Lead team presentation
Obinutuzumab in combination with bendamustine for treating rituximab-refractory follicular lymphoma

1st Appraisal Committee meeting

Cost Effectiveness

Committee A

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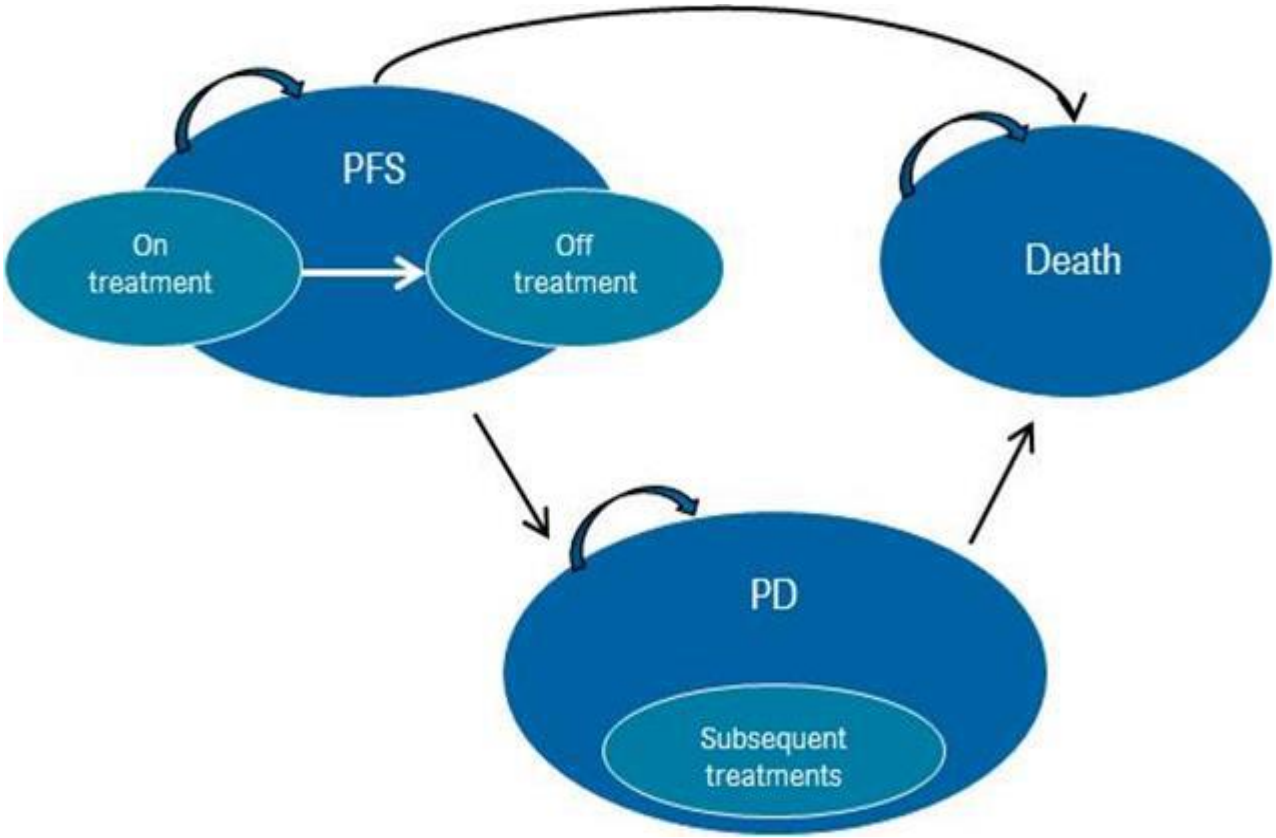
Key issues for consideration

- Modelling provides evaluation of cost-effectiveness compared with bendamustine but we don't know if bendamustine can be considered cost-effective, or if it can be considered 'standard care'
  - model combines subgroups of patients who were refractory to induction treatment with rituximab monotherapy or R-chemotherapy, or were refractory during, or within 6 months of completing maintenance treatment with rituximab monotherapy, is this appropriate?
  - Is bendamustine the appropriate comparator?
  - which approach for predicting long term overall survival benefit (Semi-Markov in the company model or the ERG estimates based on partitioned survival)?
  - company or ERG ICERs most plausible?

Model structure

- Cohort based semi-Markov model



Model basics

Perspective	• NHS and PSS for costs • Direct health impact on patients only for outcomes (i.e. no carer QALYs are included)
Primary health economic outcome	Incremental cost per QALY gained
Synthesis of health effects	Clinical effectiveness and safety estimates included in the company's model are taken from the GADOLIN trial
• Time horizon	• Lifetime (assumed to be 25 years in the base-case)
• Discount rate	• 3.5% per year for both costs and QALYs

Utility values (Table 62,company submission)

- EQ-5D data collected in GADOLIN trial but not used in company base-case –post-progression values not collected from GADOLIN (only at the point of progression so may be too high)
- Patients on and off treatment assumed to have the same utility value
- Utility values in the model base case obtained from study by Wild 2006 EQ5D data from 222 UK based patients with follicular lymphoma

	Mean utility values (Standard Error)	
Health State	GADOLIN	Wild D 2006 (used in the company base case)
Progression free survival (on treatment)	0.82 (0.01)	0.81 (0.02)
Progression free survival (off treatment)	0.81 (0.01)	0.81 (0.02)
Progressed disease (including subsequent treatments)	0.76 (0.02)	0.62 (0.06)

Clinical outcomes in model

- Overall survival is not taken directly from the trial but estimated instead as a function of
  - (1) the time in pre-progression and
  - (2) the time in post-progression.
- Pre-progression survival (mortality)
  - PFS extrapolated from observed KM curve using Weibull function (base case)
  - Probability of dying before progression (which is treatment specific) taken from the GADOLIN trial
- Post-progression survival (mortality)
  - pooled post-progression survival (PPS) KM data from both the GADOLIN trial arms
- QALY - The time spent in pre-progression and post-progression are then weighted according to QoL to estimate QALYs

Progression free survival

- Survivor functions fitted to the observed KM curves of the GADOLIN trial for PFS for each arm separately – proportional hazards assumption did not hold
- Selection of curve based partly on AIC/BIC, but mainly on plausibility of predicted PFS
  - log-logistic, log-normal and gamma) provided the best fit in terms of AIC and BIC but resulted in greater predictions of the number of people remaining in PFS at 10 years
  - Weibull and Gompertz generated more conservative predictions
  - Weibull distribution provided a balance between model and predicted long-term survival in PFS
  - Weibull used in the company's base-case

Progression free survival estimates in the company model (Table 53, company submission)

Parametric distribution	Mean years in PFS			Proportion of patients in PFS at 10 years (%)		
	O-Benda+O	Benda	Incremental	O-Benda+O	Benda	Incremental
Log-logistic	4.35	1.67	2.69	16	1	15
Log-normal	4.58	1.70	2.89	18	1	17
Gamma	5.10	1.59	3.51	22	0	22
Weibull	3.45	1.50	1.95	8	0	8
Gompertz	3.38	1.53	1.85	7	0	7
Exponential	3.38	1.68	1.70	7	0	7

Pre-progression survival (Table 21, ERG report)

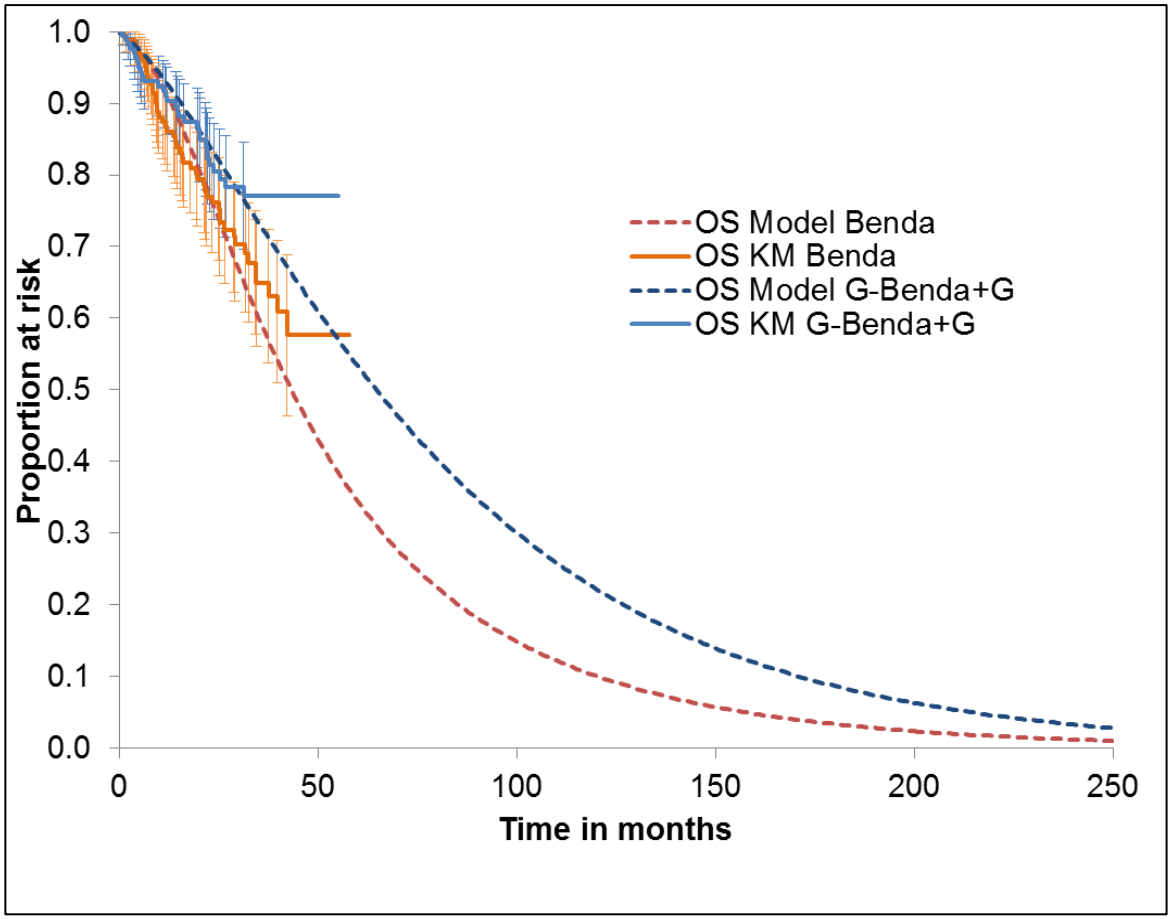
Item	O-Benda+O	Bendamustine monotherapy
Number of PFS deaths	9	8
Total number of person months spent in PFS	3,017.5	2,267.4
Monthly rate of death	0.003 (=9/3,017.5)	0.004 (=8/2,267.4)
Monthly PFS mortality probability	0.0030 (=1-exp(-0.003))	0.0035 (=1-exp(-0.004))
Benda, bendamustine induction only, O-benda+O, Obinutuzumab in combination with bendamustine followed by Obinutuzumab maintenance; PFS, progression-free survival		

Post-progression mortality (Table 22, ERG report)

- Single curve for O-benda+O and bendamustine
- As before selected based partly on AIC/BIC but mainly on predicted overall survival

Parametric distribution	AIC (rank)	BIC (rank)	O-benda+O	Benda
Log-normal	345.1 (1)	351.3 (1)	11.4	9.8
gamma	346.1 (2)	355.3 (3)	17.2	16.3
Log-logistic	348.2 (3)	354.4 (2)	10.6	9.0
Weibull	352.1 (4)	358.3 (5)	3.3	1.2
exponential	352.8 (5)	355.8 (4)	1.8	0.1
* parentheses indicate ranking				

Overall survival prediction (Figure 24, company submission)



Overall survival predictions for different PPS parametric models (Table 57,company submission)

Parametric distribution	Pooled arms AIC rank	Predicted OS at 20 years (%)	
		O-benda+O	Benda
Log-normal	1	11.4	9.8
Gamma	2	17.2	16.3
Log-logistic	3	10.6	9.0
Weibull	4	3.3	1.2
Exponential	5	1.8	0.1

The ERG accepted that the fit between the predicted overall survival estimates and the observed (Kaplan Meier) data was plausible for O-Benda+O but not for bendamustine monotherapy (see Figure 18). The ERG therefore considered that the overall survival estimates in the model were biased in favour of O-Benda+O

Resources and costs

- Drug acquisition and administration costs
- Supportive care costs for all patients in progression free survival health state (on and off treatment)
- Costs associated with subsequent treatments in progressed disease health state after disease progression
- Assumed 1 monthly visit to a haematologist during induction therapy, decreasing to every 3 months after 6 months and finally every 4 months for patients who remained progression free.

Company's base case results (Table 76 company submission)

Treatment	Total values		Incremental values		ICER (£)
	Costs (£)	QALYs	Cost (£)	QALYs	
Deterministic results					
G-benda+G	XXX	4.23	XXX	1.32	XXX
Benda	23,889	2.92			
Probabilistic results					
Old	NR	NR	NR	NR	XXX
New	XXX	4.25	XXX	1.32	XXX

At a willingness to pay of £30,000 there is a XXX probability of O-Benda+O being cost-effective

Company's sensitivity analyses

- Sensitivity analyses around
  - Utilities (PFS on treatment, PFS off treatment , in PD, for PFS& PD, decrement for AEs included)
  - Costs (for admin visits, for AEs, for supportive care in PFS and in PD, of subsequent treatments, time on treatment, vial sharing, additional administration costs, cost of palliative care)
  - Outcomes – alternative PFS parametric distribution function, Separate PPS functions (rather than pooled)
  - Discount rates (5% or 0% for health effects and for costs)
  - Time horizon (30, 20 years)

Company's sensitivity analyses (Figure 29, company submission)
(CONFIDENTIAL –NOT REPORTED)

Company's scenario analyses

- Key drivers were
  - Using the log-normal or log –logistic parametric distribution to estimate progression free survival resulted in ICERS of £XXX and £XXX per QALY gained respectively.
  - Using the utilities from the GADOLIN study increased the ICER by £913.00 per QALY gained.
  - Assuming patients in the progression free survival health state would be treated per protocol rather than as observed in GADOLIN resulted in an ICER of £XXX per QALY gained.

Evidence Review Group (ERG) comments

- Bendamustine monotherapy was the only comparator modelled
- Bendamustine monotherapy is an appropriate comparator only in:
  - people with FL refractory to induction treatment with R-chemotherapy (not including bendamustine)
- The model estimates the incremental cost per QALY gained for O-benda+O versus bendamustine monotherapy only
- Within the modelling of O-benda+O versus bendamustine monotherapy the ERG had the following criticisms of the model….

ERG's Summary of main issues identified within the critical appraisal of the company's model (Box 1, page 120 ERG report)

1. Concerns regarding the approach to modelling overall survival
2. Concerns regarding the treatment pathway for subsequent treatments
3. Concerns regarding the model selection for PFS for bendamustine monotherapy
4. Concerns regarding the assumption of constant pre-progression mortality
5. Concerns regarding the estimation of post-progression mortality.

Cont.…

ERG's Summary of main issues identified within the critical appraisal of the company's model (Box 1,page 120 ERG report)

6. Uncertainties regarding the utility values
7. Comments regarding the inclusion of the impact of adverse events on costs and quality of life
8. Comments regarding assumptions on drug administration costs
9. Concerns regarding the estimation of the costs associated with subsequent treatments
10. Comments regarding the implementation of the PSA and conduct of the sensitivity analyses
11. Other minor comments

ERG's exploratory analyses (pages 134-138, ERG report)

1. Used the partitioned survival approach to estimate overall survival (**key driver**)
2. Adjusted utility values by age
3. Assumed lower costs for subsequent treatment post-disease progression
4. Used the generic acquisition cost for bendamustine listed in BNF BNFv 72 (July 2016)
5. Corrections of minor programming errors in the model
6. Used alternative drug administration costing assumptions
7. Used utility values from the GADOLIN trial for all patients in the progression-free state health state

ERG's exploratory analyses (Tables 42-44, ERG report)

Scenario	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER
Company's base case	XXX	4.23	XXX	1.31	XXX
Model amendment 1 (OS modelling)	XXX	4.19	XXX	0.63	XXX
Amendment 2 (utility incl. age)	XXX	4.13	XXX	1.26	XXX
Amendment 3 (lower cost sub.Tx)	XXX	4.23	XXX	1.31	XXX
Amendment 4 (generic Bend)	XXX	4.23	XXX	1.31	XXX
Amendment 5 (prog. errors)	XXX	4.23	XXX	1.32	XXX
Amendment 6 (alt. drug admin)	XXX	4.23	XXX	1.31	XXX
Amendment 7 (GADOLIN utility for PFS)	XXX	4.30	XXX	1.33	XXX

ERG's exploratory analyses cont.. (Tables 42-44, ERG report)

Scenario	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER
Company's base case	XXX	4.23	XXX	1.31	XXX
ERG's preferred base case (scenario 1-6)	XXX	4.09	XXX	0.62	XXX
ERG's base case (1-7)	XXX	4.16	XXX	0.63	XXX

Comparison of predicted OS using the company's approach, the ERG approach and observed KM
(Figure 18, ERG report) Academic in confidence – not reported

ERG sub-group analysis

- Patients refractory to induction with R-chemotherapy
- Only in this sub-group might bendamustine monotherapy be considered a therapy option
- ERG reconstructed IPD data from Kaplan-Meier OS curves
- Weibull and Exponential curves used for extrapolation.

Comparison of observed KM OS and the Weibull and exponential fits for the subgroup of people with FL refractory to R-chemotherapy, Figure 21, ERG report Academic in confidence – not reported

Results of the ERG exploratory cost effectiveness analysis for the sub-group refractory to induction with R-chemotherapy (Table 46,ERG report)

	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER
Weibull distribution for PFS	XXX	4.51	XXX	0.54	XXX
Exponential distribution for PSF	XXX	4.34	XXX	0.35	XXX

End of life criteria

- Short life expectancy, normally <24 months
- Not applicable

Potential equality issues

- No potential equality issues identified
- Are there any potential equality issues?

Innovation

- How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?

- Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?

PPRS payment mechanism

- PPRS is a voluntary agreement to control the prices of branded drugs sold to the NHS
  - 2014 PPRS scheme includes a payment mechanism in which the growth rate in sales of NHS branded medicines supplied by companies in the scheme is underwritten by those companies, above agreed levels
- NICE position statement concludes that 2014 PPRS Payment Mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines
- Company did not apply PPRS to its analyses
  - Does the company consider the PPRS 2014 Payment Mechanism has an impact on the effective price/cost of the technology to the NHS?
  - Has Committee heard anything that would change the conclusion in the NICE position statement?

https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/PPRS%202014%20-%20NICE%20Position%20Statement.pdf

PPRS payment mechanism

- Does the company consider the PPRS 2014 Payment Mechanism has an impact on the effective price/cost of pirfenidone to the NHS?

- Has the Committee heard anything that would change the conclusion in the NICE position statement* on the PPRS?

"PPRS Payment Mechanism should not be regarded as a relevant consideration in the assessment of cost effectiveness"

*https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/PPRS%202014%20-%20NICE%20Position%20Statement.pdf