For Public only- redacted

Lead team presentation
Obinutuzumab for untreated advanced follicular lymphoma [1020]

1st 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, Jasdeep Hayre, Ahmed Elsada

Company: Roche

22 August 2017

Key issues - decision problem untreated follicular lymphoma

- **Comparators:** Company **excluded** 3 comparators in scope:
  1. rituximab monotherapy
  2. rituximab-based chemotherapy **without** rituximab maintenance
  3. bendamustine monotherapy
  - Are these treatment used in the NHS?
- **Chemotherapy regimens - induction:** Key trial included only 3 chemotherapy regimens combined with either obinutuzumab (intervention) or rituximab (comparator):
  1. Bendamustine
  2. CHOP [cyclophosphamide, doxorubicin, vincristine and prednisolone],
  3. CVP [cyclophosphamide, vincristine and prednisolone])
  - In the NHS, do clinicians offer other chemotherapy regimens such as:
  1. MCP (mitoxantrone, chlorambucil and prednisolone) or
  2. CHVPi (cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α)?

Key issues clinical-effectiveness

- What is the appropriateness of the evidence base given that GALLIUM (the key trial):
  - Is open label and 1∘ outcome is investigator assessed progression-free survival
  - Is immature: only 7.9% of people died during the trial
  - Did not randomise the chemotherapy accompanying obinutuzumab or rituximab for induction. Instead, they were trial-site specific
  - Has a different proportion of people receiving CHOP, CVP or bendamustine compared with UK practice
  - Has younger participants than the UK patient population which affects cost effectiveness estimates
  - Is not complete: trial is ongoing

Key issues - cost-effectiveness (1)

- **Which progression-free survival (PFS) data?**
  - Company used investigator-assessed PFS; ERG considered this prone to bias and less reliable than independent review committee (IRC) assessed progression-free survival → this is a driver of cost effectiveness
- **Which progression-free survival probability distribution?**
  - ERG preferred a Weibull curve fitted to IRC-PFS data over an exponential curve fitted to INV-PFS used by the company
- **How long is the treatment effect?**
  - In absence of long-term data, company assumed that PFS benefit with obinutuzumab maintained until 9 years (based on rituximab in another study). ERG considered this 'speculative'
  - Considering a duration of treatment effect <5 years increased the ICER of obinutuzumab compared with rituximab to >£30k/QALY in ERG base-case

Key issues - cost-effectiveness (2)

- **Estimating mortality**: To estimate mortality from progression-free and early progression states, company pooled deaths in both arms of GALLIUM and used **same** mortality rates for both treatment arms. ERG preferred different values per treatment arm. Which is better?
- **Cost of comparator**: Should this appraisal consider low-cost biosimilars for rituximab, the comparator?
- **Utility**: ERG considers company's source of utility to be "unpublished, inconsistent with the results of the GALLIUM trial and unverifiable"
- Are the end-of-life criteria met?
- Is obnituzumab an innovative treatment?
- Are there any equality issues?

Clinical effectiveness and patient perspective

Obinutuzumab

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

Obinutuzumab (Gazyvaro, Roche)	
Mechanism	• Type II anti-CD20 antibody • Targets CD20 on pre-B and B-lymphocytes • Spares haematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissue
Proposed marketing authorisation	• '…for the treatment of patients with previously untreated advanced follicular lymphoma.' • 'Obinutuzumab in combination with chemotherapy, followed by obinutuzumab maintenance therapy in patients achieving a response..'

Obinutuzumab

Administration and dose

Dose	1000 mg (fixed)
Administration	Intravenous
Frequency	
Induction	With CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or with CVP (cyclophosphamide, etoposide, doxorubicin and prednisolone): 21 day cycle 1st cycle: on day 1,8 and 15 2nd to 8th cycle: on day 1
	With bendamustine (28-day cycle) 1st cycle: on day 1,8 and 15 2nd to 6th cycle: on day 1
Maintenance in those responding to induction	Once every 2 months up to 2 years or until progression
Average course	6–8 cycle induction then up to 12 doses for responders to induction

Follicular lymphoma

- 2nd most common non-Hodgkin lymphoma (NHL) in Western Europe and United States
    - 35% of all NHLs
- UK incidence 3.3 per 100,000 per year
- 2,142 new diagnosis in England (2015)
- Prevalence (10 year-UK): 25.7 per 100,000
- Risk factors: use of immunosuppressive, age, sex, life style
- Male: Female ratio: 0.9
- Median age at diagnosis in UK ~65 years
- Median life expectancy 8–12 years (to 15 years after rituximab)
- Early progression (within 2 years) associated with increased risk of death

Follicular lymphoma grading

- Typical initial symptom: lymph nodes enlarged at multiple sites
- Other symptoms; fatigue, weight loss, fever and night sweats
- Grading done by histological examination of surgical specimen/biopsy (based on number of centroblast*/high power field)

Grade	Description
1	≤5 blasts/high power field
2	6-15 blasts/high power field
3A	>15 blasts/high power field, centroblasts with intermingled centrocytes**
3B	>15 blasts/high power field, pure sheets of blasts

* Centroblast; an enlarged and proliferating activated B cell

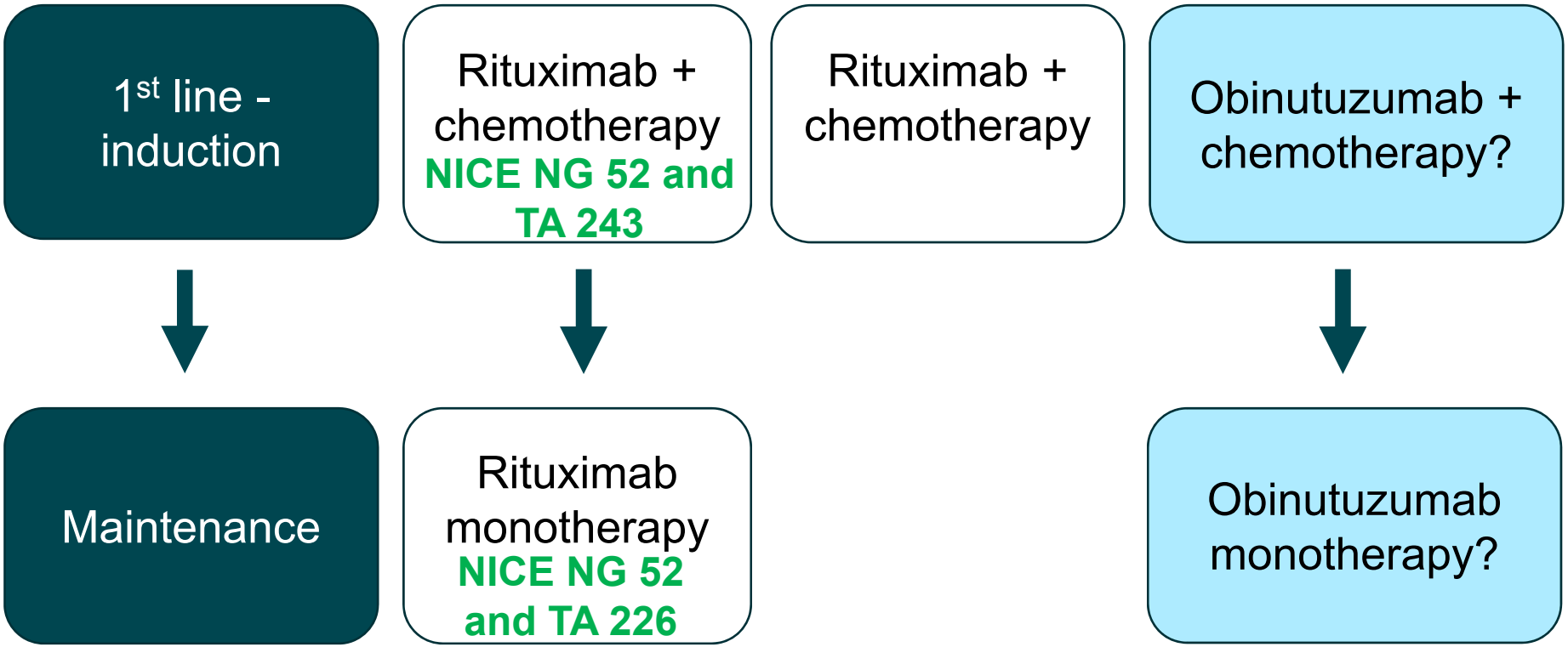
** Centrocyte: the result of proliferating centroblasts

Follicular lymphoma stages

- Staging: Ann-Arbor Classification
- Stage III-IV comprise advanced disease

Stage	Area of involvement
I (I_E)	1 lymph node region or extralymphatic (IE) site
II (II_E)	≥ 2 lymph node regions or at least 1 lymph node region + 1 localised extralymphatic site (IIE) on same side of diaphragm
III (III_E, III_S)	Lymph node regions or lymphoid structures (e.g. thymus, Waldeyer's ring) on both sides of the diaphragm with optional localised extranodal site (IIIE) or spleen (IIIS)
IV	Diffuse or disseminated extralymphatic organ involvement
For all stages	
A	No symptoms
B	*Unexplained fever of >38°C, drenching night swears; or loss of >10% body weight within 6 months

Treatment pathway **untreated** advanced stage **symptomatic*** follicular lymphoma



◉ *Is asymptomatic disease treated with active therapy in the NHS?*

* Unexplained fever of >38°C; drenching night sweats; or >10% weight loss w/i 6 months

Population and intervention

	Scope	Decision problem	Company's rationale	ERG comment
Population	People with untreated advanced follicular lymphoma		Not different	Trial excluded people with (histological) grade 3b follicular lymphoma
Intervention	Obinutuzumab combined with chemotherapy, **with or without** obinutuzumab maintenance	Obinutuzumab combined with chemotherapy (CVP, CHOP or bendamustine), **followed by** obinutuzumab maintenance in patients achieving a response	Aligned with anticipated marketing authorisation. Company did not present evidence **without** obinutuzumab maintenance	• Limited to CVP, CHOP, bendamustine • Agrees with company not providing **without** obinutuzumab maintenance

◉ *What chemotherapy accompanies rituximab in the NHS? Does this include MCP or CHVPi ? Is rituximab maintenance offered to all responders routinely?*

Comparators

Scope 'tx' = therapy	Decision problem	Company's rationale	ERG comments
1. Rituximab monotherapy (off-label) 2. Rituximab-based chemotx with or without rituximab maintenance 3. Bendamustine monotherapy (off-label but funded via the CDF)	1. Rituximab in combination with chemotx, followed by rituximab maintenance in patients achieving a response	• Rituximab without chemotx→ induction treatment only for **asymptomatic** disease • Rituximab-based chemotx, **without** rituximab maintenance not clinical practice • UK Systemic Anti-Cancer Therapy Dataset + market research show little use of bendamustine alone	• Should have included rituximab monotherapy • rituximab-based chemotx without rituximab maintenance treatment can be ignored • Should have included bendamustine mono-therapy

◉ *Is rituximab monotherapy offered to people with symptomatic disease? Is it a relevant comparator? Are treatments without rituximab maintenance relevant comparators? Bendamustine monotherapy?*

Outcomes

	Scope	Decision problem	Company rationale	ERG comments
Outcomes	• overall survival • progression-free survival • overall response rate • adverse effects of treatment • health-related quality of life		Not different	• Company provides all outcomes specified in scope • However, OS data **immature** with only 7.9% having died by GALLIUM updated analysis cut-off date (10 September 2016) • <20% of patients followed for survival for > 4 years

Professional and clinical expert feedback

- Follicular lymphoma runs a chronic relapsing course requiring multiple episodes of treatment and culminates in resistance to therapy and/or large-cell transformation.
- Median progression-free survival is 6 to 8 years and overall survival is 12 to 15 years
- Quality of life and time to next treatment important considerations for patients and clinicians
- Initial treatment for advanced-stage is 6 to 8 cycles of rituximab combined with 1 of several different chemotherapy regimens
- For patients who achieve an complete or partial response then maintenance therapy with rituximab alone is an option (recommended in TA226)

Professional and clinical expert feedback

- Clinical opinion differs on **rituximab maintenance** for 3 reasons:

1. Questionable effectiveness
   - data from a rituximab maintenance trial ('PRIMA') indicates that benefits of rituximab maintenance vs no maintenance occurs during and shortly after the 2-year maintenance and delays disease progression in ~1 in 5 patients and delays need for further chemotherapy in ~1 in 10 patients
     - *PRIMA compares rituximab maintenance vs watch and wait*
     - *Progression at 6 years 43% vs 59%*
   - rituximab maintenance does not prolong survival
2. Increases risk of infection
3. Increase in use of blood products
   - A large meta-analysis and a population-based study showed an increase in blood transfusion and growth factor usage in patients receiving maintenance treatment

◉ *In the NHS, what proportion of patients who respond to rituximab + chemotherapy induction, do not get maintenance with rituximab?*

Clinical evidence: 1 key trial GALLIUM

- Ongoing, phase III, multicentre, open-label, randomised controlled trial
- Asked question:
  - in people with follicular lymphoma (grade 1 to 3a), does obinutuzumab-chemotherapy induction followed by obinutuzumab maintenance delay progression of disease compared with rituximab-chemotherapy followed by rituximab maintenance treatment?
- Each site chose 1 of 3 chemo- regimens (CHOP, CVP, or bendamustine), and all patients at a given site received the same chemotherapy regimen in combination with obinutuzumab or rituximab for induction
- GALLIUM used by company to model:
    - time to progression
    - time on treatment
    - post progression survival for people who progress early (post progression survival for late progression see next slide)
    - n.b. time to death modelled

Other trial evidence
GAUDI and PRIMA trials

GAUDI: randomised open label phase I b study

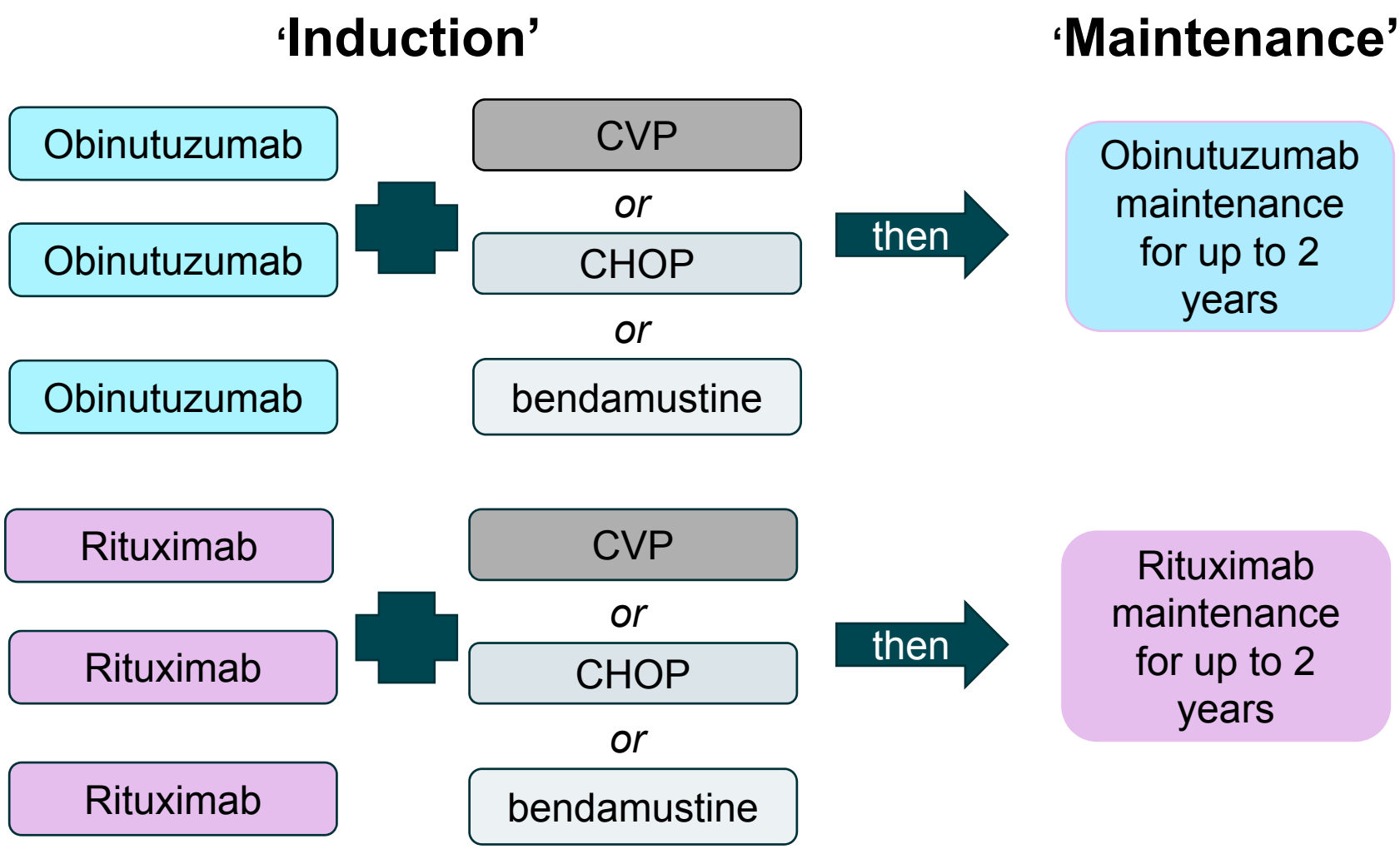
- a sub-study of GAUDI (Grigg et al., 2017) compared safety and efficacy of 2 induction regimen in previously untreated patients :
  - obinutuzumab-CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) with obinutuzumab-bendamustine
  - both followed by obinutuzumab maintenance
  - Follow-up duration, median: 51 months; maximum: 60 months
  - **includes obinutuzumab but not used in modelling**

PRIMA randomised phase III study compared rituximab maintenance therapy with observation only:

- in people with in previously untreated follicular lymphoma, following induction with rituximab+ chemotherapy
- Follow-up data up to 9.75 years
- **Does not include obinutuzumab, but used in modelling**
  - To populate time from late progression to death for both obinutuzumab and rituximab

GALLIUM

1○ endpoint investigator-determined progression
used in modelling for company's base-case



GALLIUM trial - Population

- Previously untreated CD20-positive indolent non-Hodgkins lymphoma
- Follicular lymphoma (grade 1 to 3a) n=1202 or splenic/nodal/ extranodal Marginal Zonal Lymphoma (excluded by company)
- Age ≥ 18 years
- Eastern Cooperative Oncology Group (ECOG) 0 to 2
- Stage III/IV or stage II bulky disease (≥ 7cm) requiring treatment - Any of:
    1. Bulky disease (≥7cm in diameter)
    2. Local symptoms/organ function compromise
    3. Stage 'B' symptoms (fever, drenching night sweats, or unintentional weight loss of >10% weight over a period of ≤ 6 months)
    4. symptomatic extranodal disease (e.g., pleural effusions, ascites)
    5. Cytopenias
    6. Involving ≥3 nodal sites, each with a diameter of ≥3 cm
    7. Symptomatic splenic enlargement

GALLIUM intervention and comparator

Obinutuzumab	Rituximab
8-10 doses of obinutuzumab at 1000 mg IV • **O-CHOP:** O on Days **1**, **8**, and **15** of Cycle 1 and on Day 1 of Cycles 2–8 (21-day cycles). • **O-CVP:** on Days **1, 8**, and **15** of Cycle 1 and on Day 1 of Cycles 2–8 (21-day cycles). • **O-bendamustine:** O on Days **1, 8, and 15** of Cycle 1 and on Day **1** of Cycles 2–6 (28-day cycles).	**6-8** doses of rituximab at 375 mg/m^2 IV • **R-CHOP**: R on Day **1** of cycles 1–8 (21-day cycles). • **R-CVP**: R on Day **1** of Cycles 1–8 (21-day cycles). • **R-bendamustine:** R on Day 1 of Cycles 1–6 (28-day cycles).
Patients who achieved a complete response or partial response, had maintenance every 2 months until disease progression, or for 2 years (max).	

◉ *People in obinutuzumab arm had 2 more doses of study drug than people in rituximab arm, in cycle 1. Does it affect outcomes?*

GALLIUM statistical plan

1 ◦ endpoint	PFS = day of randomisation until 1st documented disease progression, symptomatic deterioration, disease transformation, or death from any cause, whichever occurred 1st
Censoring	At last valid tumour assessment
Alpha	5% 2 sided
Control type 1 error-multiple testing	Fixed sequence testing procedure: 1. PFS overall population 2. CR rate at the end of induction therapy in FL population 3. CR rate at the end of induction therapy overall population 4. Overall survival in the FL population 5. Overall survival in the overall population etc.
Power	Follicular population; 80% to detect HR of 0.74, corresponding to an improvement in 3-year PFS from median PFS from 6 years to 8.1 years
Required number of PFS events	370 events, so 1200 patients enrolled over 49 months and followed for an additional 29 months after randomisation of the last patients; total duration for PFS follow-up 78 months (6.5 years)
Median observation	At 'cut off' date: 34.4 months (range: 0.1–54.5) in the R-chemo arm and 34.8 months (range: 0.0–53.8) in obinutuzumab arm
Subgroups	Pre-specified: Age, chemotherapy regimen, geographic region

GALLIUM - baseline characteristics

Domain	O-chemo (n = 601)	R-chemo (n = 601)
Mean age, years (SD)	58.2 (11.5)	57.7 (12.2)
Men, n (%)	283 (47.1)	280 (46.6)
ECOG 0 or 1	585 (97.5)	576 (96.2)
Mean body surface area, m2 (SD)	1.86 (0.2)	1.84 (0.2)
Caucasian n (%)	487 (81.0)	481 (80.0)
Black or African American (%)	3 (0.5)	1 (0.2)
Asian n (%)	100 (16.6)	98 (16.3)
Other	10 (1.7)	17 (2.8)

- *Is the GALLIUM population similar to patients treated in the NHS?*
- *Are differences (e.g. age, race) likely to modify clinical or cost effectiveness?*

GALLIUM – chemotherapy regimens

	GALLIUM			UK patients in GALLIUM	UK Survey*
	O-chemo	R-chemo	Total		
Chemotherapy regimen, %					
Bendamustine	57.4	56.7	57	68	29
CHOP	32.4	33.8	33	1	13
CVP	10.1	9.5	10	31	36

- * Company conducted a questionnaire based survey among UK clinicians for treatments for previously untreated follicular lymphoma (N=157, from 45 clinicians)

◉ *Does it matter that the proportions in GALLIUM and in UK practice differ?*

GALLIUM – baseline differences by chemotherapy

	Bendamustine n=686	CHOP n=399	CVP n=117
Median age, years (range)	59 (23–88)	58 (31–85)	59 (32–85)
Age ≥80 years n (%)	**23 (3.4)**	3 (0.8)	**4 (3.4)**
Male	332 (48.4)	177 (44.4)	54 (46.2)
Charlson Comorbidity Index score ≥1	163 (23.8)	69 (17.3)	22 (18.8)
ECOG PS 2	24 (3.5)	8 (2.0)	6 (5.1)
FLIPI high risk (≥3)	274 (39.9)	**187 (46.9)**	41 (35.0)
Bulky disease (≥7cm)	274 (39.9)	**206 (51.6)**	46 (39.3)

◉ *What factors do clinicians take into account while deciding about chemotherapy regimen?*
Do patients at a higher risk of progression or death receive CHOP?

Professional and clinical expert feedback

- Obinutuzumab takes longer to infuse than rituximab
- Rituximab can be given subcutaneously and cheaper biosimilars available
- In GALLIUM, the **absolute** difference in 3-year PFS between obinutuzumab and rituximab is 4% (77.9% vs 81.9%, independent review committee)
- Compared with rituximab, obinutuzumab associated with more grade ≥3 infections (20% vs 15.6%), infusion-related reactions (12.4% vs 6.8%) and 2nd malignancies (4.7% vs 2.7%)
  - could impair the quality of life of patients in remission
- In GALLIUM dose of obinutuzumab significantly higher than rituximab
  - Rituximab @ 375 mg/m^2 lower than obinutuzumab flat dose of 1000 mg
  - Obinutuzumab given day 1, 8 + 15 of cycle 1 and day 1 of each subsequent induction cycle, whereas rituximab given only once within each cycle

◉ Do patients in the NHS use subcut rituximab? Biosimilars? Is an absolute difference of 4% 'clinically' significant? What does difference in dosing imply?

NHS England comments (1)

Standard chemotherapies	In England: R-CVP, R-CHOP and R-bendamustine
Bendamustine	Not licensed but currently funded by CDF 'MHRA has recently issued a safety alert for bendamustine, particularly when used in combination with R or obinutuzumab'
chemotherapies in GALLIUM	GALLIUM trial different to that in England with: less bendamustine and CHOP but **more** CVP in use
Rituximab maintenance	'Standard therapy' – if not offered, NHS doctors should document why use declining :lack of survival benefit, small increase in time to next chemo, increased infection and hepatitis B reactivation, concerns for long-term effect of B cell depletion
Biosimilar rituximab	'very rapid introduction into practice' expected to be much cheaper
What are NOT comparators	R monotherapy B monotherapy multi-agent chemotherapies other than R-CVP and R-CHOP

NHS England comments (2)

Investigator or independent PFS?	Investigator-assessed PFS is better because some clinically assessable lymph nodes may not be seen on CT.
Costs	Duration of infusion for obinutuzumab is longer than for rituximab and therefore obinutuzumab should have a higher administration cost Rituximab could be given faster after the initial 2 cycles than that stated in the SPC. Obinutuzumab would be given as per the SPC until evidence accrues to conclude that faster administration is safe.
Immature data	'Survival data will be years away …'
Time to next chemotherapy	time to next chemotherapy is more informative outcome than progression-free survival • because many progressive disease would not be treated with chemotherapy unless became symptomatic

Study started 1st August 2011

Timings of Analyses

Estimated completion 1st September 2021

IDMC – independent data safety monitoring committee

A priori	A priori	Post hoc	Post hoc	Post hoc
Futility analysis for PFS after 111 events – Data cut 20th Feb 2014 IDMC recommended that study continue	'**Primary analysis**' Efficacy analysis for PFS after 248 (67% of) events data cut 31 Jan 2016 IDMC recommended that study be 'fully analysed'	'**Updated analysis**' Data cut 10 Sep 2016 for economic analysis and safety – **results for this appraisal**	'**Safety' data' for FDA** Data cut [redacted]	'**Safety'** for EMA Data cut [redacted] Company submitted this to NICE during 'clarification' **used in updated model**

◉ *What are the implications for so many post hoc analyses?*

GALLIUM trial results

Progression free survival results

Obinutuzumab improves progression free survival

	Updated analysis (cut-off September 2016)	
	O-chemo n=601	R-Chemo n=601
Progression-free survival (investigator-assessed)		
N (%)	120 (20.0)	161 (26.8)
Median PFS, (95% CI)	Not estimated	Not estimated
HR (stratified), 95% CI	0.68 (0.54 to 0.87)	
Progression-free survival (independently reviewed-assessed)		
N (%)	108 (18.0)	141 (23.5)
Median PFS, (95% CI), m	Not estimated	Not estimated
HR (stratified), 95% CI	0.72 (0.56 to 0.93)	

ERG: Because of open label design PFS results by independent review committee will be less prone to bias

◉ *Is investigator-assessed or independently review more appropriate to assess progression-free survival?)*

GALLIUM trial results
Overall survival (immature data)

	Updated analysis (cut-off September 2016)	
	Obin-chemo n=601	R-Chemo n=601
Overall survival		
Patients w/ event, n (%)	43 (7.2%)	52 (8.7%)
Median OS, months	Not estimated	Not estimated
HR (stratified), 95% CI	0.82 (0.54 to 1.22)	

What are the implications of such immature overall survival data?

GALLIUM trial follicular lymphoma subgroups PFS determined by investigators

Subgroup	N	HR PFS obinutuzumab vs rituximab	95% CI
ITT population	1202	0.66	0.51 to 0.85
FLIPI (interaction p value 0.14)			
Low	253	1.17	0.63 to 2.27
Intermediate	447	0.59	0.37 to 0.92
High	502	0.58	0.41 to 0.84
Chemotherapy regimen (interaction p value 0.67)			
CHOP	398	0.77	0.50 to 1.20
CVP	118	0.63	0.32 to 1.21
Bendamustine	686	0.61	0.43 to 0.86

◉ *ERG interprets results to indicate best outcomes with bendamustine. Does the committee agree?*

GALLIUM – Quality of life

- Health-related quality of life collected using 2 self-administered tools:
  1. Functional Assessment of Cancer Therapy Lymphoma (FACT-Lym)
  2. EuroQol EQ-5D-3L
- Questionnaires administered at:
  - Baseline
  - Completion of induction
  - Completion of maintenance
  - Follow-up month 36
- **Summary**: No notable differences between the treatment arms in any of the FACT-Lym questionnaire subscales or EQ-5D-3L scales over time during the induction and maintenance treatment periods, and follow-up.
- For full results – see Additional slides at end of slide-deck

◉ *Would clinicians have expected that a change in risk of progression would translate to improved quality of life?*

Safety Results based on on-treatment analyses

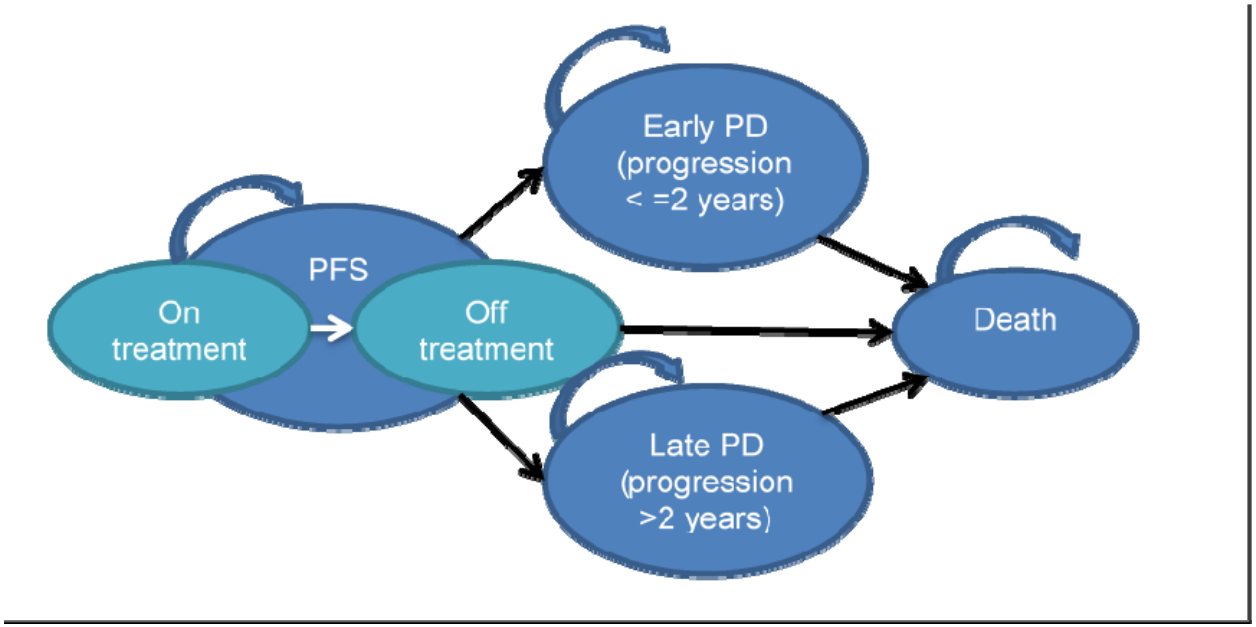
Date	[redacted]	
	Obin-chemo	R-chemo
	n = 595	n = 597
No. of patients with at least 1 AE (%):		
AE (all grades)	[redacted]	[redacted]
Grade 3-5 AE	[redacted]	[redacted]
Fatal AE	[redacted]	[redacted]
Serious AE	[redacted]	[redacted]
AE leading to withdrawal from any treatment	[redacted]	[redacted]

◉ *ERG noted higher rate of serious and higher grade events with obinutuzumab – what is committee's interpretation of results?*

Cost effectiveness

Company's model

- State transition Markov model
- 4 health states,1 month cycles, 40 year time horizon (amended to 50 after clarification)
- NHS/PSS perspective; Costs and benefits discounted at 3.5%



◉ *Is the model structure appropriate? What is the basis of the 2 year early progression state?*

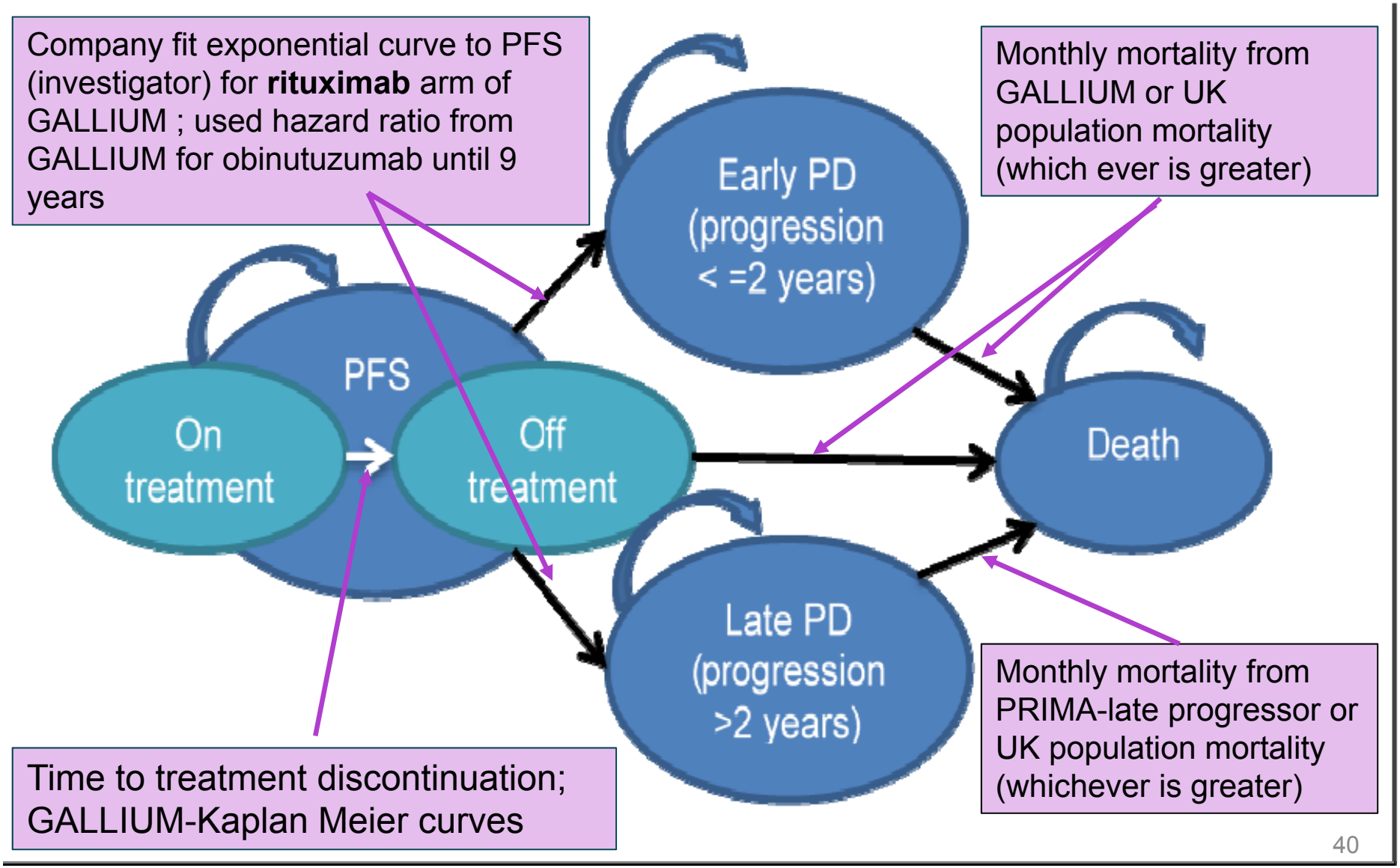
How the model works

- Patients begin in progression free survival (on treatment) state
- Patients responding to induction receive maintenance treatment
  - Continue treatment until progression or for a maximum of 2 years
- Time to treatment discontinuation from GALLIUM
- In PFS state, after completion or stopping treatment, patients remain in PFS (off treatment) state until progression or death
  - Progression free survival extrapolated
- In disease progression state:
  - Once patients enter any progressive-disease state, they remain in the corresponding progressed disease state until death

Summary of transitions in the model

Transition	Transition probability	
Progression free survival to early progressed disease (≤2 years) and late progressed disease (>2 years)	• Time dependent • Calculated from the probability of remaining in progression free survival and probability of death in progression free survival health state • Probability of remaining in PFS modelled with parametric model (base case Weibull) and proportional hazards	
Progression free survival to death	Based on trial mortality from GALLIUM	Greater of trial mortality or UK population background mortality was applied Trial mortality applied up until age specific general UK population mortality becomes higher
Early progressed disease (≤2 years) to death	Based on mortality from GALLIUM	
Late progressed disease (>2 years) to death	Based on mortality from PRIMA (late progressor)	

Company source of parameters in model



Characteristics of population in company's model based on GALLIUM

Characteristic	Baseline value
Age (years)	57.9
Body weight (kg)	75.7
Height (cm)	168.3
Calculated Body Surface Area [BSA] (m^2)	1.86

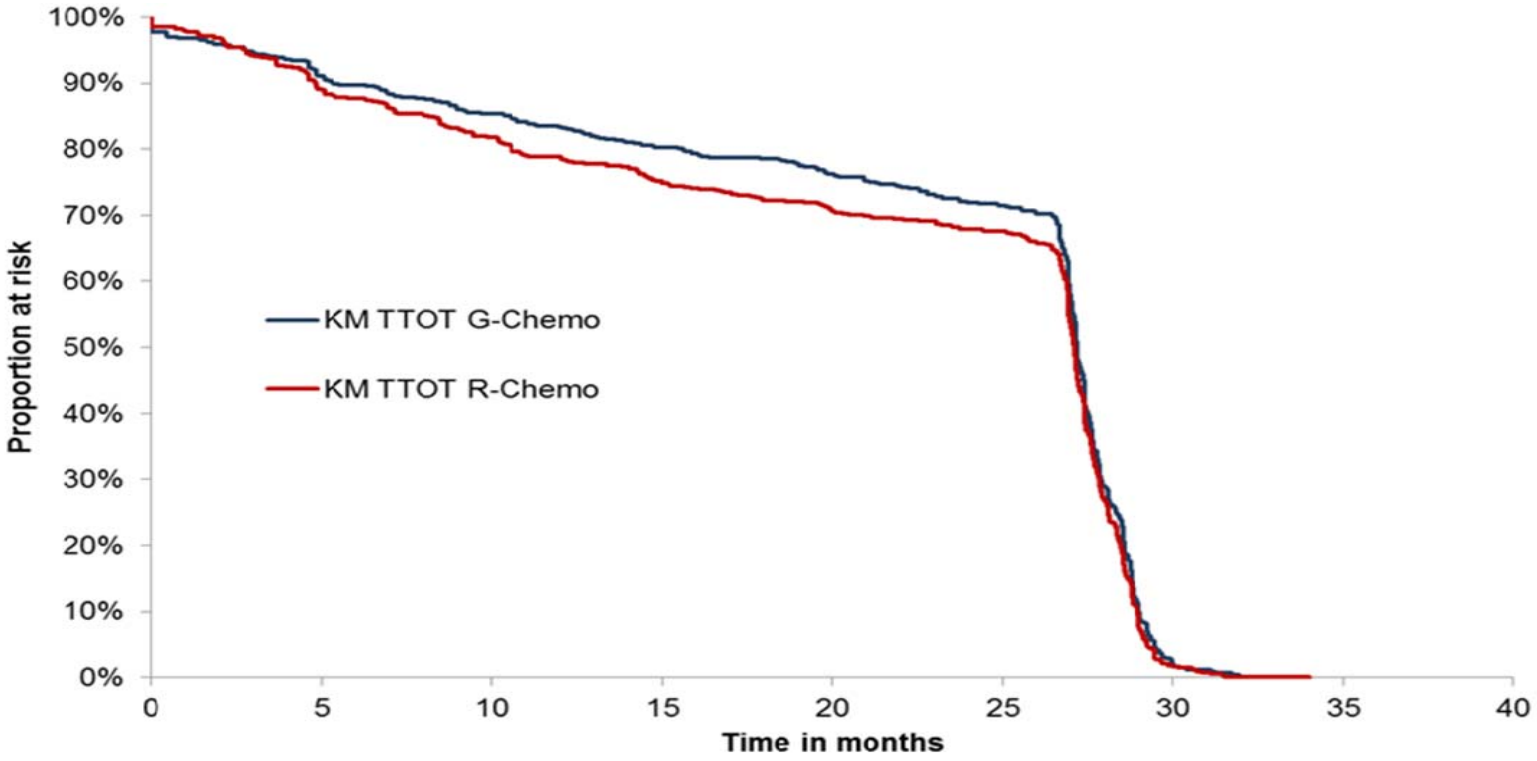
ERG's comments:

- Median age in GALLIUM is 59 years; Median age at diagnosis in Haematological Malignancy Research Network (HMRN) is 65 years
  - Company: HMRN relates to all patients with follicular leukaemia, and could include patients with less advanced disease
  - ERG: HMRN shows median age of 63.7 years for people treated with chemotherapy - **"A higher baseline age should have been used"**

◉ *What age should be used in the model?*

Modelled time to stopping treatment

- GALLIUM Kaplan-Meier curves for time-to-treatment-discontinuation
- Extrapolating not needed as all patients completed or stopped treatment
- Maintenance for a maximum of 2 years



◉ *Do different ways of determining PFS influence time to stopping treatment?*

Modelled progression free survival

- Company modelled progression-free survival using investigator assessed patient level data from GALLIUM for the rituximab arm, extrapolated with a parametric curve and then applying a constant hazard for obintuzumab's treatment effect
  - Company considered proportional hazard assumption holds by visually inspecting log-cumulative hazards plot and cumulative hazard plot
  - Company selected exponential curve by comparing the tail of the parametric fits of the rituximab arm with long-term data from:
    - PRIMA, follow-up data up to 9.75 years
    - US LymphoCare registry patients receiving R-CHOP, R-CVP or R with a fludarabine-based regimen (no R-bendamustine). Median follow-up was 7.4 years
    - Company's advisory board feedback that relapse rate 60-70% at 10 years (*that means progression free survival rate of 30-40%)*

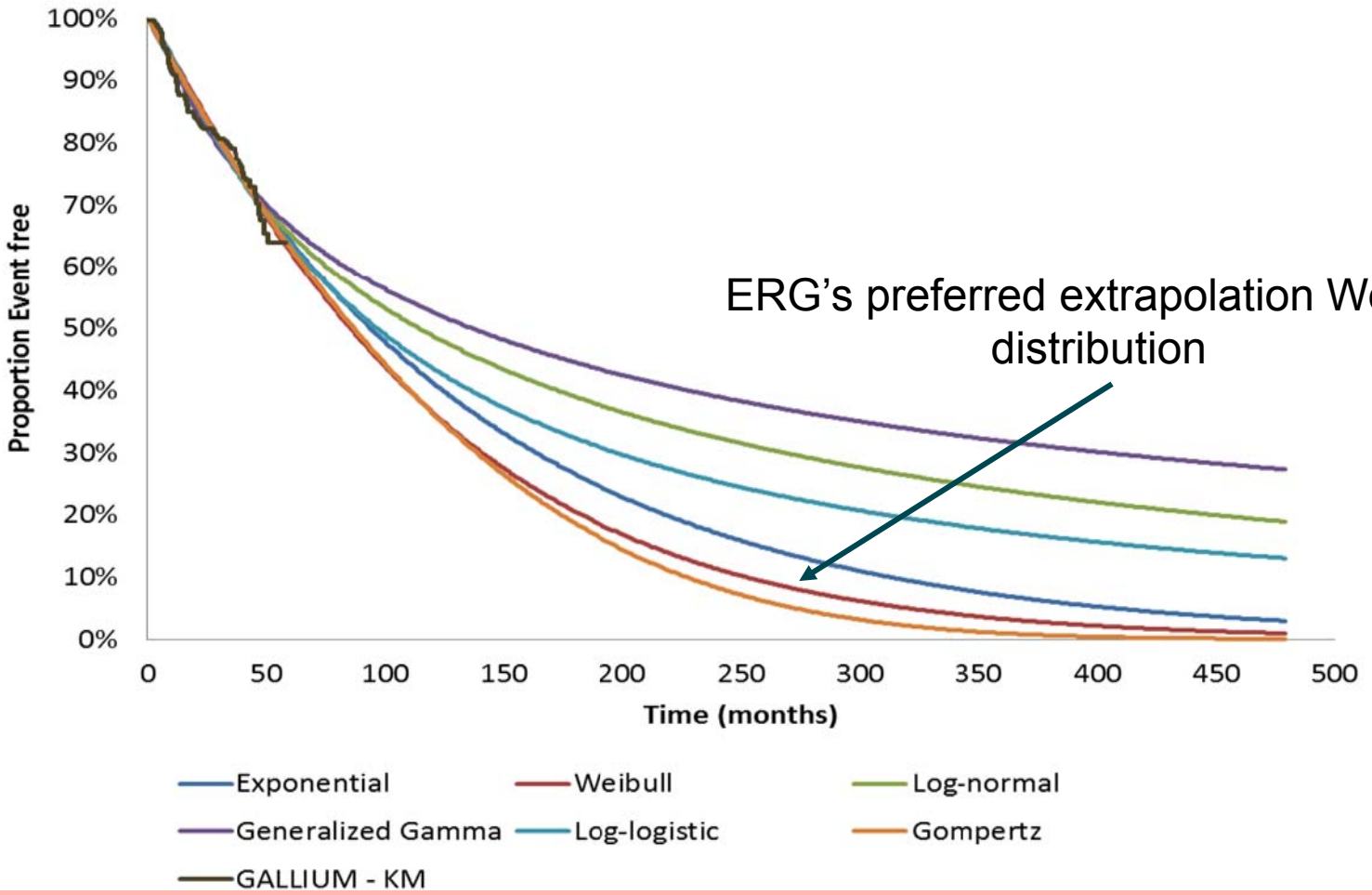
Extrapolating PFS (investigator) rituximab

External validity of long-term predictions (tail)

ERG's comments on how company modelled progression-free survival

- Company did "not properly justify" choice of PFS curve
  - difference between exponential and log-logistic unclear
- ERG selected Weibull (predicted PFS at 10 years: 36.4%) for its preferred base case, although Gompertz (predicted PFS at 10 years, 36.3%) also an option
- ERG prefers Weibull because it also fits to the PFS determined by investigator (predicted PFS at 10 years, 30.2%)
- Company stated exponential curve is more conservative and so prefers it over log-logistic
  - But, same reasoning valid for Weibull (preferred by ERG)
- PFS based on independent-review committee less prone to bias (and more conservative) than investigator-assessed PFS; company should use independently reviewed PFS

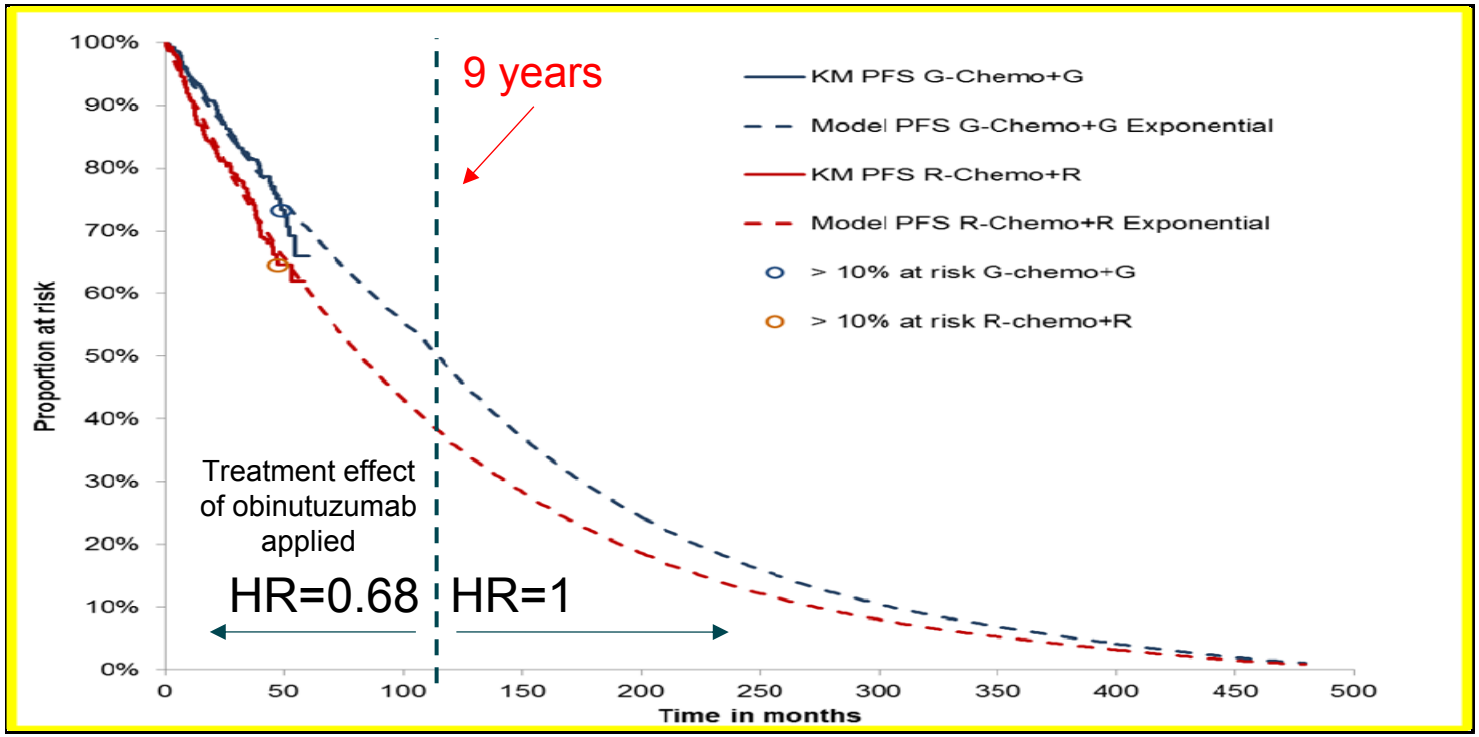
ERG's preferred extrapolation for PFS determined by independent review for rituximab



◉ *Which extrapolation is appropriate (independent or investigator assessed PFS & Exponential, Weibull or other?)*

Duration of treatment effect on progression-free survival

- **For Extrapolating long term PFS for obinutuzumab arm company**
  - applied HR for PFS to rituximab arm
  - assumed it remained unchanged (did not wane) for 9 years (based on PRIMA)
  - no treatment effect after that (HR=1)



ERG's comments on duration of effect

- ERG considers a 9 year fixed treatment effect 'speculative'
  - PRIMA compared rituximab maintenance with observation
  - Unclear if one can extrapolate to the duration of treatment effect of obinutuzumab over rituximab
- ERG explored changing the duration of a treatment effect:
  - reasonable to assume a 5-year treatment effect as this is the longest follow up duration from GALLIUM (34 months)

◉ *How long does the duration of treatment effect last? (9 years, 5 years or other?)*

Company's approach to modelling death

- Probability of dying before progression: Higher of:
  - Death rate before disease progression from GALLIUM
  - UK age-specific all-cause mortality
- Probability of dying after progression
  - During 'early' progressive state: Higher of:
    - UK age-specific all-cause mortality and
    - Pooled-over-both-arms monthly death rate from GALLIUM
  - During late progressive state: Higher of
    - UK age-specific all-cause mortality
    - Pooled-over-both-arms monthly death rates from people whose disease progressed after 2 years in PRIMA

Monthly mortality in the model

	N	Events	Monthly rate
Death rate during progression free-survival state (from GALLIUM)			
Pooled	**1202**	**38**	**0.096% (base-case)**
O-chemo	601	23	0.113%
R-chemo	601	15	0.078%
Death rates during early progression stage (from GALLIUM)			
Pooled	[redacted]	[redacted]	[redacted]
O-chemo	[redacted]	[redacted]	[redacted]
R-chemo	[redacted]	[redacted]	[redacted]

- ERG questioned pooling between obinutuzumab and rituximab arms → prefer separate rates
- In GALLIUM, death rate were higher in obinutuzumab arm during progression free stage; In rituximab during early progression stage
- In GALLIUM, no death occurred in patients who progression late

◉ *Are the death rates based on 15 deaths for R-chemo robust (GALLIUM)? Do they reflect practice? Should both arms be pooled?*

Company's monthly mortality (late progression)

- Post progression survival Kaplan-Meier curves from PRIMA

	GALLIUM	PRIMA
Early progression (<2yrs)	[redacted]	[redacted]
Late progression (>2yrs)	-	[redacted]
Early + Late (pooled)	-	[redacted]

◉ *Is PRIMA an appropriate source for death rates?*

Modelling of adverse events

- Company included adverse event costs, but not disutility
- Included only adverse events that affect more than 2% patients in GALLIUM trial
  - But, treated different grades of the same adverse event (for example grade 3, 4 and 5) as separate categories
  - only considered the **specific grades** of adverse events which affected more than 2% patients

ERG's comments:

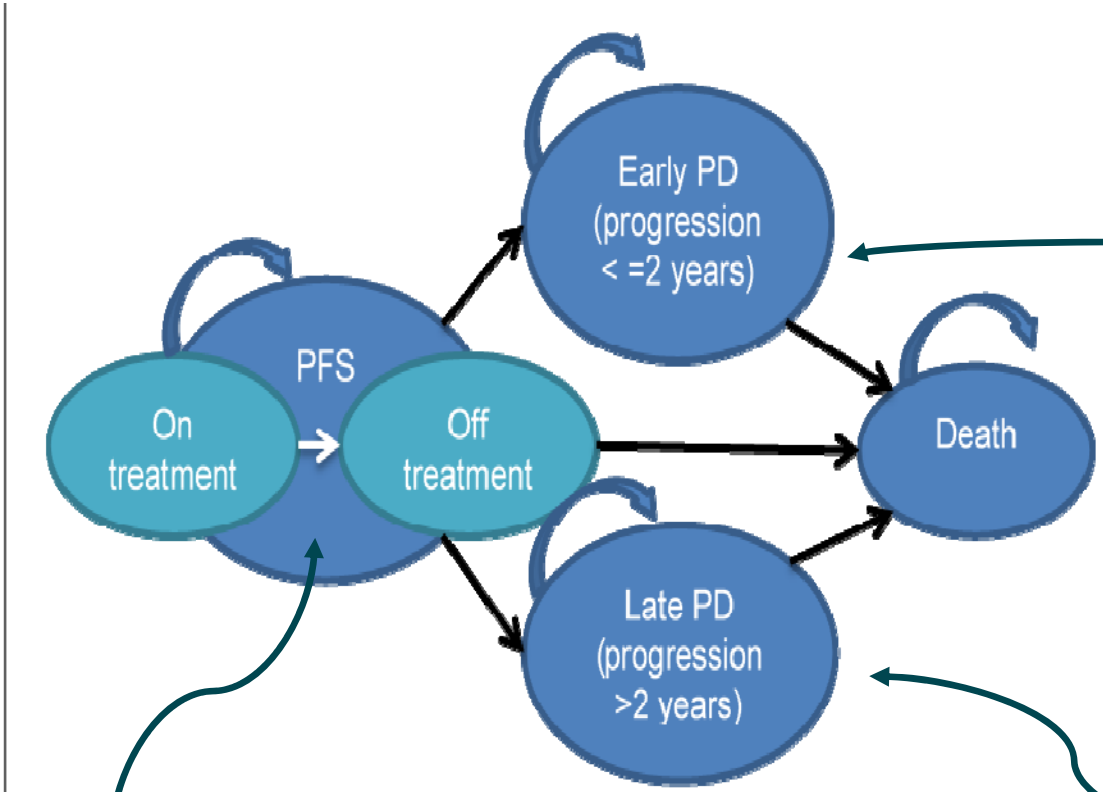
- 2% threshold arbitrary
- Considering different grades of the same adverse event separately causes illogical situations (e.g. grade 3 pneumonia was included but grade 4/5 pneumonia were excluded)
- ERG prefer to apply 2% threshold to the pooled grade 3/4/5 adverse events but didn't do it because of 'data and time limitations'
- ERG used same **list** (used by company) but considered all of grades 3/4/5 for each AE & also incorporated disutility

Disutility of adverse events used in company's scenario

	Disutility	Source	Duration of event (days)	Source
Neutropenia	-0.09	Nafees et al., 2008	15.10	NICE TA 306
Thrombocytopenia	-0.11	Tolley et al., 2013	23.20	NICE TA 306
Anaemia	-0.12	Swinburn et al., 2010	16.07	NICE TA 306
Leukopenia	-0.12	Assumed to be same as Anaemia	16.07	Assumption
Pneumonia	-0.20	Beusterien et al., 2010	14.00	NICE TA 306

◉ *Should disutility of adverse events be included (ERG) or excluded (Company)?*

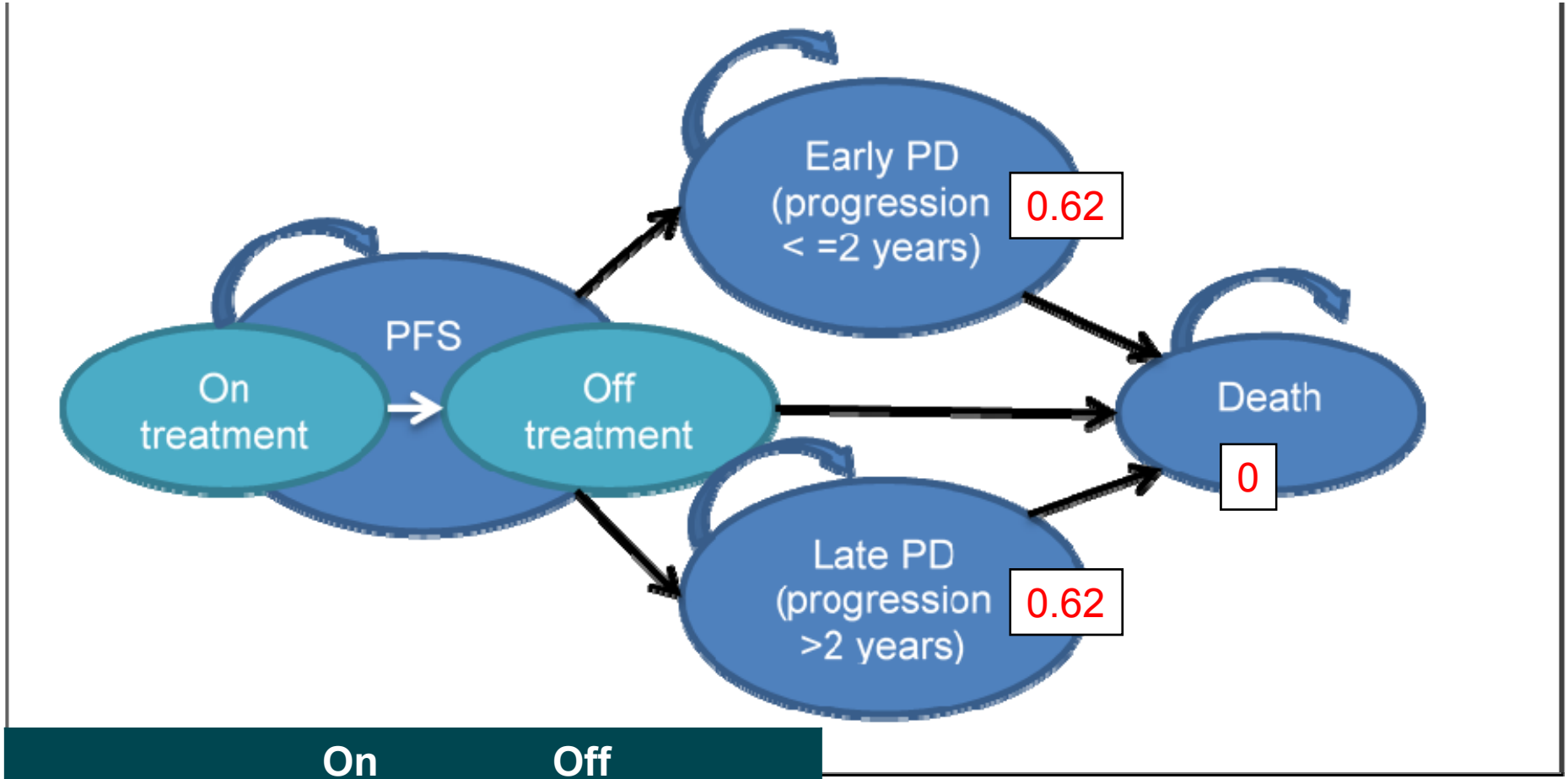
Company source of utility in model



Pre-progression
- EQ-5D from GALLIUM
- Company assumed same utility for both intervention and the comparator arm

Post progression
LITERATURE
Wild et al.

Summary: utility values used by company



	On treatment	Off treatment
Induction	0.823	0.772
Maintenance	0.831	0.818

ERG's comment on utility values

Unable to verify values

- Company used all available EQ-5D from GALLIUM regardless of geographical region → Company did not specify which tariff it applied to EQ-5D data
- Other sources and techniques identified (see below); but utility value for progressed disease health state is "non-transparent and non-replicable"
- ERG unable to decide which values were most reliable – so used values by Wild et al for progressed disease in it's base-case
- ERG explored scenarios using different utilities

Health state	Wild et al.	Bec et al.	GALLIUM	GADOLIN	Mapping FACT-Lym
PFS (on treatment)	0.81	0.71	**0.82**	0.82	NA
PFS (off treatment)			**0.77**	0.81	NA
Progressed disease	**0.62**	0.51	0.78 (early PD) 0.81(late PD)	0.76	0.73

ERG's comment on utility values

- For progression-free survival utility values:
  - Unclear if UK tariff was applied to GALLIUM estimates
  - Preferred for each treatment arms as per GALLIUM, however due to 'time constraints' did not include its base-case → probably not a big big impact on ICER
- ERG does not agree with company **not** to adjust utility by age
  - Company: "an age dependent decline is not observed" in trial
  - ERG: after seeing age distribution in GALLIUM, unlikely trial was powered to detect difference in utility between age
- Adverse events were more frequent in the obinutuzumab arm
  - But, estimated utility values higher in obinutuzumab arm vs rituximab "unexpected"
  - This is not reflected in the company's approach were utility values were pooled → AE disutility should be incorporated

◉ *Are the sources of the utility values robust?*

Resource use and costs

- **Drug and administration cost**
  - in PFS (on-treatment) health state
  - average dose for all drugs from GALLIUM
  - For rituximab maintenance, the company assumed that [redacted]% patient would receive it subcutaneously (SC)
    - SC administration cost £227 (IV administration £337)
- **Supportive care cost**
  - in all 3 health sate
  - based on ESMO guideline
  - haematologist appointment, diagnostic test and CT scan
- **Subsequent treatment cost**
  - in early and late progressive disease state
  - same for both arms, no difference in cost or outcomes
  - Subsequent treatment cost £13,427 (Papaioannou et al. 2012 for TA110)

ERG exploratory analysis – base case changes

1. Fixed coding/calculation errors
2. Demographic characteristics:
    a. Increased age at baseline: from 57.9 years in company's base-case to 62.6 to reflect UK patient population
    b. Distribution per chemotherapy regimen: proportional break down for UK patients in the GALLIUM trial
    c. Proportion of women: 53.2% in ERG's preferred base-case analysis as per GALLIUM base-line; company used 50%
3. different mortality rates for the treatment arms for progression-free disease state and early progressed disease state
4. assumed utility decrement with age
5. used independent review committee progression-free survival Weibull curve
6. Included adverse event disutility values
7. Assumed no vials shared
8. Included relevant adverse-event (grade ≥3) costs and disutilities

◉ *Which ERG changes does the committee agree with?*

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

Innovation

- Company considered obinutuzumab innovative because
  - first-in-class Type II glycoengineered anti-CD20 antibody
  - enhanced antibody dependent cellular cytotoxicity
  - increased direct cell death
  - a lower degree of complement dependent cytotoxicity
  - a meaningful improvement in PFS over rituximab
  - a 'significant unmet need for this patient population which will provide a significant positive impact on patients' 'lives'

◉ *Is this a step change in treatment? Are there any QALYs not captured in the modelling?*

End of life & Equalities issues

- End of life criteria: company did not make a case for end-of-life because patients with follicular lymphoma have a life expectancy beyond 24 months
- Equalities issues: No equality issues have been identified during scoping or evidence submission

Key issues - decision problem untreated follicular lymphoma

- **Comparators:** Company **excluded** 3 comparators in scope:
  1. rituximab monotherapy
  2. rituximab-based chemotherapy **without** rituximab maintenance
  3. bendamustine monotherapy
  - Are these treatment used in the NHS?
- **Chemotherapy regimens - induction:** Key trial included only 3 chemotherapy regimens combined with either obinutuzumab (intervention) or rituximab (comparator):
  1. Bendamustine
  2. CHOP [cyclophosphamide, doxorubicin, vincristine and prednisolone],
  3. CVP [cyclophosphamide, vincristine and prednisolone])
  - In the NHS, do clinicians offer other chemotherapy regimens such as:
  1. MCP (mitoxantrone, chlorambucil and prednisolone) or
  2. CHVPi (cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α)?

Key issues clinical-effectiveness

- What is the appropriateness of the evidence base given that GALLIUM (the key trial):
  - Is open label and 1∘ outcome is investigator assessed progression-free survival
  - Is immature: only 7.9% of people died during the trial
  - Did not randomise the chemotherapy accompanying obinutuzumab or rituximab for induction. Instead, they were trial-site specific
  - Has a different proportion of people receiving CHOP, CVP or bendamustine compared with UK practice
  - Has younger participants than the UK patient population which affects cost effectiveness estimates
  - Is not complete: trial is ongoing

Key issues - cost-effectiveness (1)

- **Which progression-free survival (PFS) data?**
  - Company used investigator-assessed PFS; ERG considered this prone to bias and less reliable than independent review committee (IRC) assessed progression-free survival → this is a driver of cost effectiveness
- **Which progression-free survival probability distribution?**
  - ERG preferred a Weibull curve fitted to IRC-PFS data over an exponential curve fitted to INV-PFS used by the company
- **How long is the treatment effect?**
  - In absence of long-term data, company assumed that PFS benefit with obinutuzumab maintained until 9 years (based on rituximab in another study). ERG considered this 'speculative'
  - Considering a duration of treatment effect <5 years increased the ICER of obinutuzumab compared with rituximab to >£30k/QALY in ERG base-case

Key issues - cost-effectiveness (2)

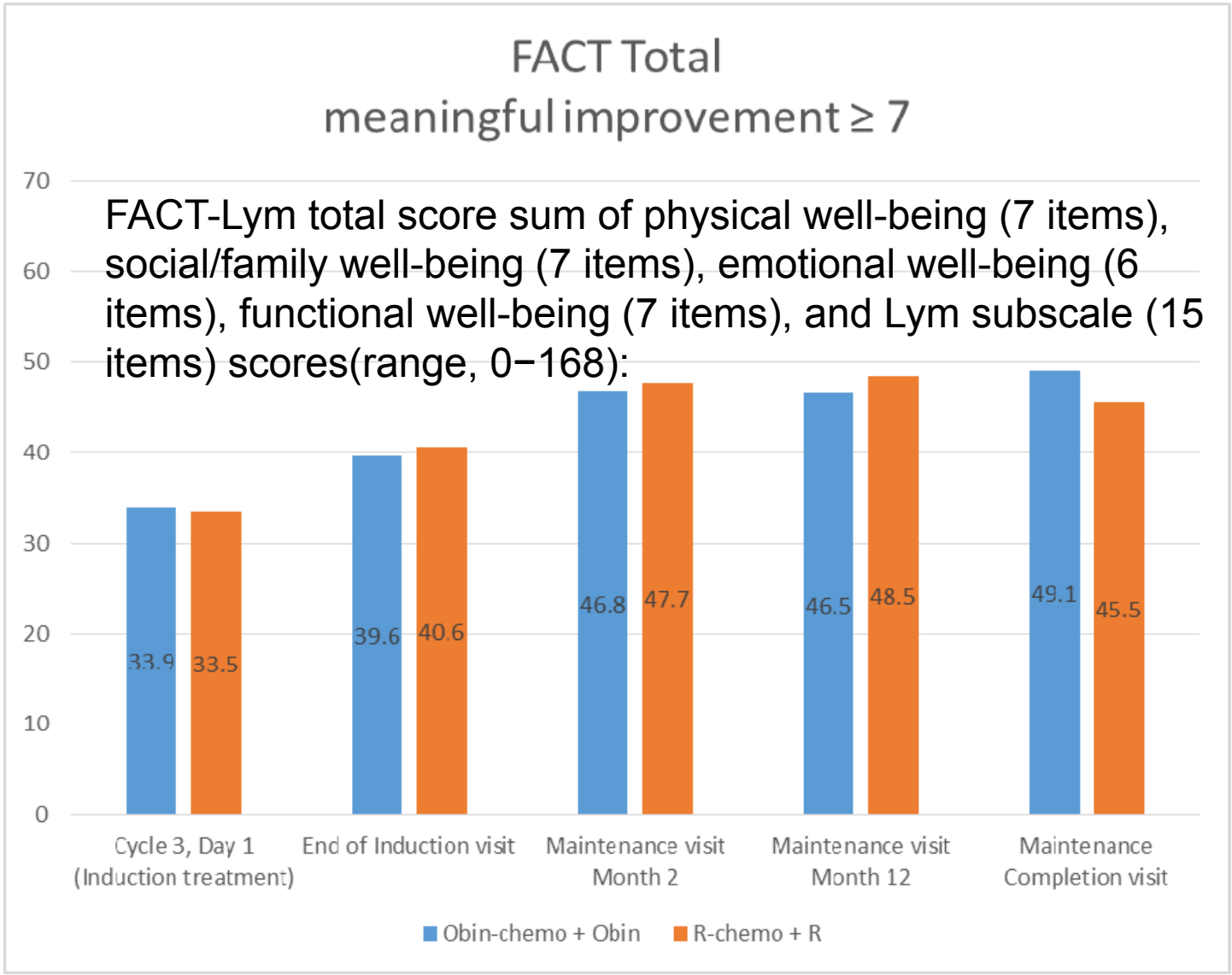
- **Estimating mortality**: To estimate mortality from progression-free and early progression states, company pooled deaths in both arms of GALLIUM and used **same** mortality rates for both treatment arms. ERG preferred different values per treatment arm. Which is better?
- **Cost of comparator**: Should this appraisal consider low-cost biosimilars for rituximab, the comparator?
- **Utility**: ERG considers company's source of utility to be "unpublished, inconsistent with the results of the GALLIUM trial and unverifiable"
- Are the end-of-life criteria met?
- Is obnituzumab an innovative treatment?
- Are there any equality issues?

Additional slides

GALLIUM trial (time to new anti-lymphoma treatment)

	Updated analysis (cut-off September 2016)	
	Obin-chemo n=601	R-Chemo n=601
Time to New Anti-Lymphoma Treatment (non-protocol)		
N (%)	86 (14.3%)	120 (20.0%)
HR (stratified), 95% CI	0.68 (0.52 to 0.90)	

GALLIUM trial result (FACT-Lym)
% with meaningful improvement



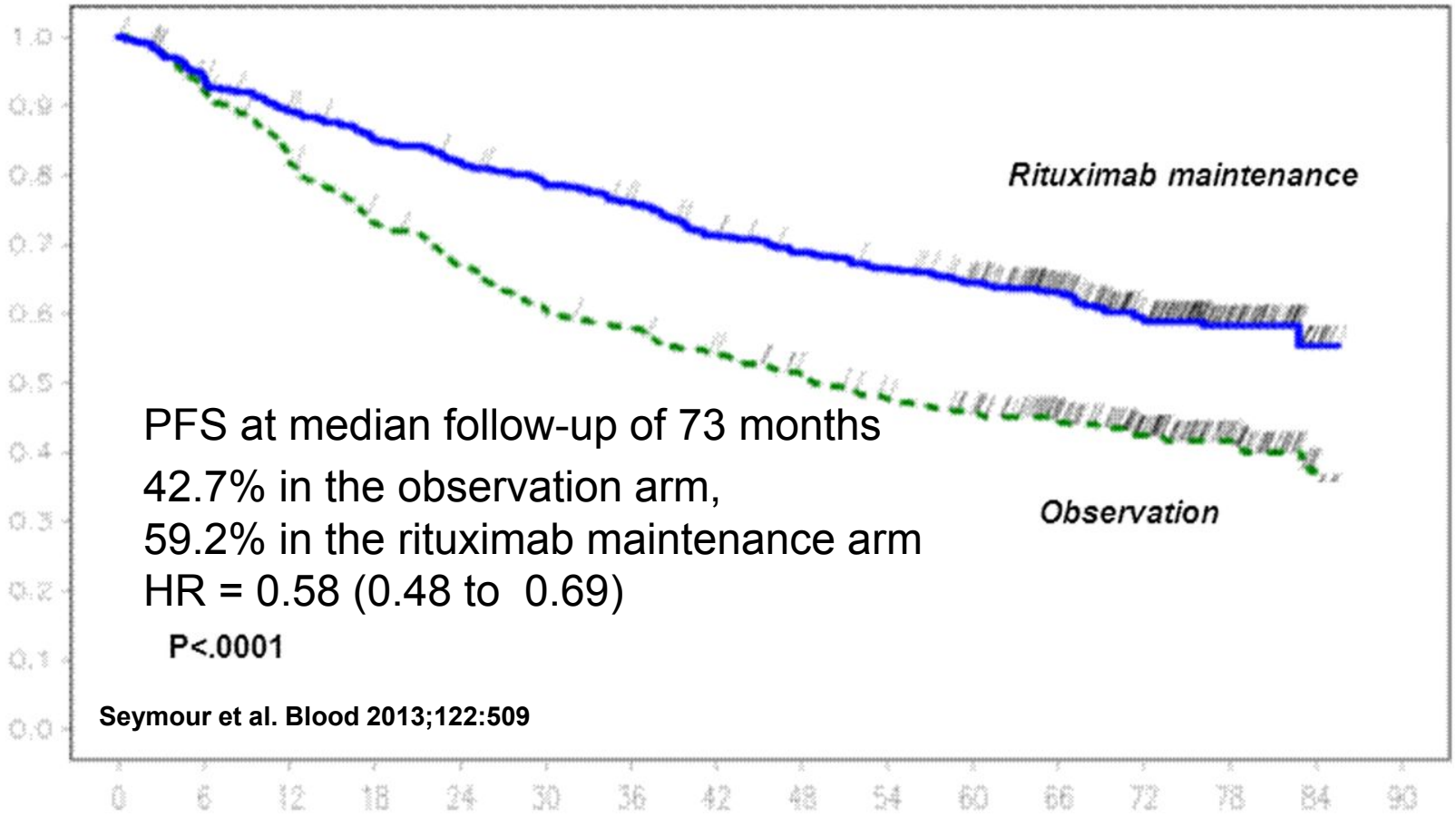
GALLIUM trial EQ-5D

	G-chemo+G		R-chemo+R		Difference	
State	Estimate	Std. Err.	Estimate	Std. Err.	Estimate	P-value
Induction - off tx	0.765	0.032	0.779	0.031	-0.015	0.72
Induction - on tx	0.823	0.015	0.824	0.015	-0.002	0.84
Maintenance & follow-up - off tx	0.826	0.015	0.810	0.015	0.017	0.13
Maintenance & follow-up - on tx	0.834	0.015	0.828	0.014	0.006	0.54
Early progression <= 2yrs	0.767	0.026	0.782	0.022	-0.015	0.62
Late progression > 2yrs	0.820	0.033	0.810	0.030	0.010	0.80

Adverse events

	O-chemo		R-chemo	
AEs of particular interest, (%):	All Grades	Grade ≥3	All Grades	Grade ≥3
Infusion-related reaction (IRR)	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Infection	[redacted]	[redacted]	[redacted]	[redacted]
Tumour lysis syndrome	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Acute thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Hemorrhagic events	[redacted]	[redacted]	[redacted]	[redacted]
GI perforation	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac events (incl. IRRs)	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac events (excl. IRRs)	[redacted]	[redacted]	[redacted]	[redacted]
Second malignancy (system organ class)[a]	[redacted]	[redacted]	[redacted]	[redacted]
StandardizedMedical Dictionary for Regulatory Activities query	[redacted]	[redacted]	[redacted]	[redacted]

PRIMA PFS K-M graph



NB the company re analysed: updated PRIMA data
to make it comparable to GALLIUM i.e. progression and death counted from induction instead of starting point of PRIMA (randomization after induction)

Modelled overall survival

- Calculated as the sum of:
  - Time spent in progression free-survival state **and either**
    - Time spent in early progressed disease state **or**
    - Time spend tin late progressed disease state
- Modelled overall survival undiscounted (company's base-cases)

	O-chemo+O	R-chemo+R	Difference
Mean life years (PFS)	11.60	9.68	1.92
Median PFS	9.58	6.83	2.75
Total Mean life years (OS)	19.42	17.97	1.45
Median OS	18.67	16.50	2.17

◉ *Without any clinical evidence, is estimated survival gain reliable?*

Company's cost of adverse events in base case

Event (Grade)	Unit Cost	Reference
Anaemia (3)	£2,117	SA03G (NL)
Febrile Neutropenia (3)	£6,226	NICE CG NHL, 2016
Dyspnea (3)	£0	Not costed
Infusion related reaction (3)	£601	SA31E (NS)
Infusion related reaction (4)	£601	SA31E (NS)
Neutropenia (3)	£867	LRiG estimate rev. TA162, TA175
Neutropenia (4)	£867	LRiG estimate rev. TA162, TA175
Pneumonia (3)	£4,155	DZ11P (NL)
Leukopenia (3)	£3,236	SA31E (NL)
Leukopenia (4)	£3,236	SA31E (NL)
Thrombocytopenia (3)	£3,236	SA31E (NL)
Thrombocytopenia (4)	£3,236	SA31E (NL)

Source: Based on Table 82 in the company's submission

***NHS reference costs 2015-16; NL, non-elective long stay; NS, non-elective short stay**