Lead team presentation: Ibrutinib for treating Waldenstrom's Macroglobulinaemia [ID884]

1st Appraisal Committee meeting

Cost effectiveness

Brian Shine

20 September 2016

For public

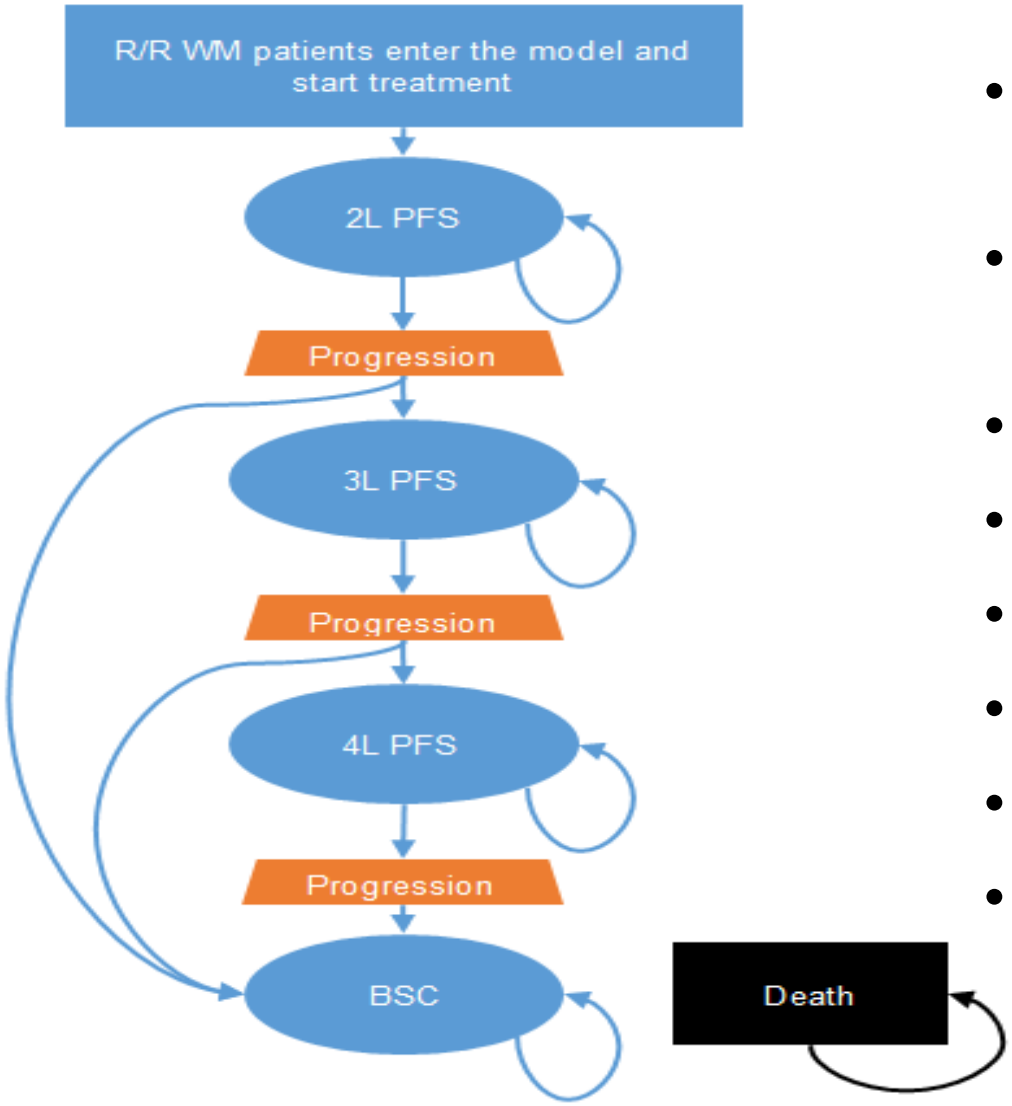
Key issues for discussion

- The company's model does not cover patients who have not received prior therapy and in whom chemo-immunotherapy is unsuitable.
  - **Can any conclusions be drawn for this group of patients?**
- The ERG raised concerns about the structure of the company's model.
  - **What is the committee's view of the company's modelling approach?**
- The ERG considered that the difference in the pre-progression survival trajectories for ibrutinib and rituximab/chemotherapy is the key driver of cost-effectiveness.
  - **What is the committee's view on the modelling of pre-progression mortality?**
- No HRQoL data were collected in Study 1118E and no HRQoL studies in WM were identified.
  - **Is the use of EQ-5D data from a CLL study a reasonable approach?**

Key issues for discussion (2)

- The company's base case deterministic ICER for ibrutinib compared with physician's choice of treatment was £58,630 per QALY gained. In the ERG's amended analysis the probabilistic ICER was £61,219 per QALY gained. The other exploratory analyses did not produce markedly different ICERs, with the exception of the scenario in which the survival gain for ibrutinib was removed from the model; in this analysis the ICER was £390,432 per QALY gained.
  - **What is the committee's view of the ICERs estimated and their robustness?**
  - **Which assumptions does the committee consider to be most plausible?**
- **Does the committee consider ibrutinib to be an innovative therapy?**
- **Does the committee consider that CDF funding is appropriate?**

Model structure



- Company presented a de novo model
- Markov state-transition model
- 5 health states
- Time horizon: 30 years
- 4 week cycle
- Half-cycle correction
- Discounted at 3.5%
- NHS and Personal Social Services perspective

Source: Figure 19, Company's submission

Model details

- Population reflects the characteristics of patients in Study 1118E, that is, previously treated patients with WM
- Ibrutinib was compared with physician's choice of treatment to reflect the distribution of therapies used in UK clinical practice
- Composition of physician's choice was defined at each treatment line, however, treatment lines 3 and 4 were assumed to be the same

Distribution of treatments included in 'physician's choice' by line of therapy

Treatments	2L	3L/4L
Fludarabine + cyclophosphamide + rituximab	11%	9%
Dexamethasone + rituximab + cyclophosphamide	31%	15%
Bendamustine + rituximab	47%	43%
Cladribine + rituximab	0%	30%
Other treatment*	11%	3%

*Other treatment in 2L: cladribine, chlorambucil +/- rituximab, and rituximab monotherapy in equal proportions; other treatment in 3L/4L: chlorambucil +/- rituximab, and rituximab monotherapy in equal proportions.

Clinical data used in the model

- For the 2nd line PFS health state
  - A parametric fitting of Study 1118E trial data for ibrutinib was used as the reference curve. Extrapolation using the Weibull function
  - Comparative efficacy was based on the Cox regression analysis conducted with the patient-level data from the pan-European chart review cohort (hazard ratio=[redacted])
  - Mortality rate was taken from general population data for ibrutinib and from the pan-European chart review for the comparator
    - ERG are unclear which data were used for pre-progression mortality in the model
- For the 3rd line, 4th line and BSC health states (post progression):
  - The progression rate and the post-progression mortality associated with the subsequent treatments (3rd and 4th line) were derived from the pan-European chart review cohort to estimate the duration of time patients spent in each health state. The same assumptions were applied to both the ibrutinib and the comparator arms of the model

Transition probabilities

Parameter	Ibrutinib	Rituximab/chemotherapy
Second-line PFS	Weibull function fitted to PFS curve from Study 1118E (full study population, n=63)	Estimated by applying the inverse of the HR for PFS of [redacted] from company's adjusted arm-based indirect comparison to the ibrutinib parametric PFS curve (matched cohorts of ≤4 prior lines of therapy: ibrutinib n=47; rituximab/chemotherapy n=175)
Second-line pre-progression mortality	Based on general population mortality hazard from ONS life tables for England	Log normal curve fitted to pre-progression mortality data from European chart review cohort (patients receiving second-, third- or fourth-line treatment, n=175)
Third- and fourth-line time to progression	Exponential distribution fitted to time to progression data from European chart review cohort (patients starting fourth-line treatment, n=52, estimated probability=[redacted] per cycle)	
Third- and fourth-line pre-progression mortality	Exponential distribution fitted to data from European chart review cohort (patients progressed from third-line treatment, n=60, probability=[redacted] per cycle)	
BSC death probability		

ERG report, table 34

Progression free survival

Progression free survival parametric fitting

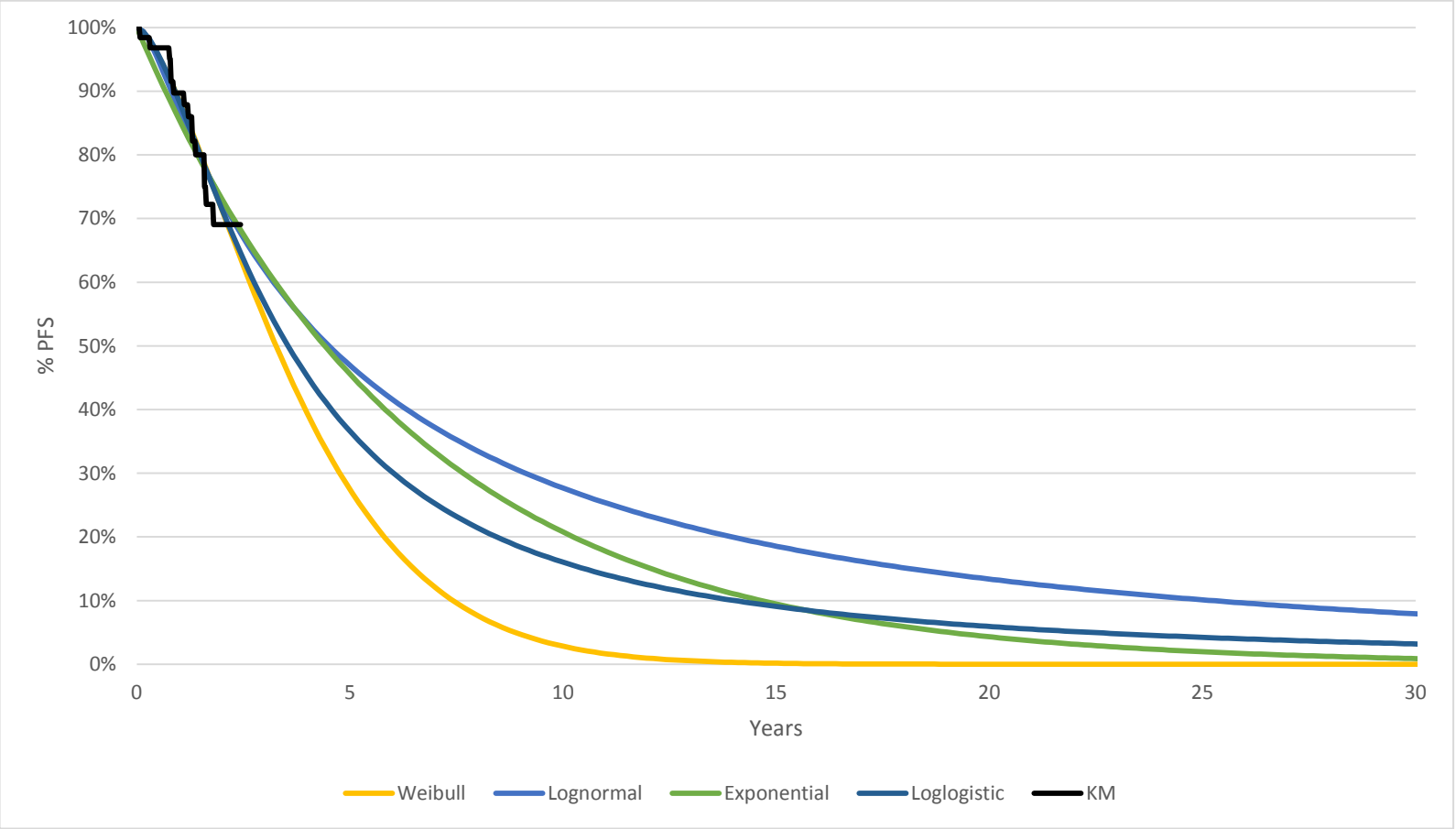


Figure 20, Company's submission

Health related quality of life (HRQoL)

- There is no disease specific instrument for measuring HRQoL in patients with WM
- No HRQoL data were collected during Study 1118E
- No HRQoL studies were identified by the company
- Utility inputs in the model were informed by the RESONATE study of ibrutinib in relapsed and refractory chronic lymphatic leukaemia, based on EQ-5D data collected during the course of treatment
  - This proxy was recommended by an EU advisory board when the lack of WM-specific data became clear
- Utility decrements associated with adverse events (ranging from 0.123 to 0.195) were applied, based on expert assumption or published literature

Utility by health state

Health State	Mean	SE
2L	0.799†	0.080†
3L	0.799†	0.080†
4L	0.799†	0.080†
BSC	0.665‡	0.067‡

BSC: Best Supportive Care; SE: standard error
† Source: RESONATE CLL trial
‡ Source: Disutility from Beusterien et al (2010) applied to RESONATE CLL trial baseline score

- Utility data were adjusted for age
- These coefficients were applied in the model
- Adverse event decrements are included for all second-line treatments and are assumed to impact both on HRQoL and costs during the first model cycle

Source: Table 43, Company submission

Company's base case deterministic results

	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	58,630
PC	[redacted]	[redacted]	[redacted]				

ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, Life years gained; QALYs, quality-adjusted life years; PC, Physician's choice

- Most of the company's sensitivity analyses did not have a substantial impact on the ICER
- However, altering the utility value for the 2nd line PFS health state changed the ICER to £52,523 - £69,607 per QALY gained, depending on the assumptions used
- The ICER was greater than £47,000 per QALY gained across all sensitivity analyses
- Probabilistic sensitivity analysis indicated a 0% probability of ibrutinib being cost-effective at a maximum acceptable ICER of £30,000 per QALY gained

Confidential

Company's scenario analysis results

Variable	Base case	Parameter change	ICER (£/QALY)
Base case			£58,630
Age adjustment for utilities	Yes	No	£56,646
Distribution for PFS of ibrutinib	Weibull	Log-logistic	£61,303
HR PFS in 2L	[redacted]	HR = [redacted] Scenario 1: Imputed pat. charac. No individual clinical measurement (risk category only)	£58,669
HR PFS in 2L	[redacted]	HR = [redacted] (Scenario 2: sample with complete pat. charac, No imputation. All Variable (individual clinical measurements & risk category)	£58,729

ERG report Table 37 (reproduce from Company submission, Table 65)

ERG comments

Population

- The population considered in the model is patients with relapsed or refractory WM who have received one prior therapy
  - inconsistent with the population in Study 1118E where [redacted] of the population had received more than one prior therapy
  - also inconsistent with the pan-European study where [redacted] of patients had previously received more than 1 therapy
- Model does not include the treatment-naive population for whom chemo-immunotherapy is unsuitable

ERG comments (2)

Model structure and logic

1. Sequencing

- The company's model imposes a sequence of treatments which is not consistent with the data from Study 1118E
- The sequence is not well defined and uses subjective expert opinion to determine the treatment options received in each line of therapy. The ERG considers that an objective source could have been used
- The same pre-progression mortality probability is applied to the 3rd and 4th line progression-free states. Despite the company's model adopting a sequence-based structure, survival following progression on 2nd line therapy is governed entirely by a single exponential function
- The same health utility score is used for all progression-free states irrespective of line of therapy

ERG comments (3)

2. Structural relationship between PFS and pre-progression mortality

- Model imposes potentially inappropriate structural relationships between progression and death
- Pre-progression mortality in the second-line progression-free state is modelled conditionally on PFS
- This means that within the ibrutinib group, the estimated contribution of PFS to overall survival will always be the same irrespective of the pre-progression mortality curve assumed in that same state.
- As such, the pre-progression mortality curve is entirely independent of survival gains accrued in the second-line progression-free state and only impacts upon the survival gains accrued in the subsequent model health states
- ERG considers the most appropriate approach would involve the independent modelling of time to progression (censoring for death) and pre-progression mortality (censoring for progression)

ERG comments (4)

3. **assumption on survival following progression after 2nd line treatment**

- Model includes a structural assumption whereby survival following progression from 2nd line therapy must follow an exponential distribution due to the use of multiple intermediate health states
- It is not possible to reflect time-variant event rates within the existing structure
- The survival curves for 2nd line pre-progression mortality and post-progression survival for rituximab/chemotherapy appear logically inconsistent
- The same structural issue applies to time to progression in the 3rd and 4th line progression-free states

ERG comments (5)

4. Pre-progression mortality for the comparison

- Potentially inappropriate data were used to inform pre-progression mortality for rituximab/chemotherapy
- Using data relating to all deaths, rather than only those occurring before progression, could result in an inflated rate of death in the comparison group but the source of data used is unclear
- If overall survival data had been used, the ICER for ibrutinib could be significantly higher than that reported by the company and the ERG

5. Assumption of general population mortality rates for ibrutinib

- Company's model assumes general population mortality hazards because only 3 patients died within the 24-month follow-up period within Study 1118E
- ERG expressed 2 concerns about this:
  i. the model assumes a zero death rate for the first 6 model cycles;
  ii. the observed death rate within Study 1118E was higher than that for the age- and sex-matched general population
- ERG considers that this assumption could bias the ICER in favour of ibrutinib. However, given the immaturity of the survival data from Study 1118E and the lack of a randomised comparator, the extent of the bias is unclear but is unlikely to improve the ICER

ERG comments (6)

6. Health Related Quality of Life

- Clinical advisors noted that HRQoL would be likely to decrease with each additional line of therapy and would likely decrease during the period in which patients are receiving chemotherapy compared with the period following treatment discontinuation

7. Errors and discrepancies relating to costs

- The cost of bendamustine in the model reflects the proprietary product; the cost of the generic version is markedly less expensive
- Several drug costs did not match the current version of the BNF
- Cost for chlorambucil includes errors which inflate the total waste-adjusted dose
- Cost for cladribine plus rituximab includes programming errors
- Incorrect administration costs for several regimens

ERG's amended base case

Probabilistic model	QALYs	Costs	Inc. QALYs	Inc. costs	Inc £/QALY gained
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	£61,219
Rituximab/ chemotherapy	[redacted]	[redacted]	-	-	-
Deterministic model	QALYs	Costs	Inc. QALYs	Inc. costs	Inc £/QALY gained
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	£61,050
Rituximab /chemotherapy	[redacted]	[redacted]	-	-	-

Includes ERG exploratory analyses (EA):

- EA1 – Re-estimation of drug acquisition and administration costs
- EA2 – Correction of errors surrounding follow-up costs
- EA3 – Use of ibrutinib pre-progression mortality rate from Study 1118E instead of general population mortality rates

Confidential

ERG's additional exploratory analyses
(based on ERG's amended base case)

EA#	Assumptions made	£/QALY gained
EA5	Assume BSC utility value to be 0.5 instead of 0.665	£63,340
EA6	Use of alternative HR of [redacted] for PFS from company's repeated analysis instead of [redacted]	£60,410
EA7	Assumption of equivalent pre-progression mortality for ibrutinib and rituximab/chemotherapy	£390,432
EA8	Use of alternative costs for rituximab/chemotherapy	£64,233
EA9	Use of the Weibull distribution for pre-progression mortality for rituximab/chemotherapy	£64,628
EA10	Threshold analysis around HR for PFS	£56,917* £59,620**

Abbreviations: BSC, Best supportive care; EA, exploratory analysis; QALY, quality adjusted life year; HR, hazard ratio; PFS , progression free survival

* the most favourable ICERs possible given any HR for PFS (using company's base case assumptions)

** the most favourable ICERs possible given any HR for PFS (using ERG's base case assumptions)

Innovation

- The company considers ibrutinib to be innovative because:
  - It is a first-in-class, oral, highly selective BTK inhibitor that offers a substantial step-change in the management of WM
  - It substantially addresses unmet need within the WM treatment pathway
  - There is currently no standard of care for the treatment of WM and no other drugs have been licensed or are recommended for this condition
  - In addition to being administered orally and as a monotherapy, ibrutinib offers the unique advantage of being specifically targeted at a common disease process in WM involving BTK

Potential equality issues

- WM is a disease of the elderly; however the current, most effective therapies are generally more suitable for young and fit patients as these treatments are toxic or immunosuppressive and therefore unsuitable for patients with a poor performance status and/or significant comorbidities

Company's CDF proposal

- The company requests the inclusion of ibrutinib on the CDF and sets out a proposed managed entry agreement including the collection of additional data as an add-on to an existing registry:
  - Longer term collection of PFS, OS and safety outcomes in newly-initiated ibrutinib patients with a minimum of 2-years data collection
  - Collection of HRQoL data in patients, and possibly, carers
  - Data on comparative effectiveness
  - Resource use and compliance data, including shifts from monitoring and management of AEs associated with infusion-based therapies to oral therapies
  - Data on first-line patients

- The ERG considers it unlikely that further data collection would lead to an improved ICER for ibrutinib

CDF entry criteria

To assess the suitability for entry to the CDF the following criteria must be met:

- ICERs presented have the plausible potential for satisfying the criteria for routine use, taking into account the application of the End of Life criteria where appropriate
- Clinical uncertainty can be addressed through collection of outcome data from patients treated in the NHS
- Data collected (including from research already underway) will be able to inform a subsequent update of the guidance.
  - This will normally happen within 24 months

Key issues for discussion

- The company's model does not cover patients who have not received prior therapy and in whom chemo-immunotherapy is unsuitable.
  - **Can any conclusions be drawn for this group of patients?**
- The ERG raised concerns about the structure of the company's model.
  - **What is the committee's view of the company's modelling approach?**
- The ERG considered that the difference in the pre-progression survival trajectories for ibrutinib and rituximab/chemotherapy is the key driver of cost-effectiveness.
  - **What is the committee's view on the modelling of pre-progression mortality?**
- No HRQoL data were collected in Study 1118E and no HRQoL studies in WM were identified.
  - **Is the use of EQ-5D data from a CLL study a reasonable approach?**

Key issues for discussion (2)

- The company's base case deterministic ICER for ibrutinib compared with physician's choice of treatment was £58,630 per QALY gained. In the ERG's amended analysis the probabilistic ICER was £61,219 per QALY gained. The other exploratory analyses did not produce markedly different ICERs, with the exception of the scenario in which the survival gain for ibrutinib was removed from the model; in this analysis the ICER was £390,432 per QALY gained.
  - **What is the committee's view of the ICERs estimated and their robustness?**
  - **Which assumptions does the committee consider to be most plausible?**
- **Does the committee consider ibrutinib to be an innovative therapy?**
- **Does the committee consider that CDF funding is appropriate?**