For Public, Projector and company (information redacted)

Chair's presentation

Obinutuzumab for untreated advanced follicular lymphoma [1020]

2nd Appraisal Committee meeting

Committee B

Lead team: Sanjeev Patel, Nigel Westwood, Mark Chapman

Chair: Amanda Adler

ERG: Kleijnen Systematic Reviews

NICE technical team: Anwar Jilani, Lucy Beggs, Jasdeep Hayre, Ahmed Elsada

Company: Roche

18th October 2017

Key issues

- Population: *Company now proposes obinutuzumab only for a subgroup - should the population be limited to intermediate or high FLIPI* score?*
- Effect of induction + maintenance on progression-free survival:
  Can company apply evidence for treatment effect duration of rituximab to obinutuzumab? What is the appropriate treatment duration?
- Proportional hazard assumption: *Would assuming non-proportional hazards reduce the need for an assumption about the duration of treatment effect?*
- Outcomes: *Which is the more appropriate - progression-free survival or time to next treatment?*
- Progression-free survival: *How best to extrapolate? (Weibull, exponential, log-logistic)?*
- Utility of progressed-disease state: *What are the most appropriate utility values? (early=0.62 & late=0.77 [literature] or early= 0.78 & late=0.81 [GALLIUM])?*
- Resource use and biosimilars:
  What proportion of patients on rituximab have biosimilars?

**Follicular Lymphoma International Prognostic Index (FLIPI)*

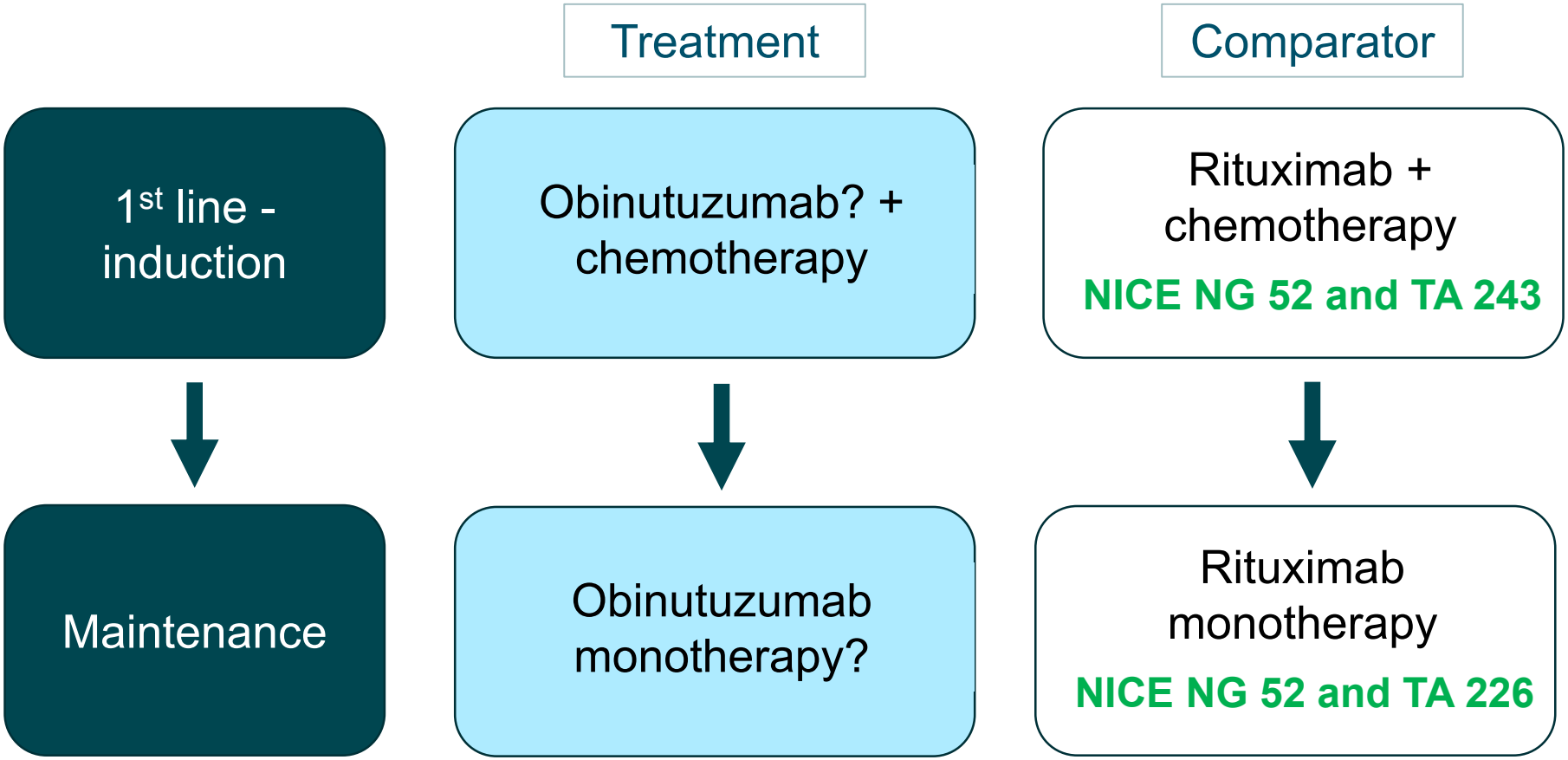
Obinutuzumab (Gazyvaro, Roche)

Positive opinion CHMP
(Committee for Medicinal Products for Human Use, EMA)

Mechanism	• Type II anti-CD20 antibody • Targets CD20 on pre-B and B-lymphocytes
Original proposed marketing authorisation	'**obinutuzumab in combination with chemotherapy**, followed by obinutuzumab **maintenance therapy** in patients achieving a response, is indicated for the treatment of patients with previously untreated **advanced follicular lymphoma**'
Administration	Intravenous infusion
Induction	With chemotherapy: 1st cycle: on day 1, 8 and 15 Subsequent cycles: on day 1
Maintenance	Every 2 months up to 2 years or until progression

Treatment Pathway

For untreated advanced stage symptomatic* follicular lymphoma



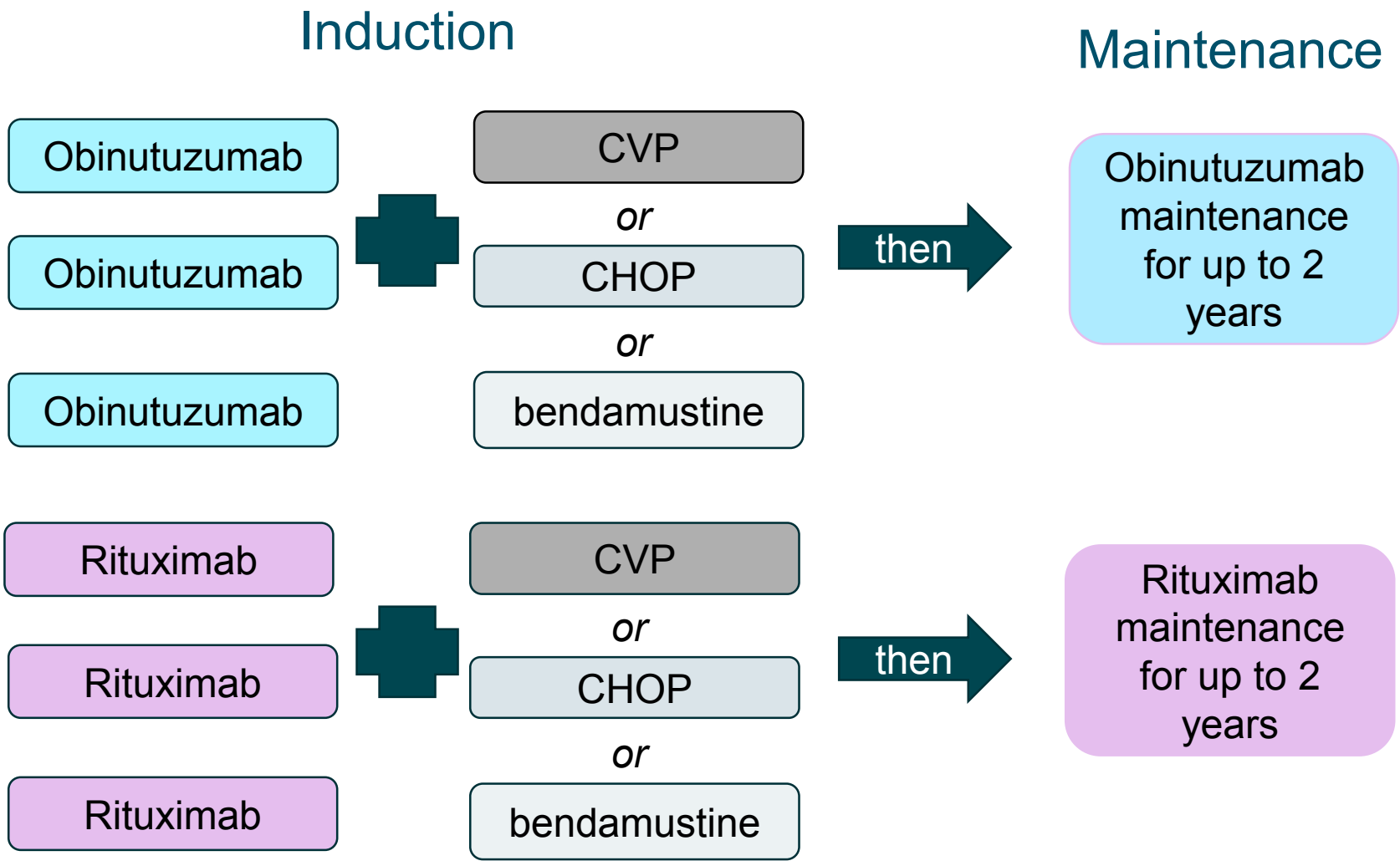
* Unexplained fever >38°C; drenching night sweats; or >10% weight loss within 6 months

Clinical Evidence

GALLIUM open-label randomised controlled trial:

- Adults with advanced follicular lymphoma (grades 1 to 3a)
- Obinutuzumab compared with rituximab
- 1◦ outcome: progression-free survival assessed by investigator
- 2◦ outcome: progression-free survival assessed by independent review committee (IRC)
- Stop treatment if disease progresses or non-tolerated
- Go on to ‘maintenance’ for a maximum of 2 years if respond to induction
- 177 trial sites in 18 countries (including UK)
- Sites had choice of 3 accompanying chemotherapeutic regimens:
    1. cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)
    2. cyclophosphamide, etoposide, doxorubicin and prednisolone (CVP)
    3. bendamustine
- Same chemotherapy given to entire site

GALLIUM Trial



GALLIUM Trial: Clinical Effectiveness

Trial data immature

1∘ outcome Progression-free survival (investigator-assessed)*	Obinutuzumab	Rituximab
Patients with event, N (%)	120 (20.0)	161 (26.8)
HR** (95% Confidence Interval)	0.68 (0.54 to 0.87)	

2∘ outcome Progression-free survival (independent review committee-assessed)*	Obinutuzumab	Rituximab
Patients with event, N (%)	108 (18.0)	141 (23.5)
HR** (95% Confidence Interval)	0.72 (0.56 to 0.93)	

Overall survival*	Obinutuzumab	Rituximab
Patients with event, N (%)	43 (7.2)	52 (8.7)
HR** (95% Confidence Interval)	0.82 (0.54 to 1.22)	

*Cut-off September 2016; Overall ITT population, **HR = Hazard Ratio (stratified)

PRIMA randomised phase III trial

Induction

Maintenance

Population – people who respond to:

Rituximab

+

Chemotherapy

then

Rituximab maintenance for up to 2 years

then

No rituximab maintenance

Trial does not include obinutuzumab, but company uses data from it to model:

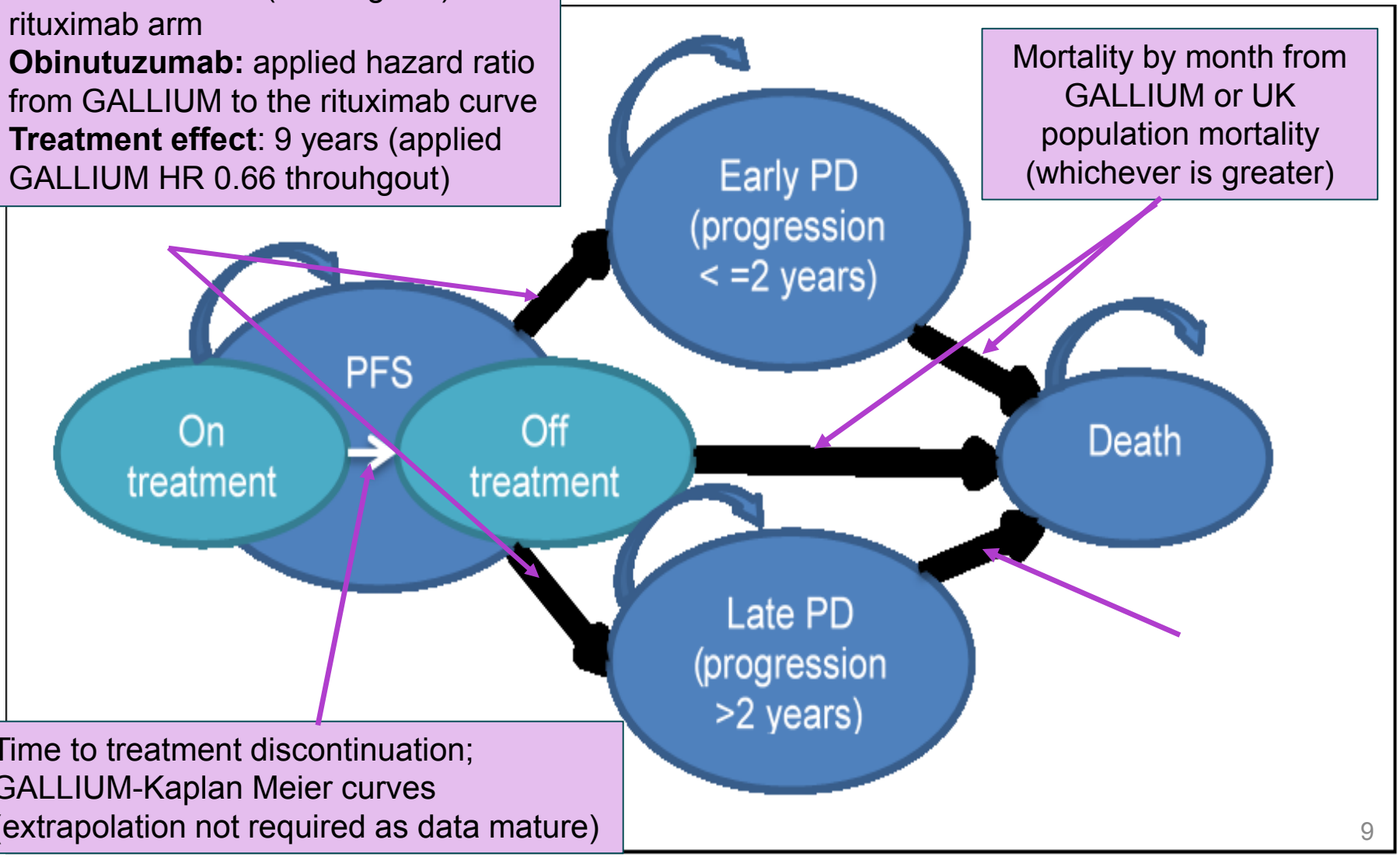
Time from 'late progression' to death for both obinutuzumab and rituximab

Follow-up to 9.75 years

Company's cost-effectiveness model: ACM1

including sources of parameters

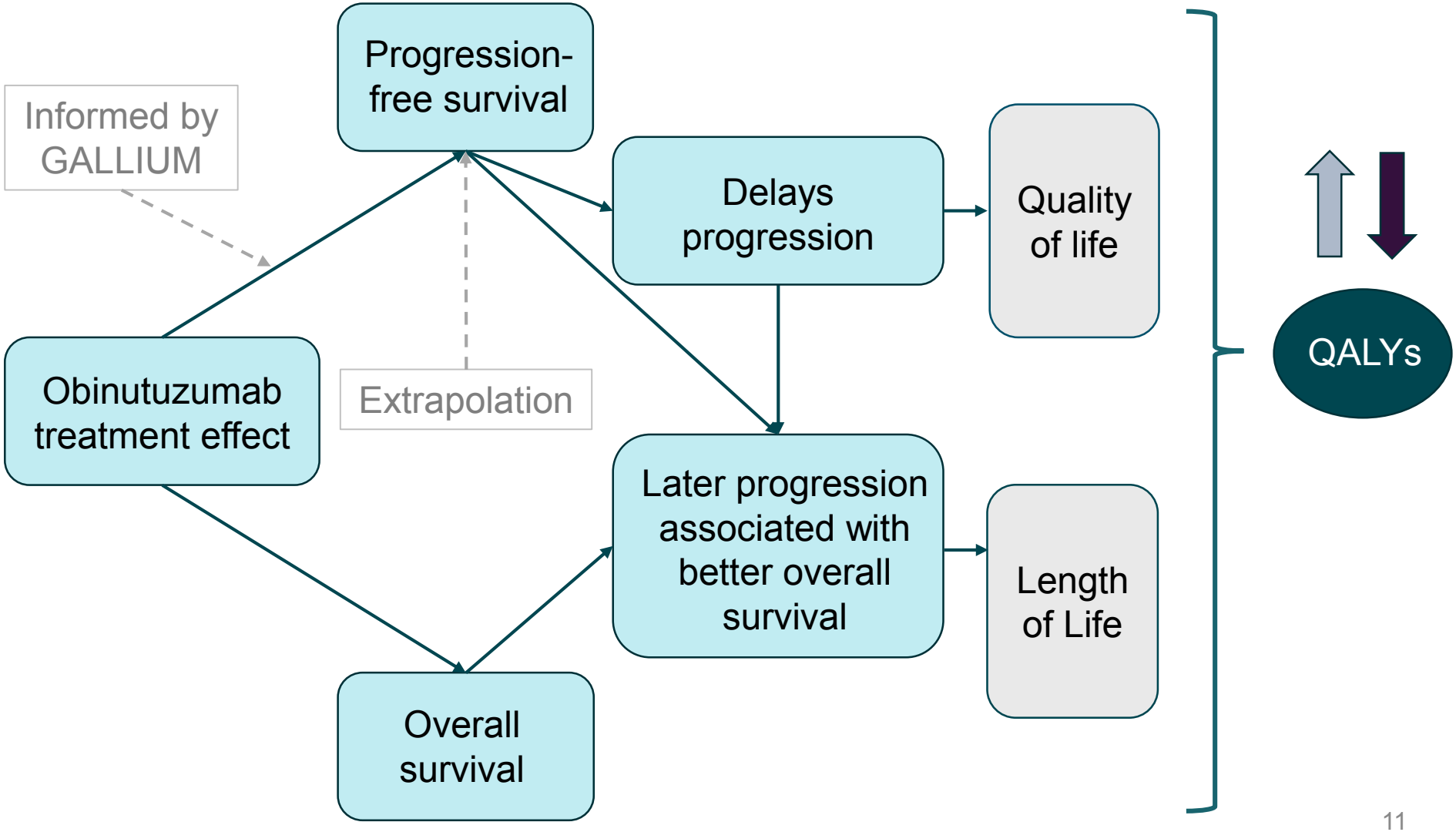
Rituximab: exponential curve fitted to GALLIUM PFS (investigator) for rituximab arm
Obinutuzumab: applied hazard ratio from GALLIUM to the rituximab curve
Treatment effect: 9 years (applied GALLIUM HR 0.66 throughout)



How the model works

- Patients begin in progression free survival state ‘on treatment’
- Patients responding to induction receive maintenance treatment (included in the ‘on treatment’ state)
  - Continue treatment until progression or for maximum 2 years
- Time to stopping treatment (including maintenance) from GALLIUM
  - Stop if progress or do not tolerate
- In PFS state, after completing or stopping treatment, patients remain in PFS ‘off treatment’ state until progression or death
  - Progression free survival extrapolated
- In disease progression state:
  - Once patients progress, they remain in either the early– or late-progressed disease state until death

Conceptual guide to QALYs: obinutuzumab



Committee's considerations in ACD (1)

Issue	Committee's consideration
Trial population	GALLIUM's population reasonably reflects the NHS population
Effectiveness vs rituximab	• Obinutuzumab effectiveness over rituximab is statistically significant, but clinically modest, in delaying disease progression in the short-term. Long-term effect unknown • GALLIUM data too immature to provide evidence of effect on overall survival • Time to next treatment may be a more meaningful outcome than progression-free survival
Safety	Associated with a higher rate of adverse events than rituximab-based therapy
Economic model structure	• Separating early- and late-progressing disease acceptable • But, structure does not reflect patients' experience: same disease state may give different quality of life at different times

Committee's considerations in ACD (2)

Issue	Committee's consideration
Treatment effect	• Company's proposed 9 year treatment effect duration "speculative" & at odds with converging Kaplan-Meier curves from GALLIUM towards end of follow-up • More appropriate to use 5 year treatment effect duration - maximum follow-up from GALLIUM • Should model treatment effects separately in each arm because proportional hazards assumption does not hold • Should model mortality separately in each arm • Preferred to see an analysis where benefit in progression-free survival does not translate to overall survival
Quality of life	• Should take values for utility in progressed-disease from GALLIUM not literature
Resource Use	• Costs of rituximab used by company higher than in the NHS → vial sharing, lower administration costs & and cheaper biosimilars • Questioned company's choice to use single cost for subsequent treatments → regardless of first treatment or whether people progressed early/late

ACD Preliminary Recommendations

Issue	Committee's consideration
Preferred analysis	Using ERG's exploratory analysis except for distribution per chemotherapy regimen (↑ ICER) & no vial sharing (↓ ICER)
ICER	Conclusion: plausible ICER "much higher" than £30,000/QALY gained
End of life criteria & innovation	• End of life criteria not met: life expectancy > 2 years • Not innovative: similar mechanism to rituximab

However, committee did not see analysis that explored:

- Using time to next treatment instead of progression free-survival to capture treatment effect
- Modelling obinutuzumab & rituximab arms separately (i.e. not using a HR, no proportional hazards)
- Assuming obinutuzumab does not prolong life more than rituximab
- Including vial sharing with rituximab & lower admin costs for rituximab
- More valid subsequent treatment costs

ACD Preliminary Recommendation

Obinutuzumab is not recommended, within its anticipated marketing authorisation (that is, first as induction treatment with chemotherapy, then alone as maintenance therapy), for untreated advanced follicular lymphoma in adults

ACD consultation responses

- Consultee comments from:
  - Roche
  - Lymphoma Association
- Web comments from:
  - 1 consultant haematologist
- Statement from 1 clinical expert
- Statement from CDF clinical lead

Consultation topic in order of discussion

1. Committee preferences and company's revised analysis
2. Company's a revised population including a subgroup
3. Company's modelling (extrapolating) progression free survival (PFS):
   - Proportional hazards assumption, extrapolation function
4. Duration of effect of treatment for progression free survival
5. Modelling overall survival
6. Most appropriate endpoint – time to progression or to next treatment?
7. Progressed-disease utility
8. Progression-free utility
9. Resource use and biosimilars of rituximab

Committee preferences and company's revised analysis (1)

Committee preference:	Did company revise?
Amend demographic characteristics: a. Increase age at start of treatment from 57.9 to 62.6 years	✓
b. Change % females from 50% to 53.2% per GALLIUM baseline	✓
Different mortality rates for the treatment arms	✓
Age-related utility decrement	✓
Independent review committee progression-free survival Weibull curve	✗ Slides 25-32
Disutility for adverse events	✓
Updated adverse event (grade ≥3) costs	✗ Slide 51
Treatment effect duration that does not continue beyond trial follow-up	✗ Slides 33-36

Committee preferences and company's revised analysis (2)

Committee preference	Did company revise?
Using utility value for progressed-disease states from GALLIUM	✗ Slides 42-44
Using time to next treatment instead of progression-free survival to capture treatment effect	✗ Slides 39-41
Modelling obinutuzumab and rituximab arms separately (i.e. no proportional hazards)	✓
Assuming patients on obinutuzumab do not live longer than on rituximab	✗ Slides 37-38
Assuming vial sharing for rituximab across disease areas	✓
Lowering administration costs for rituximab intravenous infusion	✓
Using valid costs of subsequent treatment	✗

Revised population

Company's comments

Revision to Summary of Product Characteristics (26th Sep 2017):

'Based on a subgroup analysis in previously untreated follicular lymphoma, the efficacy in FLIPI low risk (0-1) patients are currently inconclusive… A therapy choice for these patients should carefully consider the overall safety profile of Gazyvaro (obinotuzumab) plus chemotherapy and the patient-specific situation.'

- Roche: *'uncertainty of benefit in low FLIPI patients'*
- Progression-free survival (investigator) hazard ratio = 1.11 (95% CI: 0.62-1.99)
- Roche: 'prudent' to consider population with **intermediate or high FLIPI score (≥2)** (collectively: 'higher risk')
- FILIPI higher risk patients have 'highest clinical unmet need' and 'greater risk of relapse'
- FLIPI risk groups were pre-specified subgroups in GALLIUM

FLIPI scores

Follicular Lymphoma International Prognostic Index

FLIPI assessment criteria:

5 factors	Age	<60 years vs ≥60 years
	Haemoglobin	≥12g/dL vs <12g/dL
	Serum LDH	≤upper limit normal vs >upper limit normal
	Ann-Arbor stage	I-II vs III-IV
	No. of nodal sites	≤4 vs >4

Risk group	No. of FLIPI factors	5-yr overall survival (%)	10-yr overall survival (%)	Relative risk of death (Compared to 'Low/Good' group)
Low/Good	0–1	91	71	1.0
Intermediate	2	78	51	2.3
High/Poor	≥3	53	36	4.3

GALLIUM: Baseline characteristics

FLIPI higher risk and ITT populations

	FLIPI Higher risk subgroup		ITT population	
	Obinutuzumab	Rituximab	Obinutuzumab	Rituximab
Mean age, years (SD)	59.9 (11.4)	59.4 (12.4)	58.2 (11.5)	57.7 (12.2)
Men, n (%)	219 (46.2)	207 (43.5)	283 (47.1)	280 (46.6)
ECOG 0 or 1, n (%)	459 (97.0)	453 (95.4)	585 (97.5)	576 (96.2)
Mean body surface area, m^2 (SD)	1.84 (0.2)	1.83 (0.2)	1.86 (0.2)	1.84 (0.2)

Clinical expert:
Age: *'I'd expect a slightly higher average age: 60-65'*
Sex: *'I'd expect slightly more males – approx. 50%'*

⊙ *Is the FLIPI higher risk population similar to patients treated in the NHS?*

Revised population

ERG's, CDF clinical lead, and clinician comments

- FLIPI higher risk and ITT population look comparable
- New submission uses data from Sep 2016 cut-off whereas previous submission uses Jan 2016 → ERG cannot validate
- No data about distribution of CVP, CHOP and bendamustine in subgroup
- Could FLIPI score affect the initially assigned anti-lymphoma treatment?
- ERG emphasises: *'uncertainty was high in the original analyses'.* Excluding 20% of the trial population *'will only **increase the uncertainty'***

CDF Clinical Lead: *'Roche states in its post-ACD submission that 'FLIPI does not yet have a role in determining treatment selection…'. It therefore seems strange for Roche then to retrospectively use a scoring system that is validated for prognosis but not for treatment selection' & [...] 'wary of such retrospective analyses being used in this way'*

Clinical expert: FLIPI scores *'generally not'* used in clinical practice to categorise patients' severity of disease

⊙ *Should the population be limited to intermediate or high FLIPI score ?*

GALLIUM Trial: Clinical Effectiveness
Intermediate and High FLIPI subgroup (n=950)

Progression-free survival (investigator-assessed)*	**Obinutuzumab**	**Rituximab**
Patients with event, N (%)	95 (20.0)	140 (29.0)
HR** (95% Confidence Interval)	0.62 (0.47, 0.80)	

Progression-free survival (independent review committee-assessed)*	**Obinutuzumab**	**Rituximab**
Patients with event, N (%)	89 (18.8)	126 (26.5)
HR** (95% Confidence Interval)	0.67 (0.51, 0.88)	

Overall survival*	**Obinutuzumab**	**Rituximab**
Patients with event, N (%)	37 (10.1)	48 (10.1)
HR** (95% Confidence Interval)	0.76 (0.49, 1.16)	

* Updated analysis (cut-off September 2016), **HR = Hazard Ratio (stratified)

Company's modelling of progression-free survival

Company proposes:

- **Independently** assessed progression-free survival data
- A **non-proportional hazard assumption** for long-term extrapolation
- **Log-logistic** extrapolation for both the treatment and comparator groups
- **No assumption about treatment effect duration limit**

Non-proportional hazards

Company's comments

- Committee preference for separate extrapolated progression-free survival curves for each treatment arm (ie. no proportional hazards)
- Separate curves → *'long-term decline in treatment effect compared to a proportional hazards model'*
- Company proposes a **non-proportional hazard assumption** for long-term extrapolation **instead of a treatment effect duration assumption**

Non-proportional hazards
ERG's comments

- Non-proportional hazards assumption *'plausible*', as visual inspection of the original proportional hazards modelling was *'inconclusive'*
- Company has argued that modelling non-proportional hazards is more conservative (See next slide for comparison of mean/median progression-free survival times for non- & proportional hazards)
- ERG: Evidence for non-proportional hazards being more conservative is based on FLIPI higher risk subgroup and treatment effect duration of 9 years

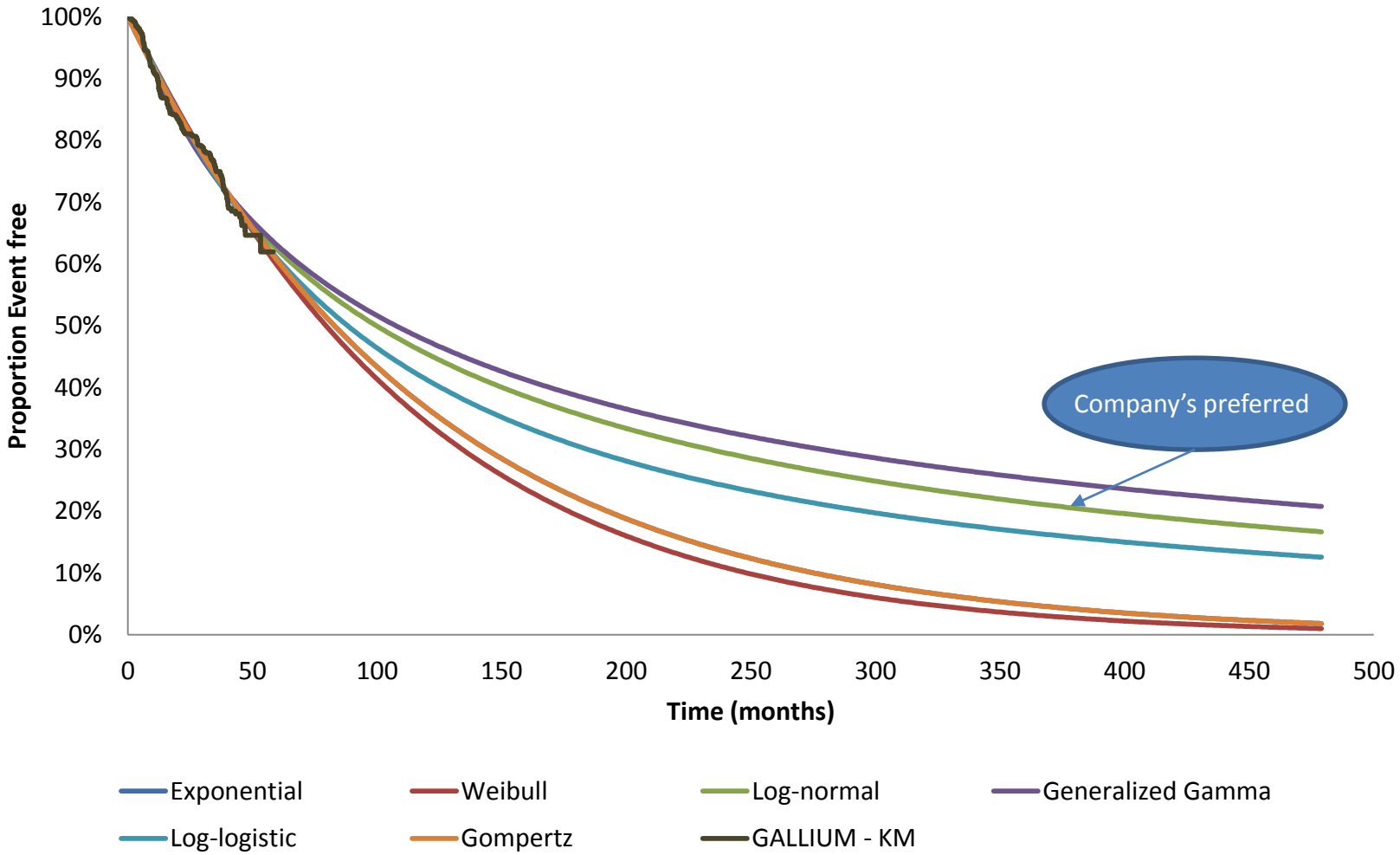
→ '*Unclear'* if non-proportional hazards would be more conservative under all subgroups/assumptions.

⊙ *Would a non-proportional hazard assumption reduce the need for an assumption about treatment effect duration?*

Comparison of extrapolation curves

*For progression-free survival extrapolation in **rituximab***

FLIPI Higher risk population:



Comparison of extrapolation curves

For progression-free survival extrapolation ***for obinutuzumab***

FLIPI Higher risk population:
PFS rates at different time points for extrapolation functions (estimated by NICE technical team using information provided by company)

	PFS at 6yrs (%)	PFS at 8yrs (%)	PFS at 10yrs (%)	PFS at 15yrs (%)
Exponential	0.67	0.59	0.51	0.37
Weibull	0.64	0.53	0.44	0.27
Log-normal	0.68	0.62	0.56	0.46
Generalised gamma	0.69	0.63	0.58	0.49
Log-logistic	0.66	0.57	0.50	0.38
Gompertz	0.61	0.45	0.30	0.01

Progression-free survival extrapolation

Company's comments

- Weibull function 'implausible' as assumes ↑ risk of progression with time spent free of progression
- Long-term rituximab data shows decline in hazard of progression after treatment (progression risk ↓ with time spent free of progression) → TA226 Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma
- Company proposes Exponential (proportional hazards) or Log-Logistic (non- & proportional hazards)
- Base case: Independently assessed, log-logistic, non-proportional hazards & indefinite treatment effect duration

Progression-free survival extrapolation

ERG's comments

- Under base case, at 10 years 45% of rituximab patients expected to be progression-free
- This overestimates clinical experts' estimates originally provided by the company (30-40%)
- Distributions had previously been excluded if had fallen outside range
- ERG: treatment effect does decline over time with independent log-logistic extrapolation
- However, not necessarily a more conservative estimate of treatment effect duration…

Progression-free survival extrapolation

ERG's comments

Justification for log-logistic choice unclear:

- AIC and BIC suggest log-normal = best statistical fit
- ERG confirmed that Weibull → ↑ hazard of progression over time
- However, log-logistic may not be only distribution with decreasing/ constant hazard over time
- Gompertz distribution was not presented → lower mean life years in progression-free survival than Weibull:

FLIPI Higher risk population: Incremental Life Years

Obinutuzumab vs Rituximab		Log-logistic (Company preferred)		Weibull		Gompertz	
	Time in PFS	Mean	Median	Mean	Median	Mean	Median
	Proportional hazards	2.25	3.17	1.95	2.75	2.69	2.58
	Non-proportional hazards	1.88	2.67	1.56	2.08	-2.05	0.42

Duration of treatment effect: Progression-free survival

Company's comments

- Originally modelled as 9 years (GALLIUM hazard ratio of 0.66 applied throughout)
- Committee preferred 5 years to reflect longest follow-up in GALLIUM
- Roche: No treatment effect beyond GALLIUM study follow up period 'implausible'
- Implications of new company model:
  - 10 year effect in intention-to-treat population (compared with rituximab)
  - Almost 20 year effect in FLIPI Higher risk group (compared with rituximab)

Duration of treatment effect: Progression-free survival

Company's comments

Obinutuzumab progression-free survival treatment effect

- (Goede et al. 2015) : obinutuzumab plus chlorambucil vs rituximab plus chlorambucil to treat chronic lymphocytic leukaemia (different disease) → median progression-free survival treatment effect 2.4 vs 1.3 years (HR: 0.46, 95% CI: 0.38, 0.55)

Generalising results from rituximab → obinutuzumab

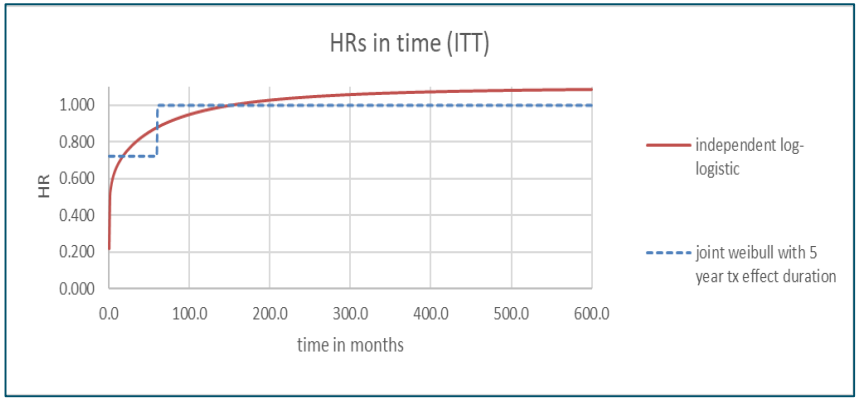
- Obinutuzumab has similar mechanism to rituximab → one can generalise for progression-free survival benefit
- (Bachy et al. 2013): CHVP-interferon vs CHVP-interferon plus rituximab in follicular lymphoma has 8.4 year treatment effect for rituximab
- (Herold et al. 2014): Mitoxantrone, chlorambucil, and prednisolone (MCP) vs MCP plus rituximab shows 8.7 year treatment effect for rituximab

Progression-free survival extrapolation

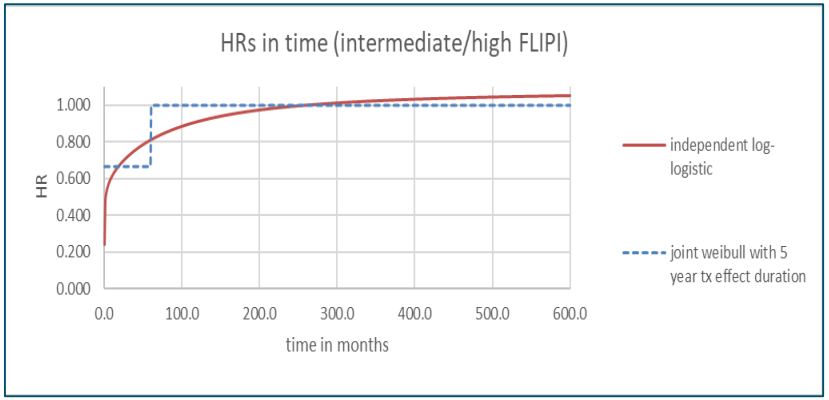
ERG's comments

Weilbull (with proportional hazards and 5 year treatment effect) vs Log-logistic (with non-proportional hazards)

Intention-to-treat population (ITT):



FLIPI Higher risk subgroup:



- Under log-logistic: ITT has 10 year effect and FLIPI has almost 20 year effect

Duration of treatment effect

ERG's comments

- Bachy et al. (2013) and Herold et al. (2015): *'unclear'* how studies of rituximab versus chemotherapy (anti-CD20 vs chemotherapy) would inform decisions about obinutuzumab against rituximab (anti-CD20 vs another anti-CD20)
- Goede et al. (2015): Study was in a different indication and only reports 40 months progression-free survival follow-up

→ long-term treatment effect of obinutuzumab still unclear

⊙ *Can the treatment effect duration for rituximab be applied to obinutuzumab?*

⊙ *What is the appropriate treatment effect duration for obinutuzumab?*

Overall survival benefit

Company's comments

- Determining overall survival benefits challenging due to indolent nature of disease
- *'well-established OS benefit of rituximab in the first line induction setting'*

→ *'PFS HR of 0.58 (95% CI: 0.50-0.68) was associated with an OS HR of 0.63 (95% CI 0.51-0.79) for R-chemo versus chemo induction'*

- '*the predictions of the model and the trend observed in GALLIUM OS data (HR 0.82, 95% CI: 0.54-1.22, p=0.32) are consistent with the OS benefit of [obinutuzumab] in the rituximab refractory [follicular lymphoma] setting'*

ERG's comments

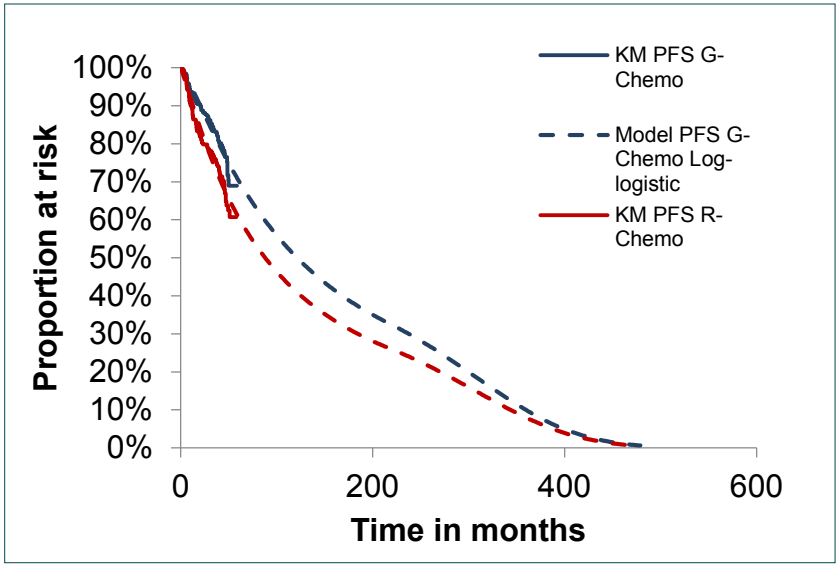
- '*Including OS [sic] benefit for obinutuzumab without any mature OS comparative data (obinutuzumab vs. rituximab in follicular lymphoma patients) would be speculative)'*

⊙ *What is the most appropriate estimate of overall survival benefit for obinutuzumab?*

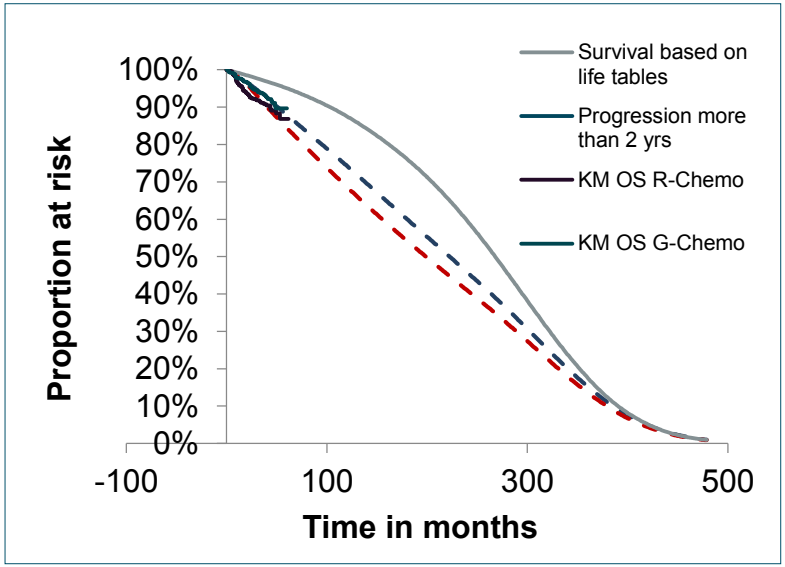
Clinical implications of survival modelling

Company's model

Progression-free survival



Overall survival



After 20 years is it realistic to expect:

1. 28% of patients progression free
2. 45% of patients surviving?

Clinical experts:
'Yes… minority of patients [with] long remission [progression-free], 20-25% as an estimate'

⊙ *Are the implications of the survival modelling clinically plausible?*

Most appropriate outcome measure

Company and consultee's comments

Company:

- Time to next treatment effect ≥ Progression-free survival treatment effect

Outcome measure	Hazard ratio (95% confidence interval)
Progression-free survival (investigator)	0.68 (0.54 to 0.87)
Progression-free survival (independent)	0.72 (0.56 to 0.93)
Time to next anti-lymphoma treatment	0.68 (0.52, 0.90)

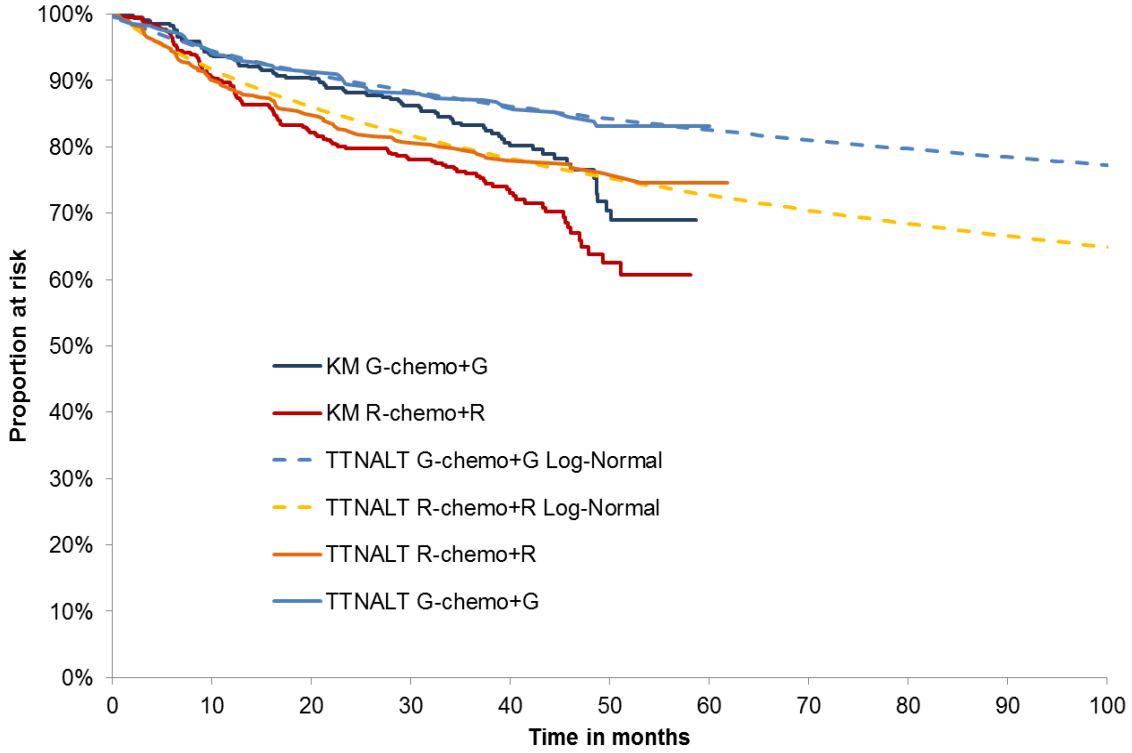
Professional and patient groups, web comments:

- *'follicular lymphoma patients are aware that each period of remission will be shorter than the previous one… length of remission after first line treatment is an important factor'*
- *'The PFS benefit of 30% is significant for all patients as clinically their concern is time to next treatment. This is significant for younger patients who want to delay 2nd treatments as long as possible.'*

Most appropriate outcome measure (2)

Company's comments

Time-to-next-treatment, extrapolation & progression-free survival (independent)



- Mean time to next treatment greater than mean time in progression-free survival
- Progression-free survival is more 'conservative' outcome than time to next treatment → Lower ICER
- Company base case uses independently assessed progression-free survival

Most appropriate outcome measure (3)

ERG's comments

- Time-to-next-treatment *'with different extrapolations under the new company base-case, for both ITT and intermediate/high risk subgroup populations, would result in lower ICERs'.*
- However, ERG could not check whether time-to-next-treatment implemented correctly
- Could not check whether using time-to-next-treatment would lead to a lower ICER in all possible scenarios

⊙ *Is progression-free survival or time to next treatment the most appropriate primary outcome?*

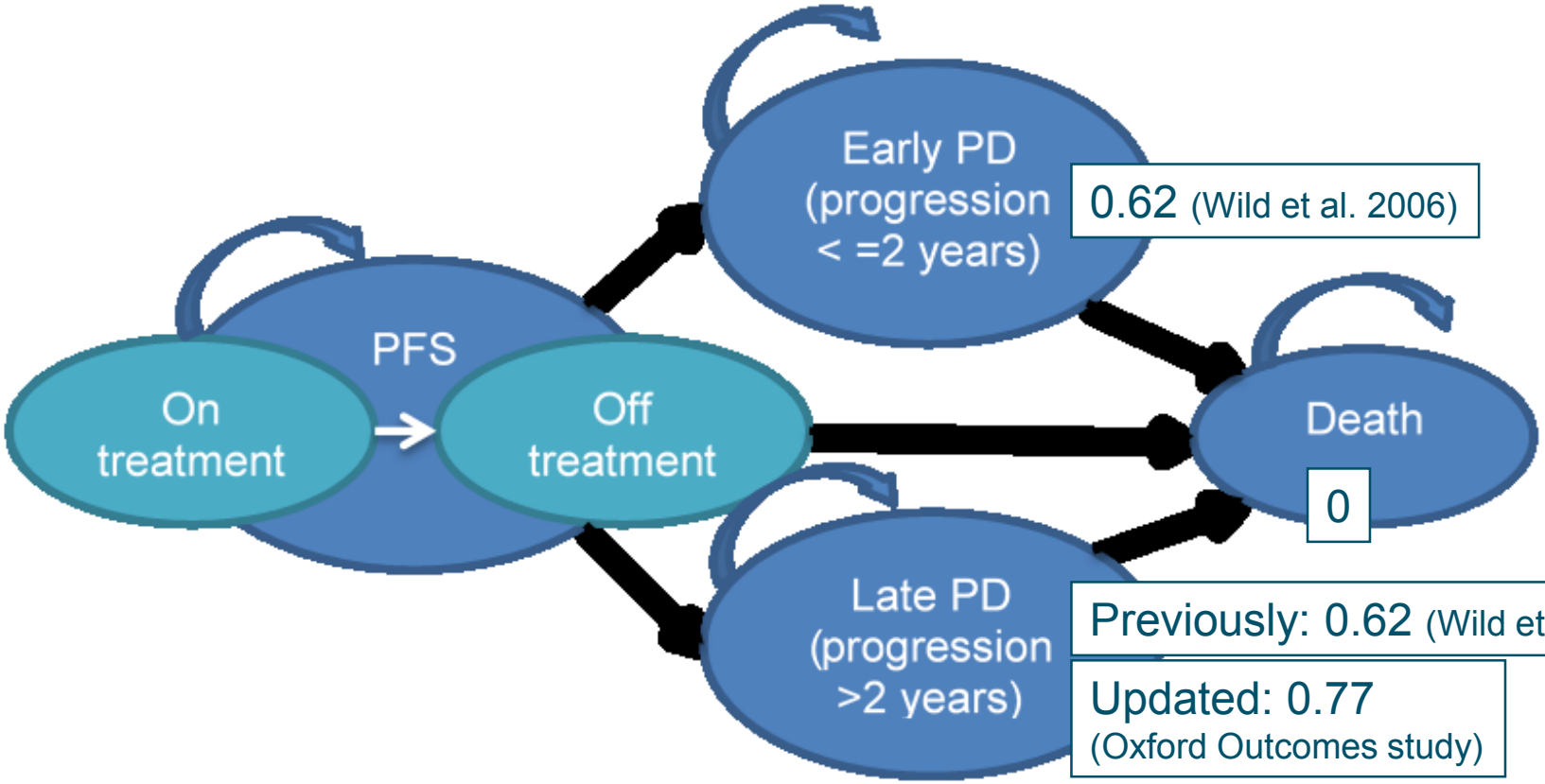
Progressed disease utility

Company's comments

- Company originally proposed 0.62 (Wild et al. 2006) for both early and late progressed-states
- Committee preferred utilities from GALLIUM (0.78 for early and 0.81 for late)
- Roche: GALLIUM EQ-5D *'collected only during one assessment visit after progression'* so not representative of health related quality of life in progressed state
- *'As* [follicular lymphoma] *may progress slowly towards symptomatic disease requiring further treatment… utility decline is expected to be delayed.'*
- Late-progressed utility updated to 0.77 (Oxford Outcomes study; Wild et al. 2005)

Company suggests that utility values of 0.62 and 0.77 (early and late progression) are taken from literature rather than GALLIUM

Progressed disease utility values used by company



Previous ACM1 preferred	Early progression	Late progression
GALLIUM	0.78	0.81

Progressed disease utility

ERG's comments

- ERG agrees with approach of having different utility values for early and late progressed-disease
- However, Wild et al.'s Oxford Outcomes study (2005) has limitations:
  - Unpublished
  - Inconsistent with results of GALLIUM
  - Utility values from 2006 may not be generalisable to current UK population

⊙ *What are the most appropriate **utility values to use for progressed-disease states** (early=0.62 & late=0.77 [literature] or early= 0.78 & late=0.81 [GALLIUM])?*

Progression-free survival utility
ERG's comments

Use of pooled progression-free survival data from GALLIUM instead of treatment-specific utilities:

- Company originally used progression-free utility values pooled across GALLIUM treatment arms
- ERG previously suggested using treatment specific utility values for progression-free survival → Company updated

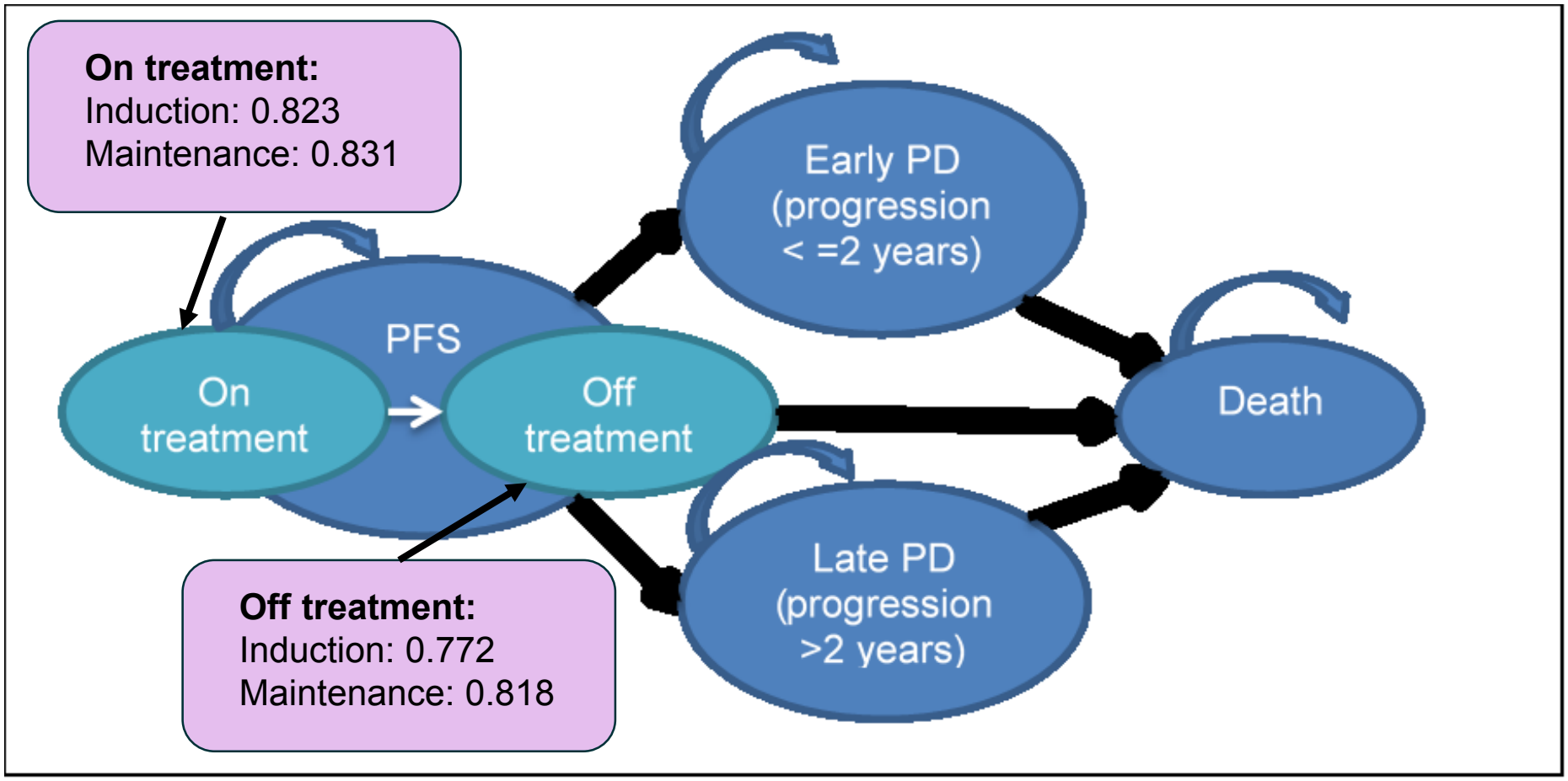
- However, now that AE disutilities have been incorporated, treatment specific utility values = double counting
- Full statistical output for utility analyses were not provided (only coefficients, standard errors and p-values) → ERG could not judge where treatment specific health state utility values were plausible
- **Because of this, ERG now prefers utility values for progression free survival to be pooled across treatment arms (using GALLIUM utilities)**

Progression-free survival utility

ERG's comments

		ERG preferred	Company used
Progression-free survival health states	**Treatment arm**	**Pooled utility**	**Treatment-specific utility**
Induction - off treatment	Obinutuzumab	0.772	0.765
	Rituximab		0.779
Maintenance & follow-up - off treatment	Obinutuzumab	0.818	0.826
	Rituximab		0.810
Induction - On treatment	Obinutuzumab	0.823	0.823
	Rituximab		0.824
Maintenance & follow-up - on treatment	Obinutuzumab	0.831	0.834
	Rituximab		0.828

Progression-free survival utility values preferred by ERG



⊙ *What are the most appropriate **utility values** to use for **progression-free survival states**?*

Resource use and Biosimilars

Company's comments

- Model updated from no vial sharing to assume vial sharing in intravenous rituximab **and** obinutuzumab (committee preference was for vial sharing for rituximab only as obinutuzumab fixed dose)
- Rituximab administration costs taken from national chemotherapy list administration codes and NHS reference costs → should be representative

- Committee preferences assumes *'…displaced technology for IV rituximab is 100% biosimilar. This assumption is unrealistic…'*
- NHS England biosimilar medicines commissioning framework shows that *'uptake only reaches 80% several years after market entry'*
- Rituximab biosimilar should represent *'realistic market shares'*
- Compared to market uptake of etanercept and infliximab biosimilars

Resource use and Biosimilars

CDF Clinical Lead's comments

Resource use:

Company have used incorrect Healthcare Resource Group chemotherapy and administration tariffs

Costs (£)	CVP/Chop		Bendamustine		Maintenance
	1st Cycle	Subsq.	1st Cycle	Subsq.	
Rituximab	449	299	748	598	150 (Subcutaneous)
Obinutuzumab	1047	449	1352	748	449

Biosimilars:

'Uptake in NHS England of biosimilar rituximab is currently rapid and faster than anticipated and much faster than previous biosimilars…NHS England expects a [redacted] *uptake of biosimilar rituximab to be in place by Q3/2018 and* [redacted]

Resource use and Biosimilars

ERG's comments

- Rituximab biosimilar uptake of 100% *'plausible'*

- Etanercept and infliximab biosimilars may not be comparable as they were for different indications and the originator prices decreased after biosimilars entered the market
- Vial sharing assumption assumed for rituximab AND obinutuzumab
- Dose for obinutuzumab + CVP for induction was missing in model

Clinical experts:
Uptake of biosimilars in England 100% for induction.
Many centres would use subcutaneous MabThera for maintenance.

⊙ *What is the most appropriate administration cost for rituximab?*

⊙ *What proportion of rituximab biosimilar uptake should be assumed?*

Adverse effects

Consultee's comments

Professional and patient groups, web comments:

- *'…many patients, particularly fitter ones, may prefer the option to balance a limited increase in side effects against a longer period of remission.'*

Company:

- Progressed-disease adverse event costs not explicitly modelled (assumed to be captured in subsequent treatment costs)

ERG revised preferred base case

ERG preferred	Company base-case?
5 year maintenance of treatment effect	✗
Use of pooled progression-free survival utility data from GALLIUM instead of treatment-specific utilities: • ERG previously suggested using treatment specific utility values • However, incorporating both treatment specific utility values and AE disutilities = double counting • ERG could not judge plausibility of treatment specific health state utility data (based only on coefficients, standard errors and p-values)	✗
Vial sharing for rituximab only (NO vial sharing for obinutuzumab)	✗
Non-proportional hazards	✓
Independently assessed PFS	✓
Log-logistic PFS extrapolation	✓

Company's revised results – see part 2 slides

All results are confidential and will be presented in private part of appraisal committee meeting (part 2) because the comparator (rituximab) & biosimilars have confidential discounts

Back-up slides

Model structure (1)
Company's comments

Committee consideration	Company comment
Disease progression assessed more frequently in trials than in practice	• *'model used the costs of follow up visits according to clinical practice, rather than the trial based frequency'* • Indolent nature of disease means progression-free survival (investigator) likely to be similar to clinical practice
Explicit modelling of response to determine whether patients offered maintenance therapy	• *'it was not necessary to model response in the model explicitly as patients in both arms were eligible to receive maintenance if they responded to the respective induction therapy'* • Proportion of patient receiving maintenance ≈ time-to-off-treatment in GALLIUM

Model structure (2)

Company's comments

Committee consideration	Company comment
Time between disease progression and subsequent treatments	• Progression-free survival gives conservative estimate of time to next treatment • *'the difference in the time-to-next-treatment between the arms is larger than the difference in PFS'*
Patients' experience during disease progression	• *'in the indolent disease setting, there are limited long-term follow up data sets that would allow more accurate modelling, especially on HRQoL'* • Could use patient level simulations but this relies on literature, assumptions about treatment pathway and 2nd line treatment data to be clinically plausible

Model structure

ERG's comments

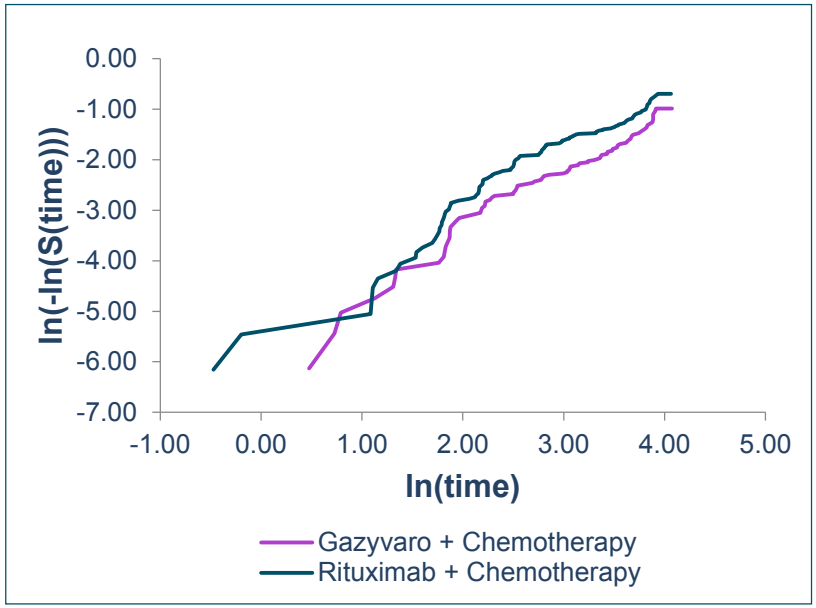
Committee consideration	ERG's comment
Disease progression assessed more frequently in trials than in practice	-
Explicit modelling of response to determine whether patients offered maintenance therapy	• Company's proposal to capture through time-to-off-treatment *'might be plausible'*
Time between disease progression and subsequent treatments	• Company's argument that progression-free survival is more conservative than time-to-next-treatment is based on FLIPI higher risk time-to-next-treatment data
Patients' experience during disease progression	-

⊙ *Is the proposed model structure appropriate?*

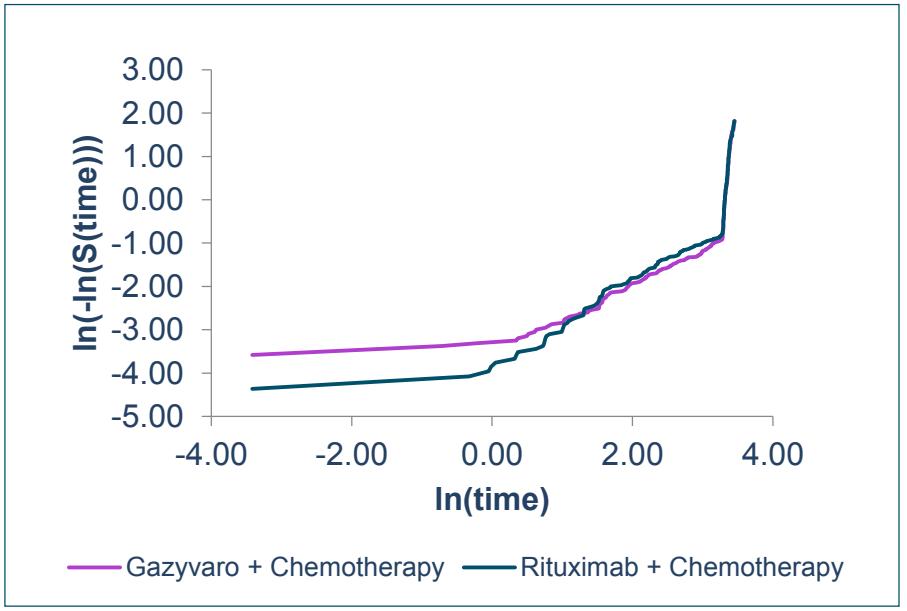
Clinical implications of survival modelling

(Log-cumulative hazard plots)

Progression-free survival (independent)



Time to treatment discontinuation



Comparison of extrapolation curves

For progression-free survival extrapolation

FLIPI Higher risk population:

Model	Time in PFS	Incremental LY in PFS (undiscounted) Obinutuzumab vs. Rituximab	
		Proportional Hazards	Non-proportional hazards
Log-logistic	Mean	2.25	1.88
	Median	3.17	2.67
Weibull	Mean	1.95	1.56
	Median	2.75	2.08
Gompertz	Mean	2.69	-2.05
	Median	2.58	0.42

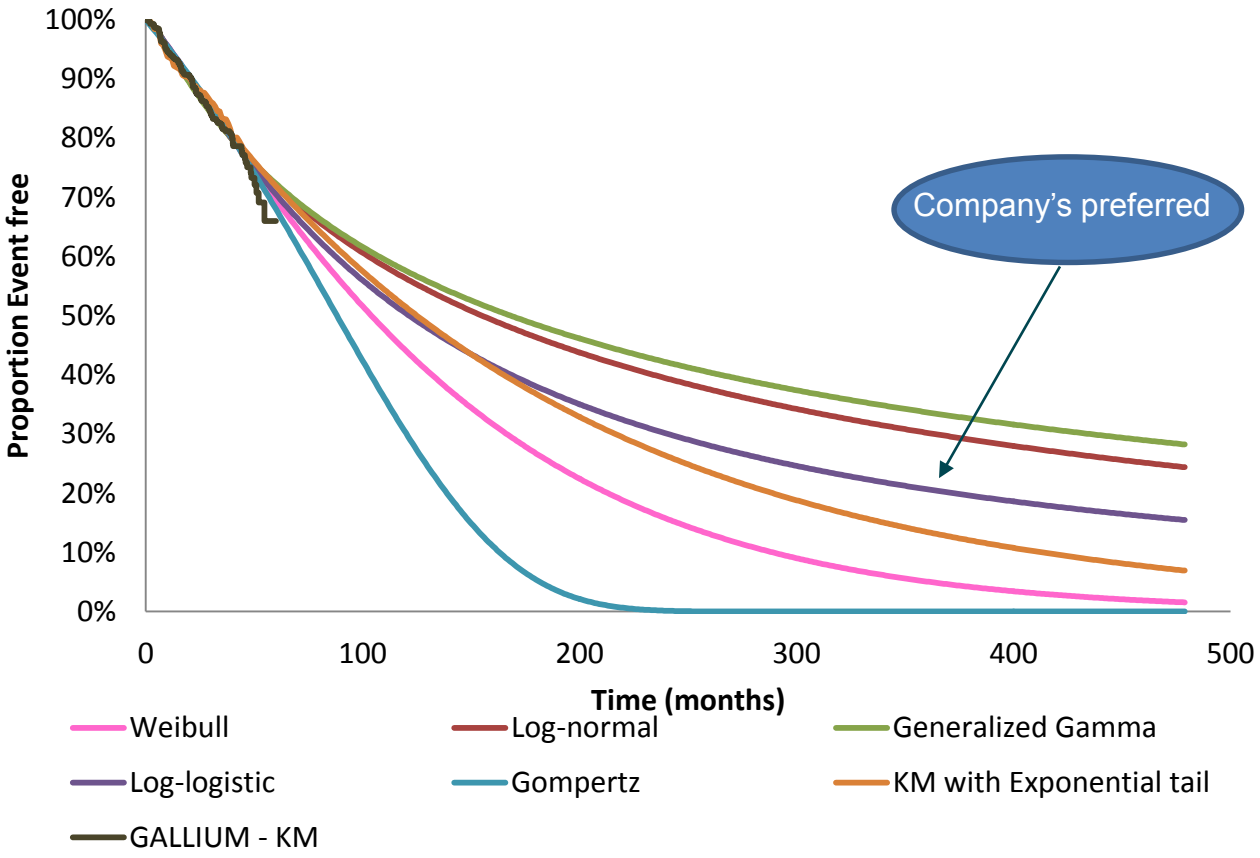
Intention-to-Treat population:

Model	Time in PFS	Incremental LY in PFS (undiscounted) Obinutuzumab vs. Rituximab	
		Proportional Hazards	Non-proportional hazards
Gompertz	Mean	2.45	-2.04
	Median	2.33	0.33

Comparison of extrapolation curves

For progression-free survival extrapolation in obinutuzumab

FLIPI Higher risk population:



Estimated by NICE technical team using information supplied by company