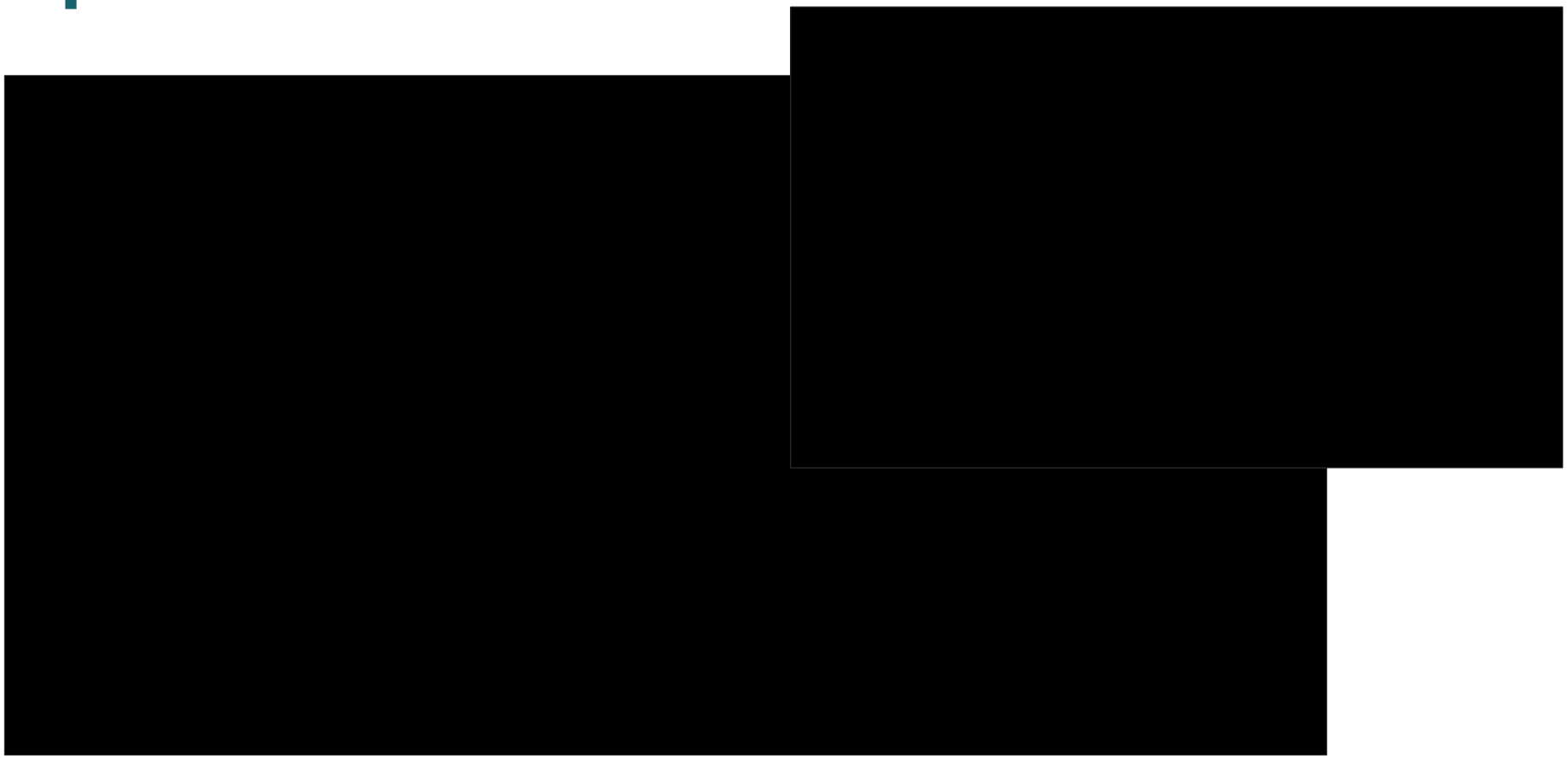
OS 6 years (Weibull) with tech team assumptions



	6 years
Life years (lenalidomide+R)	[redacted]
Incremental life years	[redacted]
ICER	£32,752

[redacted]

OS 7 years (Weibull) with tech team assumptions



	7 years
Life years (lenalidomide+R)	[redacted]
Incremental life years	[redacted]
ICER	£45,803

[redacted]

OS 5 years (exponential) with tech team assumptions

[redacted]

	5 years
Life years (lenalidomide+R)	[redacted]
Incremental life years	[redacted]
ICER	£20,156

[redacted]

OS 6 years (exponential) with tech team assumptions

[redacted]

	6 years
Life years (lenalidomide+R)	[redacted]
Incremental life years	[redacted]
ICER	£18,248

[redacted]

OS 7 years (exponential) with tech team assumptions

[redacted]

	7 years
Life years (lenalidomide+R)	[redacted]
Incremental life years	[redacted]
ICER	£16,925

[redacted]

Issue 4: Utilities

- The AUGMENT trial generated health-related quality of life (HRQoL) values, all of which are above the UK general population norm (0.80):
  - Progression-free disease: 0.867
  - Post-progressed disease (off treatment): 0.841
  - Post-progressed disease (on-treatment). 0.806

- **Clinical experts:** post-progressed disease may be relatively symptomless and painless.
  – differences in post-progressed HRQoL and progression-free HRQoL may not be too different.

- **The company:** HRQoL should be capped at general population norms, but should also use relative decrements for post-progression HRQoL from the AUGMENT trial:
  - Progression-free disease: 0.803
  - Post-progressed disease (off treatment): 0.780
  - Post-progressed disease (on-treatment). 0.747

- **The ERG:** agrees with company approach in principle, but is concerned that the post-progressed on treatment decrement is larger for the FL-only population than the original FL-MZL population, despite FL patients being relatively younger and fitter.

- **The technical team** agrees with the capping of HRQoL values, with relative decrements.

[redacted]

Which utility method should be used in the model?

Cost effectiveness results (vs R-CVP)

Note: ICERs include the confidential **discount for lenalidomide only**. ICERs with confidential comparator discounts will be discussed in part 2.

Revision	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company base case ICER	[redacted]	[redacted]	**£20,156**
Issue 3: Choice of OS extrapolation			
Weibull*	[redacted]	[redacted]	£26,444
Exponential	[redacted]	[redacted]	£20,156
Log-normal	[redacted]	[redacted]	£17,586
Log-logistic	[redacted]	[redacted]	£20,791
Gompertz	[redacted]	[redacted]	£24,165
Generalised-gamma	[redacted]	[redacted]	£15,534
Issue 3: Choice of PFS extrapolation			
Kaplan-Meier + comparator hazard*	[redacted]	[redacted]	£20,156
Log-log/Weibull curves	[redacted]	[redacted]	£23,997
Issue 4: Choice of utilities			
Use decrements for utilities*	[redacted]	[redacted]	£20,156
Do not use decrements for utilities	[redacted]	[redacted]	£20,046

[redacted] *technical team preferred choice

Results from latest company model (13/12/2019)

Cost effectiveness results (vs R-CVP)

Note: ICERs include the confidential **discount for lenalidomide only**. ICERs with confidential comparator discounts will be discussed in part 2.

Revision	Incremental costs	Incremental QALYs	ICER (£/QALY)
Issue 5: treatment effect duration			
5 years (Weibull)*	[redacted]	[redacted]	£26,444
6 years (Weibull)	[redacted]	[redacted]	£32,752
7 years (Weibull)	[redacted]	[redacted]	£45,803
5 years (exponential)	[redacted]	[redacted]	£20,156
6 years (exponential)	[redacted]	[redacted]	£18,248
7 years (exponential)	[redacted]	[redacted]	£16,925
8 years (exponential)	[redacted]	[redacted]	£15,974
9 years (exponential)	[redacted]	[redacted]	£15,258
10 years (exponential)	[redacted]	[redacted]	£14,690
Technical team preferred ICER (all preferred choices)	[redacted]	[redacted]	**£26,444**
Technical team ICER (exponential OS + all other preferred choices)	[redacted]	[redacted]	**£20,156**

[redacted] *technical team preferred choice

Results from latest company model (13/12/2019)

Cost effectiveness results (vs R-mono)

Note: ICERs include the confidential **discount for lenalidomide only**. ICERs with confidential comparator discounts will be discussed in part 2.

Revision	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company base case ICER	[redacted]	[redacted]	**£17,233**
Issue 3: Choice of OS extrapolation			
Log-logistic*	[redacted]	[redacted]	£17,233
Generalised-gamma	[redacted]	[redacted]	£14,466
Issue 3: Choice of PFS extrapolation			
Log-logistic*	[redacted]	[redacted]	£17,233
Generalised-gamma	[redacted]	[redacted]	£16,829
Issue 4: Choice of utilities			
Use decrements for utilities*	[redacted]	[redacted]	£17,233
Do not use decrements for utilities	[redacted]	[redacted]	£17,432
Issue 5: treatment effect duration			
5 years (log-logistic)*	[redacted]	[redacted]	£17,233
6 years (log-logistic)	[redacted]	[redacted]	£15,092
7 years (log-logistic)	[redacted]	[redacted]	£13,717

[redacted] *technical team preferred choice

Results from latest company model (13/12/2019)

Cost effectiveness results (vs R-mono)

CONFIDENTIAL

Note: ICERs include the confidential **discount for lenalidomide only**. ICERs with confidential comparator discounts will be discussed in part 2.

Revision	Incremental costs	Incremental QALYs	ICER (£/QALY)
Issue 5: treatment effect duration			
8 years (log-logistic)	[redacted]	[redacted]	£12,780
9 years (log-logistic)	[redacted]	[redacted]	£12,113
10 years (log-logistic)	[redacted]	[redacted]	£11,623
5 years (gen-gamma)	[redacted]	[redacted]	£14,466
6 years (gen-gamma)	[redacted]	[redacted]	£12,698
7 years (gen-gamma)	[redacted]	[redacted]	£11,587
8 years (gen-gamma)	[redacted]	[redacted]	£10,851
9 years (gen-gamma)	[redacted]	[redacted]	£10,340
10 years (gen-gamma)	[redacted]	[redacted]	£9,975
Technical team preferred ICER (all preferred choices)	[redacted]	[redacted]	**£17,233**
Technical team ICER (gen-gamma PFS/OS + all other preferred choices)	[redacted]	[redacted]	**£14,466**

[redacted]

Results from latest company model (13/12/2019)

End of life criteria / CDF recommendation

- **Company:** life expectancy of relapsed/refractory FL with rituximab-based treatment exceeds 24 months, and as such, lenalidomide with rituximab is not relevant for end-of-life considerations – company submission, section B.2.13., p.105.

- **Company:** not put forward a suggestion for CDF inclusion.
- **Technical team:** inclusion in the CDF may resolve some uncertainty. Extrapolation choices for lenalidomide with rituximab, and treatment duration, may be better informed with a further data cut from the AUGMENT trial. Structural uncertainty is unlikely to be resolved through further data collection (issue 6, issue 1, issue 2), unless a UK based study for R-CHOP/R-CVP is commissioned with a larger sample size, to generate a closer-matched MAIC.
- Are any further data cuts for the AUGMENT trial expected?

Innovation

- The technical team believes that the innovation of lenalidomide with rituximab is captured within the economic model.

Equality considerations

- None identified
- Are there any equality issues?

[redacted]

Key issues:	Status
1 – Matched adjusted indirect comparison ◇	
R-CHOP and R-CVP: same efficacy?	For discussion
Can the matched-adjusted indirect comparison be improved?	Resolved
Is the matched-adjusted indirect comparison good enough?	For discussion
6 – Early relapse status ◇	
Is it suitable to replace rituximab refractory status with early relapse status?	For discussion
2 – Model structure ◇	
Is a state transition model for R-CHOP/R-CVP required?	For discussion
3 – Long term survival ★	
Which distributions are most suitable for extrapolation of overall survival and progression-free survival?	For discussion
5 – Treatment effect duration ★	
How long is the treatment effect of lenalidomide with rituximab expected to last?	For discussion
4 – Health-related quality of life values	
Should utility values be capped at the general population with or without decrements?	For discussion

[redacted]

Key: high ICER impact: ★ , structural uncertainty: ◇