Ibrutinib for the treatment of relapsed or refractory mantle cell lymphoma (MCL)

Post consultation appraisal committee meeting

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Slides for Projector and Public

Preliminary recommendations

1.1 Ibrutinib is not recommended, within its marketing authorisation, for treating relapsed or refractory mantle cell lymphoma in adults

1.2 The committee would consider a proposal for inclusion in the Cancer Drugs Fund

ACD 2 conclusions: clinical effectiveness

- Efficacy trial data limited; no comparison against any current UK treatment
- Ibrutinib significantly improves progression-free survival (PFS, primary endpoint in RAY trial) compared with temsirolimus, but this is not used in UK
- Overall survival (OS) benefit uncertain due to immature data, crossover of 23% of patients in the temsirolimus arm to the ibrutinib arm, and the use of subsequent anticancer systemic therapies
- Appropriate to pool the results from the 3 ibrutinib studies: one vs. temsirolimus (RAY), others single arm
- Considerable uncertainty associated with the indirect comparisons: benefit of ibrutinib compared with rituximab in combination with chemotherapy (R-chemo) is unclear but evidence and experience from clinical practice strongly suggest that ibrutinib is more effective

ACD 2 conclusions: cost effectiveness

- Company's Markov approach, using PFS data from the pooled ibrutinib dataset to model OS not unreasonable
- The ERG's partitioned survival approach (exploratory analysis Set B, using OS data for ibrutinib from the trials rather than PFS), not considered clinically plausible: ibrutinib less effective than R-chemo
- Company's Markov approach led to more plausible results, acknowledging the considerable uncertainty associated with the results
- ICERs presented by the company for ibrutinib vs R-chemo were substantially above the range normally considered cost-effective (£62,650 in base case)
- Only one of the company's scenario analyses was below £50,000 - in the 1 prior therapy subgroup (£49,849) - method of modelling used for this subgroup was reasonable, but noted subgroup identified post hoc
- Minded not to accept the results of the ERG's adjustments to some of the parameter values in the company's model (exploratory analysis Set A) because these represented the extreme (lowest) end of the ERG's wide estimate of possible ICERs, depending on the model and parameters used

ACD 2 – other conclusions

- End of life criteria: Accepted
- Innovation: Accepted that ibrutinib has several advantages i.e. oral administration, low toxicity, manageable adverse reactions. Could be considered a step change in the management of relapsed or refractory mantle cell lymphoma
- Cancer Drugs Fund: Would consider a proposal for inclusion in the (new) CDF (Janssen has declined this invitation)

ACD 2 Consultation Comments

- Consultee comments from:
  - Janssen
  - National Cancer Research Institute – Advanced Care Planning – Royal College of Physicians – Royal College of Radiologists (NCRI-ACP-RCP-RCR)
  - Lymphoma association
  - Bloodwise

Company consultation comments

One-prior-line subgroup

- Janssen: requests that 1 prior line (1PL) subgroup of patients within the RR MCL population considered for baseline commissioning because:
  - Addresses the unmet need within RR MCL
  - Efficacy in this subgroup is supported by ongoing data collection
    - Additional data from RAY continue to support that earlier use of ibrutinib in the treatment pathway (1PL setting) is highly beneficial
  - Is a cost-effective option when PAS applied
  - Meets the end-of-life criteria
- ACD 2: Committee was concerned that the subgroups had been defined post hoc -> reluctant to draw any firm conclusions about the relative efficacy of ibrutinib in these groups

Ibrutinib in 1PL subgroup addresses unmet need within RR MCL

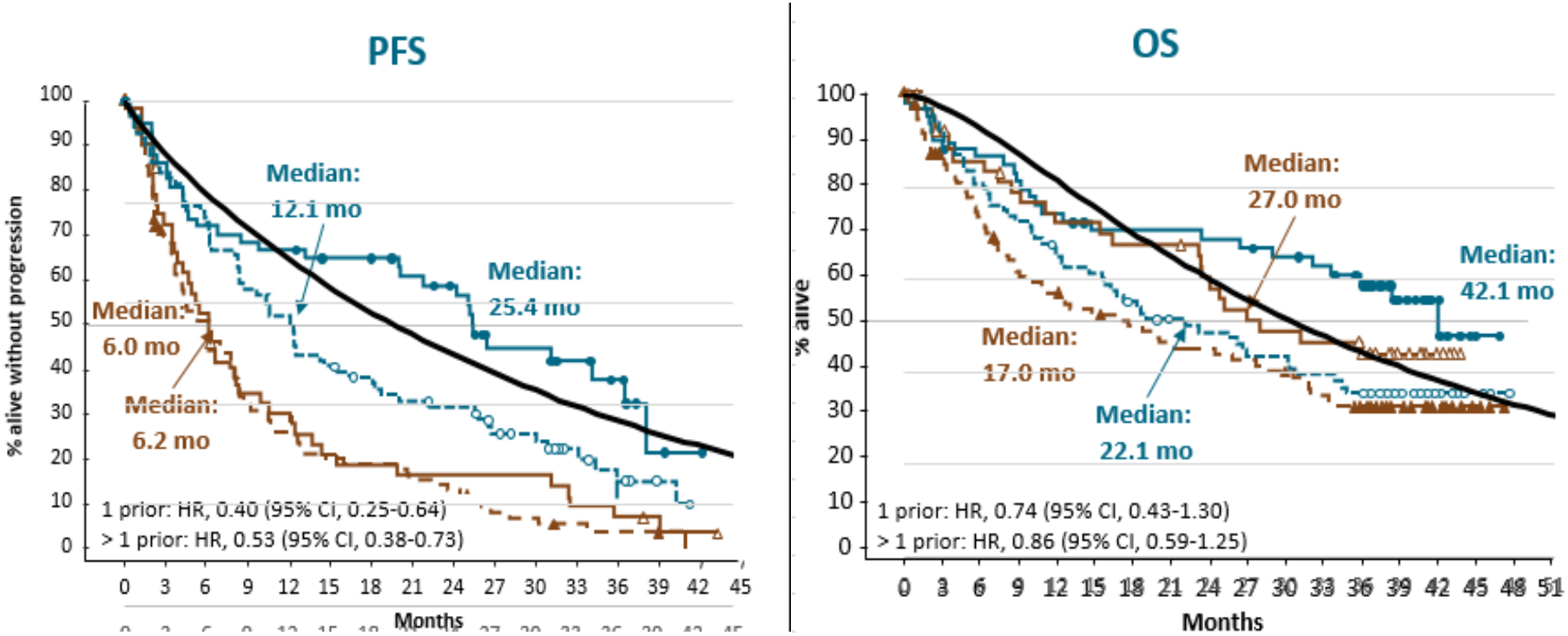
- Since ibrutinib has become available via the CDF, it has become the standard of care in England
- Data as of August 2017 show that ibrutinib had [redacted] uptake within the 1PL subgroup -> supports the clinically-driven relevance of positioning ibrutinib in the 1PL setting

Efficacy of ibrutinib in 1PL subgroup: further supportive evidence

- Updated data from RAY study
- Based on median follow-up of 39 months (vs. previously 20 months)
- Results: Crossover unadjusted median OS - ibrutinib vs. temsirolimus
  - 1PL subgroup:
    - 42.1 vs. 27.0 months
  - Overall RR MCL population:
    - 30.3 vs. 23.5 months
  - >1PL subgroup:
    - 22.1 vs. 17.0 months
- Limitation: Crossover of 39% of patients in the temsirolimus arm to the ibrutinib arm

Modelled vs. updated trial KM PFS and OS data

- 1PL data validate the current modelled results for ibrutinib



- Projected PFS for ibrutinib (solid black line) tracks very closely to the updated trial results (solid blue line)
- Projected OS for ibrutinib (solid black line) is notably conservative compared to the updated trial results (solid blue line): 31 vs 42.1 months

Cost-effectiveness in the 1PL subgroup

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Subgroup results with original PFS HR (0.28) and with a differential PPS HR based on HMRN data as presented in company submission							
Ibrutinib	£[redacted]	[redacted]	[redacted]	£93,196	2.64	1.87	**£49,849**
R-chemo	£[redacted]	[redacted]	[redacted]				

- Equivalent to the company's scenario analysis in which a HR was applied to PPS of R-chemo to adjust survival to be as close as possible to HMRN anticipated survival
- The ERG considered this analysis highly uncertain because:
  - The subgroup was defined *post-hoc*
  - The company's model does not provide a good fit to the observed PFS or OS data for the 1 prior LOT subgroup
  - Analysis assumes an additional survival advantage for patients in ibrutinib arm compared with R-chemo arm (slower rate of death) even after they have discontinued treatment. May be optimistic and is difficult to judge due to the presence of censoring and treatment switching in the trial data, and due to the poor fit of the model

ERG's estimate of cost effectiveness in the 1PL subgroup

- The ERG's original exploratory analysis in the 1 prior LOT subgroup produced a more favourable ICER than the company's analysis due to the use of observed Kaplan-Meier curves for time to treatment discontinuation/death rather than a parametric function
- Using the current PAS, this ERG exploratory analysis gives an ICER of £37,318 per QALY gained. This analysis assumes the same post-progression survival curve for both treatment groups
- It should be noted that the ACD states that:
  "…the committee was minded not to accept the results of the ERG's amendments because these represented the extreme (lowest) end of the ERG's wide estimate of possible ICERs, depending on the model and parameters used."

End-of-life criteria met

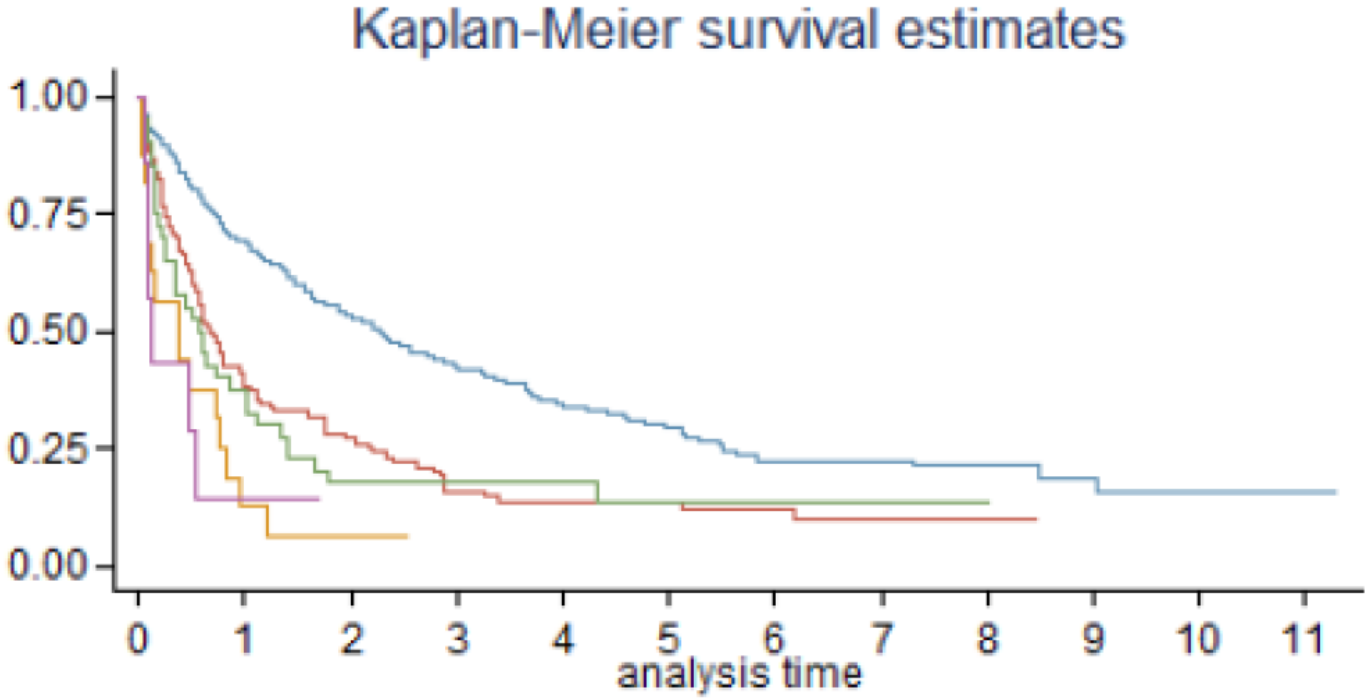
Committee agreed that ibrutinib met the criteria for the overall RR MCL population

- Indicated for people with a short life expectancy (estimates ranging from 5.2 months to 9.7 months)
- Enough evidence to indicate that ibrutinib offers an extension to life of at least an additional 3 months

Janssen: this remains applicable in the 1PL subgroup as evidenced by:

- The trial data and clinical opinion supporting the extension to life criterion (> 3 months)
- The later data-cut from the HMRN audit (August 2016) supporting a short life expectancy of less than 24 months

Overall Survival by Treatment Line, August 2016 updated HMRN audit



Number at risk

1st	262	175	124	89	58	43	25	18	10	6	3	1
2nd	112	42	27	15	11	9	5	4	2	0	0	0
3rd	41	15	7	4	4	2	1	1	1	0	0	0
4th	16	2	1	0	0	0	0	0	0	0	0	0
5th	7	1	0	0	0	0	0	0	0	0	0	0

1st 2nd 3rd 4th 5th

Post-hoc analyses

- ACD: The committee's main objection to the consideration of the 1PL subgroup data was because the subgroup had been defined post hoc

Janssen:

- Notes that post-hoc analyses have been used in the past to inform decision making by NICE Appraisal Committees, especially when they have found to have clinical relevance and the evidence base was strong

NCRI-ACP-RCP-RCR joint response

- Further analysis of the RAY trial with 3 years of follow up:
  - PFS remains strongly positive
  - OS still shows no significant difference between arms, however:
    - a quarter of patients remain on ibrutinib and there are no patients still receiving temsirolimus
    - 39% of patients have subsequently crossed over to ibrutinib
    - therefore, unlikely that longer follow up will lead to a significant OS advantage, however the hazard ratio is 0.74 (p=0.06)
- Study demonstrates a very strong correlation between when ibrutinib is given and its efficacy as defined by PFS and OS - earlier use is more beneficial

NCRI-ACP-RCP-RCR joint response (continued)

- Ibrutinib has transformed the treatment paradigm for MCL, it is highly active with modest side effects
- In addition to trial data, UK based unpublished population data (n>60) on the use of ibrutinib within an expanded access program appear identical to that seen within existing clinical trials of ibrutinib
- Can be given to patients with multiple co-morbidities

Lymphoma association

- Via its availability on the CDF, ibrutinib has become the standard of care for RR MCL
- Provides significant quality of life benefits being less toxic, better tolerated and administered orally and at home
- Non-availability of ibrutinib will have a detrimental impact on patients and their carers' lives
- Support differential pricing systems for treatments that work across different indications
- Encourage more flexibility in relation to methodology particularly in relation to the use of temsirolimus as the only licensed comparator and where there is no gold standard treatment

Web comment – Bloodwise

- Ibrutinib is regarded by patients as a step change in the way MCL is treated, significantly out-performing current treatments with no comparable treatments available
- Patients report a rapid reduction in symptoms, such as swelling, pain and fatigue, allowing many to return to their normal life very quickly
- Oral treatment that can be taken at home – particularly beneficial for patients with mobility issues or without access to transport who cannot easily get to hospital appointments
- The side effects are mild and generally only last for around a couple of weeks

Issues for consideration

- What is the committee's view on the company's request for considering 1PL subgroup for baseline commissioning?
- Does the committee agree that the end-of-life criteria remains applicable in the 1PL subgroup?