Lead team presentation Ibrutinib for treating relapsed or refractory mantle cell lymphoma - STA

1st Appraisal Committee meeting

Background & Clinical Effectiveness

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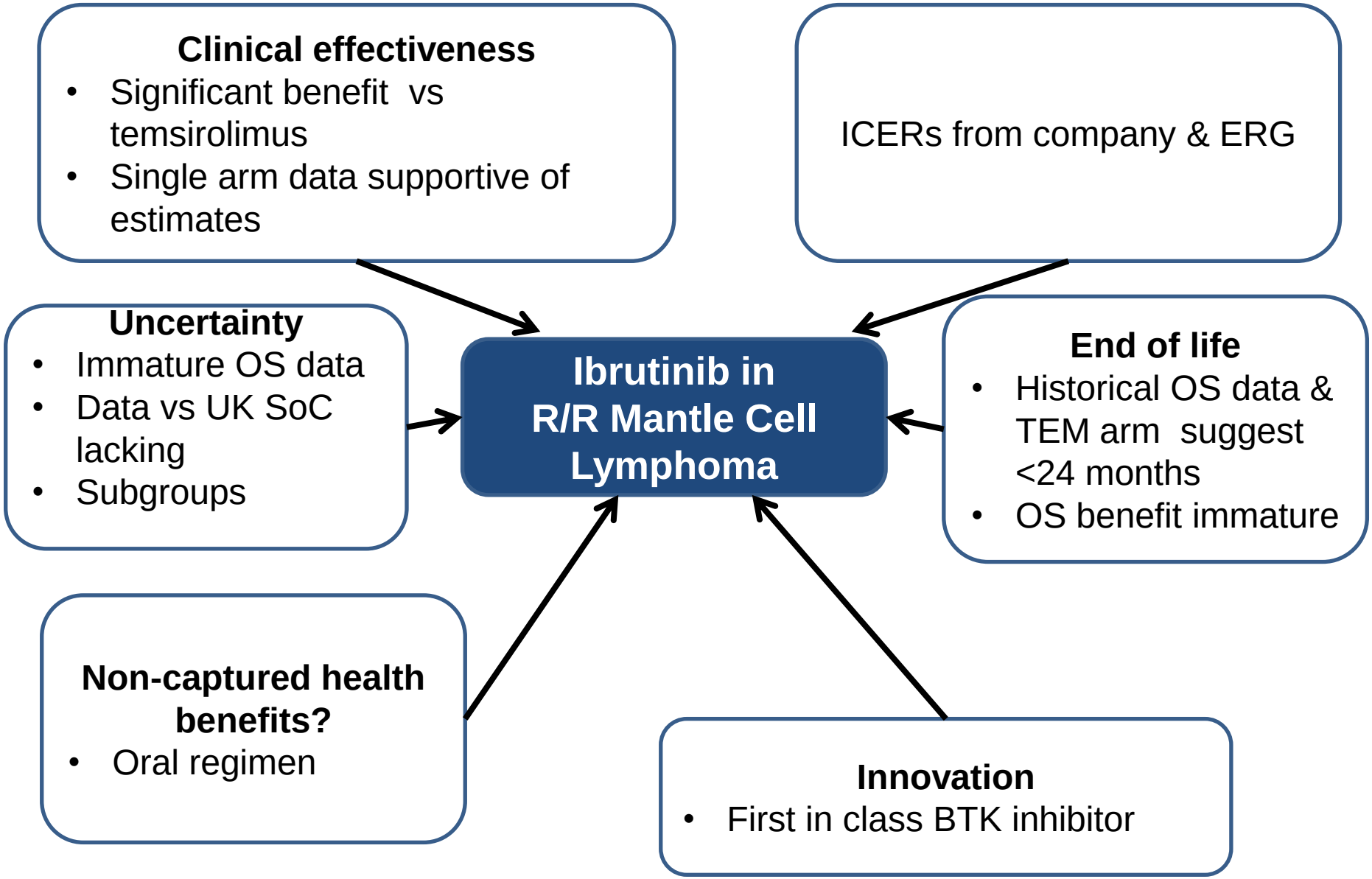
19/7/16

Slides for Public

Summary of evidence and key issues



Key questions for commitee

- Does the committee agree with the company that R-CHOP is the most relevant chemotherapy for R/R MCL? Is it reasonable for the company to assume that R-chemo regimens have equal efficacy?
- To what extent can temsirolimus be used as a proxy for UK current care?
- What is the committee's view of the quality of the 3 ibrutinib studies?
- What is the committee's view on the generalisability of the studies to the UK clinical setting?
- What is the committee's view of the pooled analyses?
- What is the committee's view of the indirect comparisons? Does the committee prefer the company's 2 stage approach or the ERG's single stage approach?
- What is the committee's view of the strength of the clinical evidence for ibrutinib:
  - For the overall population with R/R MCL
  - For subgroups e.g. number of prior lines of treatment, blastoid histology

Disease background

- Aggressive form of Non Hodgkin's Lymphoma (NHL)
- ~6% of all NHL – about 500 new cases each year in England of which ~370 will require therapy for refractory or relapsed disease
- Most people have advanced disease at diagnosis
- More common in men and older people (median 63 yrs)
- Involves lymph nodes & spleen, bone marrow but also extra nodal sites such as liver & gut
- Systemic symptoms such as fever, night sweats

Current management

- First-line treatment may include rituximab+chemotherapy and, if fit, stem cell transplant
- No uniformly accepted standard of care for relapsed or refractory mantle cell lymphoma (R/R MCL)
- May include:
  - Further attempt at Stem Cell Transplant
  - Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP)
  - Rituximab, cyclophosphamide, vincristine and prednisolone (R-CVP)
  - Fludarabine, cyclophosphamide and rituximab (FCR)
  - Rituximab and cytarabine (RC)
  - Temsirolimus (licensed)
  - Bortezumab (off label)
  - Lenolidamide (off label)

NICE guidance

- Draft clinical guideline (CG) - diagnosis and management of NHL
  - No clear recommendation for R/R MCL
- Temsirolimus for the treatment of relapsed or refractory mantle cell lymphoma (terminated appraisal) [TA207]
  - NICE is unable to recommend the use in the NHS of temsirolimus…..because no evidence submission was received from the manufacturer or sponsor of the technology
- Lymphoma (mantle cell, relapsed, refractory) - lenalidomide [ID739]
  - The company has indicated that they will not be making a submission for this appraisal. Consequently, NICE will suspend the appraisal whilst we consider the next steps

The Patients Perspective

Symptoms and impact:

- “Rubbery” lumps in neck, armpit, groin, stomach
- Frequent and persistent infections, fever, drenching night sweats, severe fatigue, itching, weight loss and pain in chest, abdomen, bones
- Symptoms develop quickly and are extremely debilitating, causing great anxiety
- Huge impact on quality of life
- Quality of life of carers, family and friends also reduced
- Frequent quick relapse after treatment

Treatment side effects

Very common treatment side effects may include:

- Infections such as pneumonia and urinary tract infections, blood and lymphatic disorders such as neutropenia, vascular disorders, gastrointestinal disorders, skin and tissue disorders, musculoskeletal disorders (Ibrutinib SmPC)
- Ibrutinib considered to have a manageable side-effects and a well-tolerated toxicity profile compared with current treatment options available on the NHS

The impact of side effects varies:

- Many patients are willing to endure increased or different side effects if treatment has improved efficacy. Some are unable to do so because of frailty, co-morbidities etc.
- Oral tablets are generally popular because they result in less travel/fewer hospital visits

What patients want

Earlier diagnosis and additional effective treatment options to:

- Extend progression-free survival
- Increase response rates
- Increase duration of response
- Extend treatment free interval
- Reduce side effects
- Improve quality of life
- Extend life

Treatment being appraised

- Ibrutinib (IMBRUVICA®) is indicated for the treatment of:
  - adult patients with R/R MCL
  - chronic lymphocytic leukaemia (first or subsequent therapy*)
  - Waldenström's macroglobulinaemia (first or subsequent therapy*)
- Method of administration and dosage
  - R/R MCL: Oral; 4 x 140 mg capsules (560 mg) once daily.
  - Taken until disease progression or the treatment is no longer tolerated by the patient.

*some details omitted for brevity

Mechanism of Action

- In MCL, mutation and overexpression of cyclin D1, a cell cycle gene, contributes to the abnormal proliferation of malignant B-cells
- The B-cell receptor pathway (BCR) plays an important role in normal B-cell regulation
- By irreversibly inhibiting BTK, ibrutinib disrupts the BCR signalling pathway, interfering with malignant B-cell survival and proliferation

Decision problem

	NICE scope	Company
Population	Adults with R/R MCL	As scope
Intervention	Ibrutinib	As scope
Comparator(s)	Established clinical management without ibrutinib, including: • R-CHOP • R-CVP • FCR • RC	As scope but no direct comparative data vs UK standard Company submission states that R-CHOP is the most widely used in R/R MCL
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • Overall response rate (ORR) • Duration of response (DOR) • Time to new anti-lymphoma treatment/time to progression • Adverse effects of treatment • HRQoL	As scope
Subgroups	Not specified	1 previous LOT >1 previous LOT

Clinical evidence

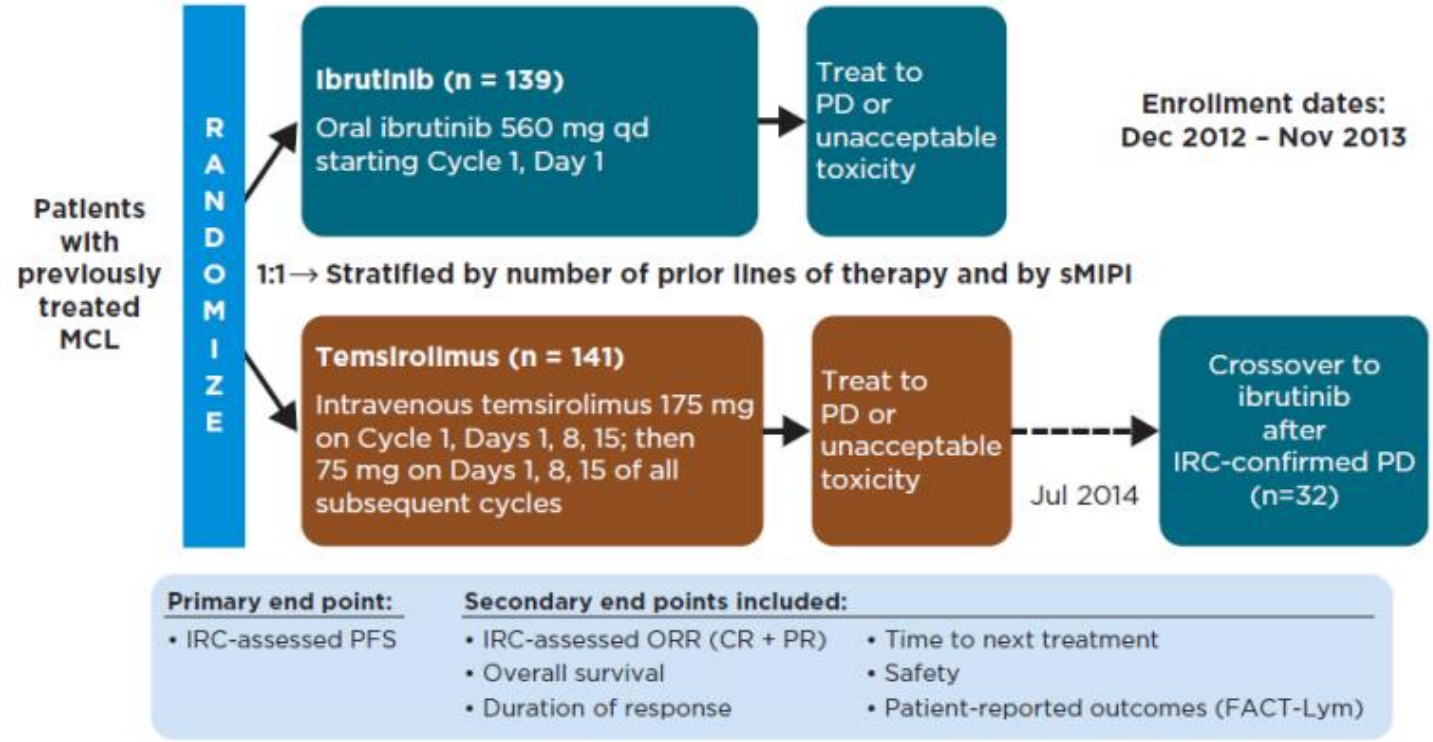
- **RAY Study phase III open label RCT vs temsirolimus**
  n=280 (n=139 ibrutinib); 27 patients from UK
  R/R MCL following R-chemo regimen
  Primary endpoint PFS
  Data cut of April 2015 with median follow-up of 20 months

- **PCYC1104 phase II single arm open label study**
  n=115 (n=110 ibrutinib); 21 patients from UK
  R/R MCL
  Primary endpoint ORR

- **SPARK Phase II single arm open label study**
  n=120; 6 patients from UK
  R/R MCL after R-chemo & bortezomib
  Primary endpoint ORR

Clinical evidence – RAY study

Figure 7: Study design of RAY (MCL3001)



Progression Free Survival

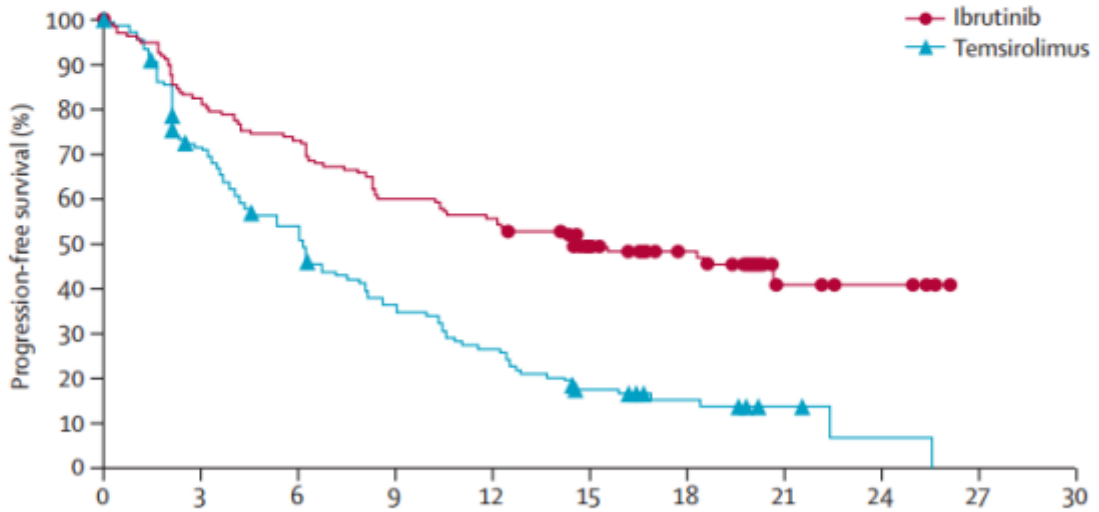
Table 19: Summary of primary analysis PFS results in RAY (MCL3001), ITT analysis set

	Ibrutinib (n=139)	TEM (n=141)
PFS rate at 2 years, %	41%	7%
Median (95% CI) PFS, months	14.6 (10.4; NE)	6.2 (4.2; 7.9)
HR (95% CI) ibrutinib versus TEM	0.43 (0.32; 0.58), p<0.0001	

ITT: intention-to-treat, CI: Confidence interval, HR: Hazard ratio, NE: Not estimable, PFS: Progression-free survival, TEM: temsirolimus

Source: Dreyling *et al.*, 2015[35] RAY (MCL3001)

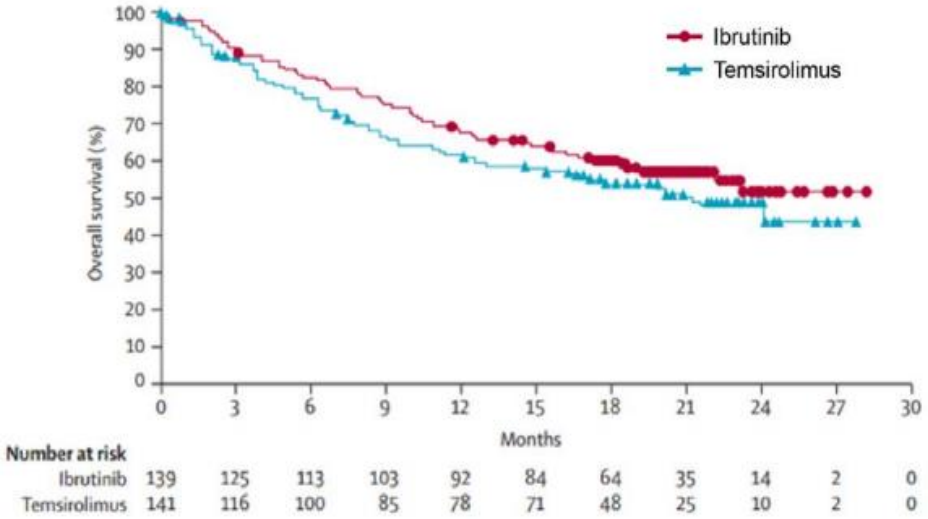
Figure 9: KM plot of PFS by IRC assessment in RAY (MCL3001); ITT analysis set



Source: Dreyling *et al.*, 2015[35]

Overall Response & Overall Survival

	Ibrutinib (n=139)	Temsirolimus (n=141)
ORR (CR & PR) n (%)	100 (71.9%)	57 (40.4%)
Difference	31.5% (20.5, 42.5) p<0.0001	
Odds Ratio	3.98 (2.38, 6.65)	
Median OS	Not reached	21.3 months
Odds Ratio @ 20 months f/up	0.76 (0.53, 1.09) p=0.13)	



Indirect comparison – step 2

- Takes the 0.19 PFS hazard ratio from step 1 (vs chemo)
- Estimates the additional benefit of adding rituximab to chemotherapy from HMRN* data set (hazard ratio 0.69)
- Estimates the hazard ratio of ibrutinib over R-chemo

  0.19 /0.69 = 0.28

- An alternative is to accept temsirolimus data are equivalent to UK practice and use results from RAY (PFS hazard ratio = 0.43)

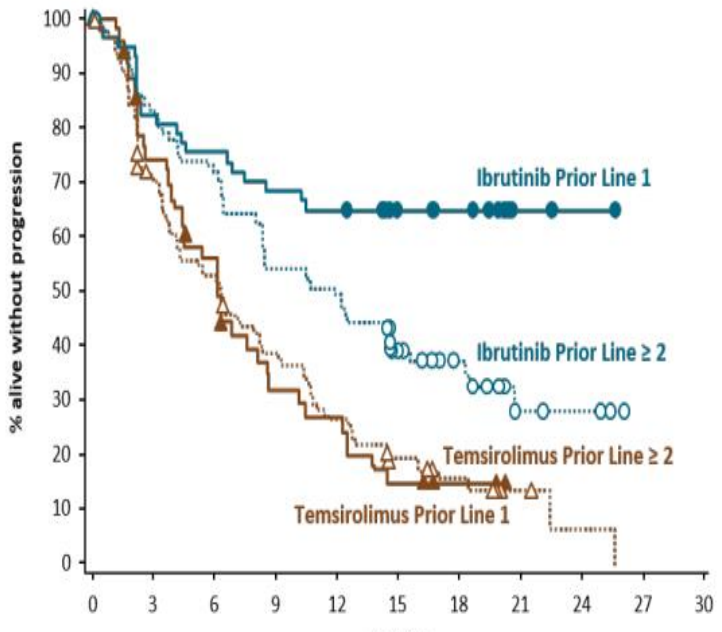
*Haematological Malignancy Research Network – First line use

Subgroup analyses

- Results of pre-planned subgroup analyses showed consistency with primary analysis across most subgroups
- Patients with blastoid histology derived no statistically significant benefit for PFS. Small population (n=33) a limitation, therefore results to be treated with caution
- Post-hoc analysis of PFS demonstrates benefit for patients receiving ibrutinib following 1 prior therapy, as opposed to 2 or more

Post hoc

Figure 15: KM plots for *post-hoc* subgroup analysis of PFS by number of prior LOTs in RAY (MCL3001)



Patients at risk

Ibr 1 prior	57	47	43	39	37	21	19	3	2	0	0
Tem 1 prior	50	33	24	13	11	6	4	0	0	0	0
Ibr ≥2 prior	82	67	58	44	40	24	15	5	3	0	0
Tem ≥2 prior	91	60	45	32	22	13	7	3	1	0	0

Source: Rule *et al.*, 2015[60]

Clinical evidence – Single Arm Studies

- PCYC1104 n=111 evaluable
  Primary endpoint: ORR
  Older, more heavily pre-treated population

- SPARK Study
  Primary endpoint ORR
  Previous treatment had to have included bortezomib

	PCYC1104 n=111	SPARK N=120
ORR	68%	62.7%
Median PFS	13.0 months	10.5 months
Median OS	22.5 months	Not evaluable

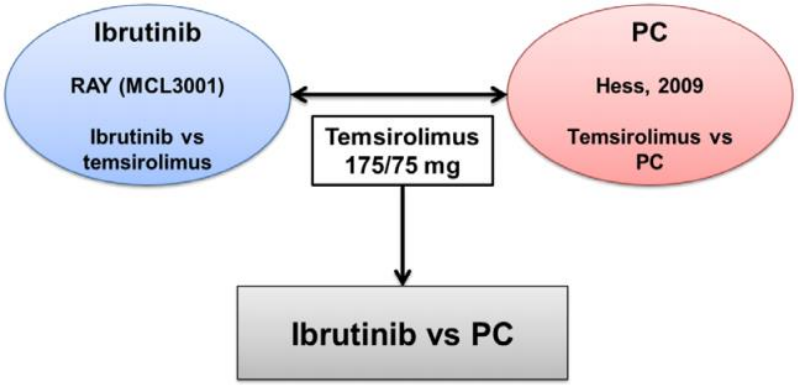
Clinical evidence – Pooled analysis

- Pooled analysis of RAY (n=139), PCYC1104 (n=111) & SPARK (n=120)
- Larger number of patients
- Longer duration of treatment
- Latest dataset shown here

Outcomes	Pooled analysis (n=370)
PFS (IRC)	12.8 months (8.48,16.56)
OS	25 months (21.59, NA)
ORR (IRC)	66%
Complete Response (IRC)	XXXX
Partial Response (IRC)	XXXX

Indirect comparison – step 1

- No direct comparisons with commonly used UK treatments
- One randomised trial of temsirolimus vs physician's choice of monotherapy chemotherapy
- Indirect comparison to compare ibrutinib vs physician's choice of monotherapy chemotherapy



	ORR	PFS	OS
Hazard Ratio	60.26 (7.07, 513.4)	0.19 (0.1,0.36)	0.61 (0.34, 1.1)

Adverse events

- Median duration treatment exposure 5-fold higher for ibrutinib compared with temsirolimus in RAY. However, overall incidence of treatment emergent adverse effects lower for ibrutinib
- 6.5% of patients discontinued treatment due to adverse effects in the ibrutinib arm compared with 25.5% in the temsirolimus arm
- Most frequently occurring grade 3 or higher adverse effects were:
  - neutropenia (ibrutinib: 12.9%, temsirolimus: 16.5%),
  - thrombocytopenia (ibrutinib: 9.4%, temsirolimus: 42.4%),
  - anaemia (ibrutinib: 7.9%, temsirolimus: 20.1%)
  - XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX.
- XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXX
- XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
- Non-randomised data from the 2 single arm ibrutinib studies followed a similar safety profile to RAY

Evidence Review Group's critique

- Relevance to NHS uncertain as comparators in both head to head and indirect comparisons not generally used in the NHS
- Open label studies BUT endpoints independently adjudicated
- Overall survival not adequately powered and may be confounded by crossover and by subsequent therapy choice
- Pooling of data acceptable given paucity of evidence for ibrutinib
- Indirect comparison: did not agree with company's 2 stage approach and proposed a single stage approach using a random effects network meta-analysis for estimating treatment effects for ibrutinib vs R-chemo (random effects HR = 0.27, 95% CI 0.06 to 1.26)
- Uncertainty in the indirect comparisons mean they need to be viewed with caution

Key issues for consideration

- Does the committee agree with the company that R-CHOP is the most widely used chemotherapy for R/R MCL? Is it reasonable for the company to assume that R-chemo regimens have equal efficacy?
- To what extent can temsirolimus be used as a proxy for UK current care?
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