Lead team presentation
ID753: Ibrutinib for treating relapsed or refractory mantle cell lymphoma

1st Appraisal Committee meeting

Ellen Rule (Cost Effectiveness)

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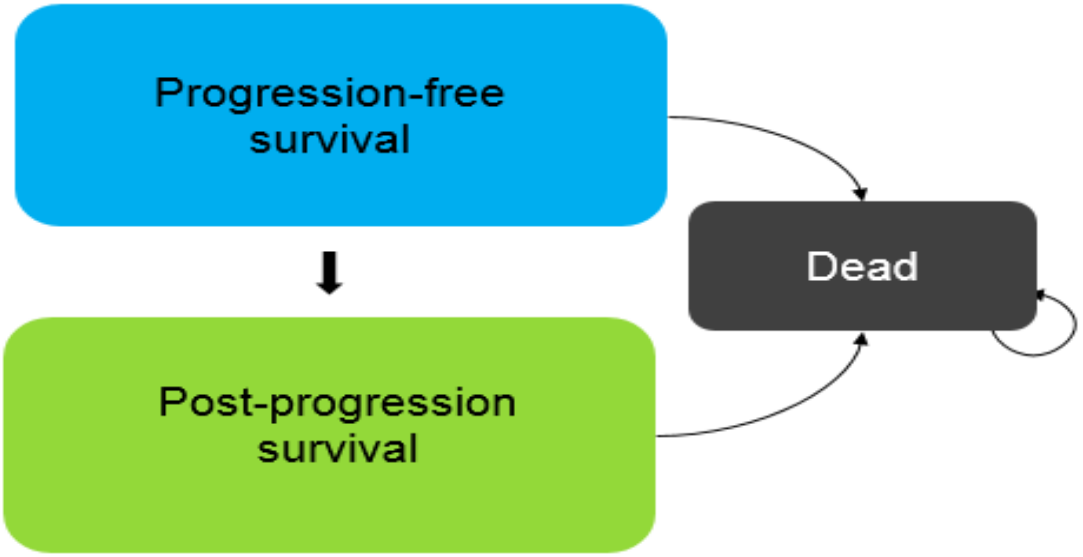
Committee A

ERG: School of Health and Related Research (ScHARR), The University of Sheffield

NICE technical team: Sana Khan, Zoe Charles

Slides for Public

Model Structure



Time horizon: 15 years
Cycle length: 4 weeks with half cycle correction
Costs and benefits discounted at 3.5%

Assumptions and clinical inputs

- Pooled dataset for RAY, SPARK and PCYC1104 used to inform efficacy of ibrutinib
- Progression free health state informed by progression free survival (PFS) curve based on parametric fitting of 4 distributions (exponential, Weibull, log-logistic and log-normal) to the patient level data from the pooled database for ibrutinib
- To model PFS, Weibull selected for the base case analysis based upon clinicians' feedback
- Pre-progression mortality and post-progression survival (PPS) were modelled using exponential distributions.
- Probability of being in the post-progression state was informed by the PFS curve less pre-progression mortality. PPS was then used to model survival in progressed patients
- Survival curves used to derive transition probabilities

Assumptions and clinical inputs

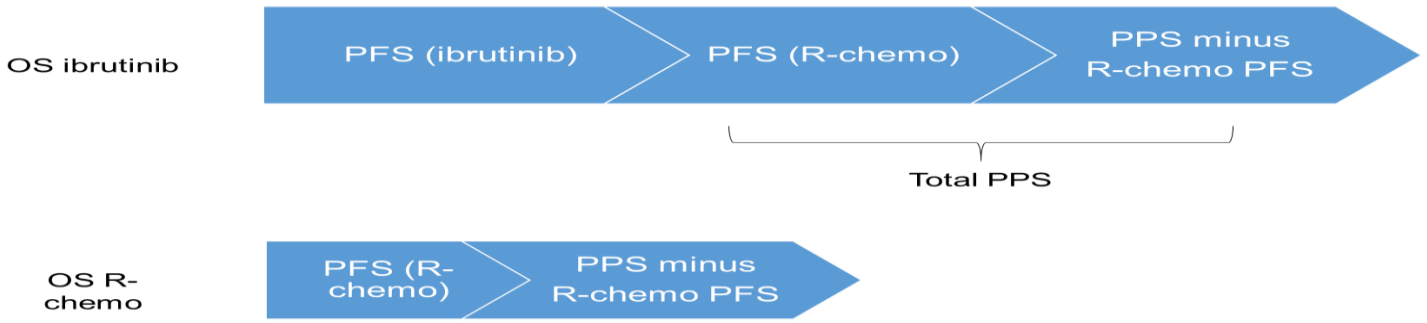
- Comparator: R-chemo (base case: R-CHOP; scenario analyses: R-CVP, FCR, RC and a blended comparison of all 4 options weighted according to expected usage; RC=0 in blend)
- Comparator efficacy obtained by applying a hazard ratio to the relevant parametric curve selected for PFS
- Equal effectiveness assumed for all rituximab containing regimens due to non-availability of efficacy data. Two approaches were tested to estimate effectiveness

Comparator efficacy estimation

	Scenario 1 (base case) OPTIMAL (Hess 2009) & RAY ITC	Scenario 2 Efficacy of temsirolimus
Approach	• ITC results using the 'Physician's choice' arm from OPTIMAL, and RAY. Results were adjusted for the expected impact of rituximab from HMRN data • PFS HR for ibrutinib versus R-chemo = 0.28	• Assuming R-chemo is equivalent to temsirolimus within RAY • PFS HR for ibrutinib versus R-chemo = 0.43
Strengths	• Provides a comparison to R-chemo • Use of a formal ITC maintains randomisation and provides a statistically robust comparison	• Uses information directly from the ibrutinib RCT undertaken in a R/R MCL population • Use of treatment effect from RAY provides a statistically robust comparison
Weaknesses	• Single chemotherapy agents do not reflect standard UK clinical practice • The HR for the rituximab treatment effect is based on a different population sample in newly diagnosed MCL (HMRN data)	• Temsirolimus is not a relevant comparator in UK clinical practice • No evidence is available to determine whether temsirolimus is more or less effective than R-chemo

Survival modelling

- Survival data from the trial were not directly extrapolated
- 2 methods used to estimate long term survival:
  - Fixed PPS approach (PFS + PPS applied same way in both arms) was used in the base case analysis. PPS calculated assuming a constant rate of mortality throughout the time horizon (10.83% per cycle). Median PPS in pooled dataset considered to be representative for R-chemo in UK clinical practice
  - Sequential approach used in secondary analysis (PFS of ibrutinib + PFS of R-chemo after ibrutinib + PPS).



Utility values

- Linear mixed model based on post baseline EQ-5D pooled data from RAY and SPARK to inform both PFS and PPS HRQoL
- Adjusted to account for natural decline in HRQoL associated with age

State	Utility value: mean (SE)	HRQoL per 28 days	95% CI	Reference in submission (section)	Justification
Pre-progression	0.78	0.060	0.762 – 0.799	Section 5.41	Pooled ibrutinib EQ-5D data from first treatment for R/R MCL
Post-progression	0.68	0.052	0.634 – 0.727	Section 5.41	
R-chemo decrement (to reflect toxicity)	0.2	0.015	0.1 - 0.3	Section 5.41	Clinician feedback

SE: standard error, HRQoL: health related quality of life, CI: confidence interval, R/R MCL: relapsed or refractory mantle cell lymphoma, R-chemo: rituximab plus chemotherapy

Resources and costs

- Drugs
  - Ibrutinib (simple PAS agreed with the Department of Health)
  - Comparator drug acquisition costs :eMit, MIMS
  - Comparator drug administration costs: NHS reference costs, Personal Social Services Research Unit 2015 (PSSRU)
  - R-chemo patients modelled to stay on treatment for the maximum number of cycles permitted for specific chemotherapy received and ibrutinib was administered until progression or unacceptable toxicity
- Resource use
  - Resource use based upon clinicians' feedback estimated using data generated via on-line survey completed by actively practising experts and outcomes validated by expert opinion from leading UK haematologists experienced in MCL.
- Adverse events
  - Incidence of adverse events derived from pooled dataset for ibrutinib and available literature for R-chemo. All grade 3 or higher AEs that occurred in at least 5% of patients treated with ibrutinib in the pooled data were included.
  - Clinically meaningful AEs occuring at lower rates with either ibrutinib or R-chemo were also included.
- Costs of subsequent therapy were not included in either arm except when modelling OS using the sequential approach for ibrutinib

Company model results

Scenario	Total cost	Inc. cost	Inc. QALY	ICER
Base case	XXXXXXX	XXXXXXX	**0.94**	XXXXXXXX
Comparator efficacy HR for PFS using temsirolimus data	XXXXXXX	XXXXXXX	0.82	XXXXXXX
Time horizon: 10 years	XXXXXXX	XXXXXXX	0.93	XXXXXXX
Time horizon: 20 years	XXXXXXX	XXXXXXX	0.94	XXXXXXX
Comparator: R-CVP	XXXXXXX	XXXXXXX	0.94	XXXXXXX
Comparator FCR	XXXXXXX	XXXXXXX	0.94	XXXXXXX
Comparator RC	XXXXXXX	XXXXXXX	0.94	XXXXXXX
Treatment mix	XXXXXXX	XXXXXXX	0.94	XXXXXXX
No wastage included	XXXXXXX	XXXXXXX	0.94	XXXXXXX
Utility decrement for R-chemo based on Schenkel *et al.* 2014	XXXXXXX	XXXXXXX	0.93	XXXXXXX
No age-adjusted utilities	XXXXXXX	XXXXXXX	0.95	XXXXXXX
Sequential approach (OS ibrutinib = PFS ibrutinib + PFS R-chemo + PPS)	XXXXXXX	XXXXXXX	1.08	XXXXXXX
Including FCR as subsequent treatment	XXXXXXX	XXXXXXX	0.94	XXXXXXX
Pre-progression mortality for R-chemo equal to ibrutinib	XXXXXXX	XXXXXXX	0.92	XXXXXXX

Company model results (2)

Scenario	Total cost	Inc. cost	Inc. QALY	ICER
Base case	**XXXXXXX**	**XXXXXXX**	**0.94**	**XXXXXXX**
Response rates of R-chemo equal to temsirolimus response	XXXXXXX	XXXXXXX	0.94	XXXXXXX
Response rates of R-chemo equal to response in Hess, 2009	XXXXXXX	XXXXXXX	0.94	XXXXXXX
Response rates of R-chemo equal to ibrutinib	XXXXXXX	XXXXXXX	0.94	XXXXXXX
No benefit from rituximab in PFS HR (rituximab HR = 1)	XXXXXXX	XXXXXXX	1.00	XXXXXXX
Rituximab PFS HR applied to Hess, 2009 ITC = 0.75	XXXXXXX	XXXXXXX	0.95	XXXXXXX
Rituximab PFS HR applied to Hess, 2009 ITC = 0.89	XXXXXXX	XXXXXXX	0.98	XXXXXXX
Rituximab PFS HR applied to Hess 2009 ITC = 1.6	XXXXXXX	XXXXXXX	1.05	XXXXXXX
Applying a HR to PPS of R-chemo to adjust survival to be as close as possible to HMRN anticipated survival (8.4 months for patients on 2nd line treatment)	XXXXXXX	XXXXXXX	1.87	XXXXXXX

Company model results - subgroups

Company presented subgroup analyses for ibrutinib compared with R-CHOP by number of prior lines of treatment (LOT):

- 1 prior LOT subgroup
  - incremental costs XXXXXXX ;incremental QALYs 1.67
  - **ICER** XXXXXXX per QALY gained

- 2 or more prior LOTs subgroup
  - incremental costs XXXXXXX; incremental QALYs 0.72
  - **ICER** XXXXXXX per QALY gained

Evidence Review Group (ERG) comments

- Concerns about company's model structure:
  - Use of PPS may introduce a selection bias if there is a true difference in survival outcomes between patients who progress earlier and those who progress later
  - Markov approach imposes structural constraints which can preclude the model from making the best use of available evidence
  - The PFS-based model makes a number of restrictive structural assumptions which lead to a poor model fit to the available OS data for ibrutinib
  - Company's model-predicted OS did not provide a good visual fit to the observed Kaplan-Meier OS curve, overestimating OS up to around 15.6 months and under-predicting OS beyond this time-point, suggesting that the survival gain in the ibrutinib group is likely to be underestimated

ERG comments

- Raised concerns about the company's parametric survival modelling, in particular the limited set of survivor functions considered for PFS and that the hazards of pre-progression mortality and PPS were assumed to be constant
- None of the fitted parametric survival curves provided a reasonable fit to the observed Kaplan-Meier curve for time to treatment discontinuation or death (TTD/D), and the tail of the TTD/D curve is uncertain
- Raised concerns about the reliability of the HRQoL estimates, including uncertainty surrounding progression-free (0.78) and post-progression (0.68) utility values, and issues with the duration of the disutility (0.20) associated with R-chemo. However, it acknowledged that these factors did not have a material impact on the ICER
- Acknowledged that there may be a disconnect between the EQ-5D evidence from RAY and clinical experience using ibrutinib
- Raised concerns about the validity of the company's sequential model which compared ibrutinib followed by R-chemo against R-chemo alone in a secondary analysis, and believed this analysis should be disregarded
- Concerned about the post hoc nature of the subgroup analyses and poor fit of the PFS survivor function to the 1 prior LOT subgroup
- The company's scenario analyses included the use of a blended comparison of 3 alternative R-chemo options which may lead to misleading conclusions on the cost-effectiveness of ibrutinib

ERG's exploratory analyses

- The ERG undertook 2 sets of exploratory analyses
- The first set ("Set A") involved amending the parameter values of the company's model
- The ERG's preferred analysis within Set A involved:
  - using the hazard ratio for PFS for ibrutinib versus R-CHOP from the ERG's random effects network meta-analysis
  - the use of the Kaplan-Meier curve instead of a parametric (Weibull) curve to model TTD/D for ibrutinib
  - the truncation of the R-chemo QALY loss upon treatment discontinuation

ERG's exploratory analyses 'Set A'

Scenario	Total cost	Inc. cost	Inc. QALY	ICER
Company's base case	XXXXXXX	XXXXXXX	0.94	XXXXXXX
Exploratory Analysis A1 - HR for PFS derived from ERG's random effects NMA	XXXXXXX	XXXXXXX	0.94	XXXXXXX
Exploratory Analysis A2 - TTD/D for ibrutinib group based on Kaplan-Meier curve	XXXXXXX	XXXXXXX	0.94	XXXXXXX
Exploratory analysis A3 - Truncation of R-chemo disutility following treatment discontinuation	XXXXXXX	XXXXXXX	0.91	XXXXXXX
Exploratory analysis A4 - ERG's preferred analysis using the company's model (combining amendments in analysis A1-A3)	XXXXXXX	XXXXXXX	0.92	XXXXXXX
Exploratory analysis A5 (based on the ERG's preferred analysis) – Use of alternative utility values for progression-free and post-progression states- (i) Utilities for progression-free and post-progression based on Lachaine et al.	XXXXXXX	XXXXXXX	0.95	XXXXXXX

ERG's exploratory analyses 'Set A'

Scenario	Total cost	Inc. cost	Inc. QALY	ICER
Exploratory analysis A5 – (based on the ERG's preferred analysis) – Use of alternative utility values for progression-free and post-progression states- (ii) Utilities for progression-free and post-progression based on Yoong et al.	XXXXXXX	XXXXXXX	0.96	XXXXXXX
Exploratory analysis A6 – (based on the ERG's preferred analysis) – Cost-effectiveness of ibrutinib versus chemotherapy for rituximab-resistant patients (i) Cost of rituximab set to zero	XXXXXXX	XXXXXXX	0.92	XXXXXXX
Exploratory analysis A6 – (based on the ERG's preferred analysis) – Cost-effectiveness of ibrutinib versus chemotherapy for rituximab-resistant patients (ii) Cost of rituximab set to zero and PFS HR=0.19	XXXXXXX	XXXXXXX	0.99	XXXXXXX
Exploratory Analysis A7: (based on the ERG's preferred analysis) – Ibrutinib versus R-CHOP in the 1 prior LOT subgroup	XXXXXXX	XXXXXXX	1.63	XXXXXXX

ERG's exploratory analyses 'Set B'

- The ERG's exploratory analyses "Set B" explored the impact of using a partitioned survival approach
- This approach not possible with company's model as OS data for ibrutinib not used as an input and involved amending the structure of company's model
- The ERG considered that this approach provided a better fit to the OS data for ibrutinib but involved using the outputs of a highly uncertain random effects network meta-analysis
- Based on the NMAs for PFS and OS, this analysis suggested ibrutintib was XXXXXXXXXXXXXXXXXXX
- The ERG estimated that, for the ICER to be below £50,000 per QALY gained, the hazard ratio for OS for ibrutinib compared with R-CHOP would need to be 0.39-0.40

ERG's exploratory analyses 'Set B'

Scenario	Total cost	Inc. cost	Inc. QALY	ICER
Exploratory analysis B1 – partitioned survival analysis using alternative NMA-derived hazard ratios for OS, probabilistic model- NMA – rituximab effect informed by Forstpointner et al	XXXXXXX	XXXXXXX	-1.28	XXXXXXX
Exploratory analysis B1 – partitioned survival analysis using alternative NMA-derived hazard ratios for OS, probabilistic model- NMA – rituximab effect informed by HMRN	XXXXXXX	XXXXXXX	-0.05	XXXXXXX
Exploratory analysis B1 – partitioned survival analysis using alternative NMA-derived hazard ratios for OS, probabilistic model- NMA rituximab effect informed by Forstpointner et al and HMRN	XXXXXXX	XXXXXXX	-0.31	XXXXXXX
Abbreviations: Inc., incremental; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio; NMA,network meta-analyses				

End of life criteria

- Short life expectancy, normally <24 months
  - UK data from the HMRN reveals median OS of 8.4 months in patients with R/R MCL.
  - Median OS of 9.7 months in patients receiving physician choice (PC) of treatment in OPTIMAL trial (Hess, 2009), comparing temsirolimus with PC
  - Median OS of 5.2 months in a real-world registry of patients treated at the Skåne University Hospital in Sweden between 2000 and 2012
  - The ERG agreed that using treatments currently available on the NHS, the expected OS for the R/R MCL population is typically less than 24 months.
- Extension to life, normally ≥3 months, compared with current NHS treatment
  - The pooled analysis of the RAY, SPARK and PCYC1004 trials found a median OS estimate of 25 months for patients receiving ibrutinib.
  - The ERG noted considerable uncertainty in the incremental survival benefit driven by the absence of a direct head-to-head trial against any relevant comparator, the immaturity of the OS data within the pooled ibrutinib dataset and the weaknesses in the studies included in the ERG's network meta-analyses of OS.

Potential equality issues

- Company considered that equality issues would be alleviated with the use of ibrutinib, such as restriction to certain chemotherapy agents known to be less active but better tolerated in older, frailer patients
- Lymphoma Association: “If the treatment is not approved for use on the NHS, then older people may be disadvantaged, as they will potentially have reduced access to effective treatments with reduced toxicity profiles, compared to younger people”
- Oral administration of ibrutinib allows an effective treatment option to be given to patients who may not have local access or transport to an appropriate infusion unit
- Are there any potential equality issues?

Innovation

- How innovative is ibrutinib 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?
- The company considered ibrutinib to be innovative because:
  - it offers the opportunity for daily dosing whilst minimising the duration of side effects
  - it addresses a significant unmet need within the MCL treatment pathway
  - the oral administration of ibrutinib reduces the patient, carer and NHS burden associated with current intravenous treatments

Key issues for consideration

- What is the committee's view of the company's model structure?
- What is the committee's view of the parametric survival modelling?
- What is the committee's view on the company's methods for modelling TTD/D?
- What is the committee's view of the HRQoL estimates used? Does the committee consider that HRQoL is adequately captured by the EQ-5D?
- The ERG expressed concern about the model-predicted overall survival results. What is the committee's view?
- What is the committee's view of the subgroup analyses?
- What is the committee's view of the ERG's exploratory analyses 'Set A' and 'Set B'?
- Which approach to modelling the cost-effectiveness of ibrutinib does the committee prefer? What is the committee's view on the most plausible ICER and the robustness of the estimates?