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

1st Appraisal Committee meeting

Background & Clinical Effectiveness

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Background and decisions for committee

- There is limited evidence on the clinical effectiveness of ibrutinib for treating Waldenström's macroglobulinaemia (WM) – one single arm study
- Long disease trajectory - median overall survival ranges from less than 4 years to 12 years
- Company presented a base case ICER of £58,630 per QALY gained and has requested a recommendation for inclusion in the Cancer Drugs Fund (CDF)
  - Can ibrutinib be considered for routine commissioning?
  - Is it appropriate to recommend ibrutinib for inclusion in the CDF?

Key clinical effectiveness issues

- **What is the clinical need for this treatment?**
- The 1 ibrutinib study is a single arm, open label study of 63 patients who had received at least 1 prior therapy. The ERG considered the study to contain a high risk of bias

  What is the committee's view of the strength of the clinical evidence?
- Study 1118E was a US based study, and patients may have been younger with less severe disease than those who might routinely present in practice

  Are the results of Study 1118E generalisable to the UK clinical setting?
- No clinical evidence is presented on the effectiveness of ibrutinib in patients who have not received prior therapy and in whom chemo-immunotherapy is unsuitable

  Are the results from Study 1118E generalisable to patients who have not received prior therapy?
- The ERG had concerns regarding the company's indirect comparison

  What is the committee's view of the indirect comparison, and the estimated relative treatment effect?

Disease background

- WM is a type of non-Hodgkin's lymphoma. Lymphomas are cancers of the lymphatic system, which is a part of the immune system. It is caused by abnormal B cells which produce immunoglobulin M (IgM)
- IgM molecules are very large and can thicken the blood, reducing its flow through capillaries which can cause nerve damage in the hands and feet
- As the bone marrow can't make as many normal blood cells as usual, the key morbidities that patients experience are anaemia, neutropaenia and thrombocytopaenia
- Symptoms include severe fatigue, night sweats, vision loss, lack of concentration, frequent/persistent infections, breathlessness, sinus problems, and unexplained weight loss
- WM is incurable and develops slowly, most people have no symptoms in the early stages of the disease. As a result, most people are diagnosed in the advanced stages (approximately 25% of patients are asymptomatic at diagnosis)

Disease background (2)

- Approximately 330 people are diagnosed with WM in England annually
- It is more common in men and mainly affects people 70 years and older
- WM meets the European Medicines Agency prevalence criteria for rare disease
- The International Prognostic Staging System for WM is used to assess the likelihood of disease progression and to guide treatment. Patients can be classified as:
  - Low risk – with an estimated 142.5 months median survival
  - Intermediate risk – with an estimated 98.6 months median survival
  - High risk – with an estimated 43.5 months median survival
- Nearly half of people diagnosed with WM die from causes unrelated to WM

Current management

- No published NICE guidance relating to the diagnosis or treatment of WM
- Asymptomatic:
  - observation until it becomes symptomatic
- Symptomatic:
  - Number of treatment options (generally rituximab based) suggested in guidelines by:
    - British Committee for Standards in Haematology
    - European Society for Medical Oncology
- Choice dependent on the performance status, clinical features and comorbidities
  - No established standard of care for treating WM, and a high unmet need

Current management in clinical practice

Treatment options for patients who have received at least 1 prior therapy	**First line treatment options for patients unsuitable for chemo-immunotherapy**
• Rituximab and bendamustine	• Rituximab
• Cladribine with or without rituximab	• Chlorambucil
• Rituximab and fludarabine with or without cyclophosphamide	• Bortezomib (delisted from CDF in 2015)
• Rituximab and fludarabine	• Best supportive care
• Rituximab, dexamethasone and cyclophosphamide	
• Rituximab	
• Chlorambucil	
• Stem cell transplantation	
• Alemtuzumab	
• Bortezomib (delisted from CDF in 2015)	

Ibrutinib

Marketing authorisation

- Ibrutinib is indicated for the treatment of adult patients with WM
  - who have received at least one prior therapy, or
  - in first line treatment for patients unsuitable for chemo-immunotherapy (May 2015)
- Ibrutinib is also indicated for the treatment of:
  - adult patients with relapsed or refractory mantle cell lymphoma
  - adult patients with previously untreated chronic lymphocytic leukaemia (as a single agent)
  - adult patients with chromic lymphocytic leukaemia who have received at least one prior therapy

Ibrutinib (2)

Mode of administration	• Administered as an oral monotherapy
Dosage	• 3 x140 mg capsules once daily. • Administered until disease progression or until the treatment is no longer tolerated by the patient.
Mechanism of action	• Inhibitor of a protein called Bruton's tyrosine kinase, which stops B-cell (lymphocyte) proliferation and promotes cell death.
Cost	• £4,599 per pack of 90 capsules (£51.10 per capsule), list price (BNF, edition 67) • Cost per year of treatment £55,954.50 • Company has agreed a patient access scheme with the department of health. The agreement is commercial in confidence • Company is in discussions with NHSE about a managed entry agreement

The Patient's Perspective

- WM is a difficult condition to live with; an incurable condition with no targeted treatment
- Constant threat of relapse can put a huge burden on patients and carers
- Quality of life off treatment and the time between relapse is key
- Since the removal of bortezomib from the CDF there are limited treatment options
- Patients find many of the current treatment options far less acceptable than some clinicians suggest
- Side effects of current treatment are substantial and often permanent, tinnitus and digestive tract dysfunction
- Chemotherapy can be disruptive to patients and carers
- Survey found that important factors for patients were:
  - Bringing about a remission
  - Controlling the symptoms of the disease
  - Extension of life
  - Reducing the strain on carers

The Patient's Perspective (2)

Treatment being appraised:

- Patient want a treatment that is as well-tolerated as possible with the least detrimental impact on their quality of life
- Ibrutinib is a breakthrough therapy and meets an unmet need for WM treatments
- Ibrutinib is innovative as it is the first drug to specifically target the BTK cellular pathway
- Adverse effects of ibrutinib are more tolerable than alternative treatments
- Carers and patients appreciate that, as an oral treatment, ibrutinib can be easily administered
- Tolerability and convenience means that patients can have a good quality of life
- Patients are able to return to work
- Overwhelming desire from patients to see ibrutinib as a treatment option

Decision problem

Population in scope

- Adults with WM who have received at least one prior therapy
- Adults with WM who have not received prior therapy and for whom chemo-immunotherapy is unsuitable

Company states that the population is in line with the NICE scope but no data has been provided for the second group

Intervention in scope

- Ibrutinib

Comparators in scope

- For adults with WM who have received at least one prior therapy:
  - Rituximab and bendamustine
  - Rituximab, dexamethasone and cyclophosphamide
  - Rituximab and fludarabine with or without cyclophosphamide
  - Cladribine with or without rituximab
  - Rituximab
  - Chlorambucil

Company has combined the comparators into a 'physicians choice', comprising a blend of the above options based on clinical opinion

Decision problem (2)

Comparators in scope cont.

- For adults with WM who have not received prior therapy and for whom chemoimmunotherapy is not suitable:
  - chlorambucil
  - rituximab
  - best supportive care (BSC)

  Company states that the decision problem is in line with the NICE scope <u>but no data has been provided for this subgroup</u>

Outcomes in scope

- Overall survival (OS)
- Progression free survival (PFS)
- Response rate
- Duration of response / remission
- Adverse effects (AEs) of treatment
- Health-related quality of life (HRQoL)

  Company states that the decision problem is in line with the NICE scope

Clinical effectiveness

- One single-arm study of ibrutinib identified - Study PCYC-1118E
  - 63 adult patients with WM who had at least 1 prior therapy

Study PCYC-1118E characteristics	
Location	United States
Trial design	Open label, multicentre, phase 2 trial (non-randomised)
Trial drugs	Ibrutinib 420 mg daily for 26 four-week cycles Treatment continued until the disease progressed or unacceptable AE Patients without disease progression could continue beyond 26 cycles

Primary outcomes	• Overall response rate (≥25% reduction in serum IgM levels) including:
	  ○ Minor response rate (≥25% reduction in serum IgM levels)
	  ○ Partial response rate(≥50% reduction in serum IgM levels)
	  ○ Very good partial response rate (≥90% reduction in serum IgM levels)
	• Complete response, major response rate (≥50% reduction in serum IgM levels)

Secondary outcomes	• Progression free survival • Safety and tolerability

Table 12, Company submission

Summary of results from PCYC-1118E

Overall response rate	90.5% (95% CI: 80.4 – 96.4)
Major response rate	73.0% (95% CI: 60.3 – 83.4)
Progression free survival (PFS)	Median PFS has not been reached. At 24 months, the estimated rate of PFS was 69.1% (95% CI: 53.2 – 80.5)
Overall survival (OS)	Median OS has not been reached. At 24 months, the estimated rate of OS was 95.2% (95% CI: 86.0 – 98.4)
Duration of response	Not reached

Table 15, Company submission

Progression free survival

Kaplan-Meier curve of PFS in Study 1118E

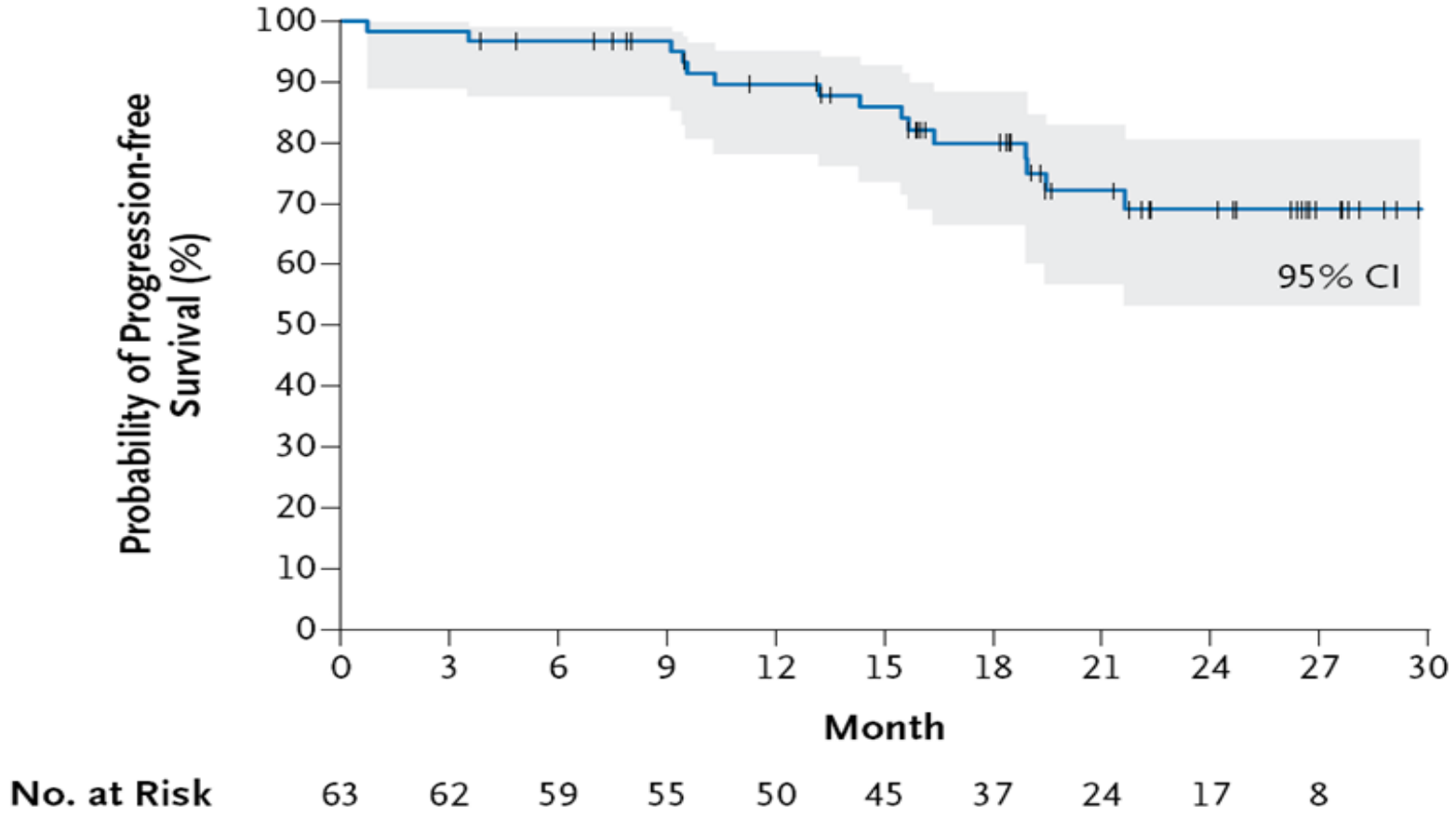


Figure 11, Company submission

Progression free survival across WM studies

Naïve unadjusted comparison of PFS in patients with WM from Study 1118E and selected trials of other monotherapies in previously treated and treatment-naïve WM populations

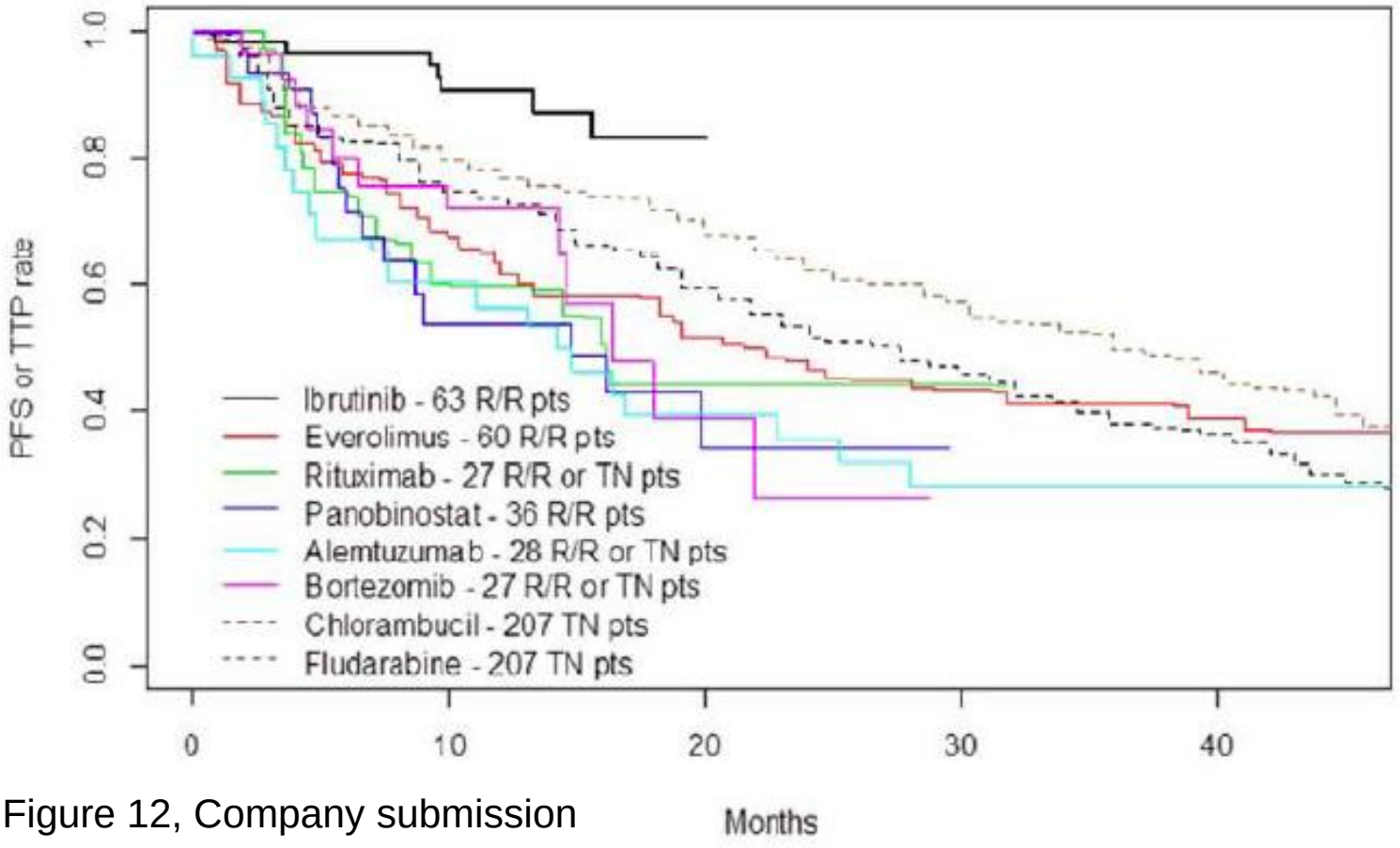


Figure 12, Company submission

Indirect comparison

- Given the absence of randomised head-to-head evidence comparing ibrutinib with any other WM treatment, the company presented an indirect comparison
- This estimated the hazard ratio for PFS for ibrutinib versus standard therapies
- Patient-level efficacy data from the pan-European chart review study were used

Indirect comparison: Pan-European chart review study

- A retrospective observational study based on the chart review of WM patients
- Conducted in collaboration with the European Consortium for Waldenström's Macroglobulinemia (ECWM)
- Generated data on epidemiologic/treatment patterns and efficacy outcomes for WM over 10 years
- Data from treatment-naïve and relapsed WM patient records across 10 European countries (including the UK) were gathered by survey from December 2014 to January 2015
- Included patients, n=454; UK patients, n=72
- Physicians completed a retrospective electronic record for patients
- Key study endpoints included:
  - Initial/subsequent lines of treatment
  - PFS
  - OS

Indirect comparison: Pan-European chart review study (2)

- Choice of therapy varied with line of treatment
- Across all lines, rituximab followed by cyclophosphamide, and to a lesser extent, chlorambucil, fludarabine, vincristine, and bendamustine, were the most common agents (excluding steroids) that were used as monotherapy or in combination.
- Use varied between countries

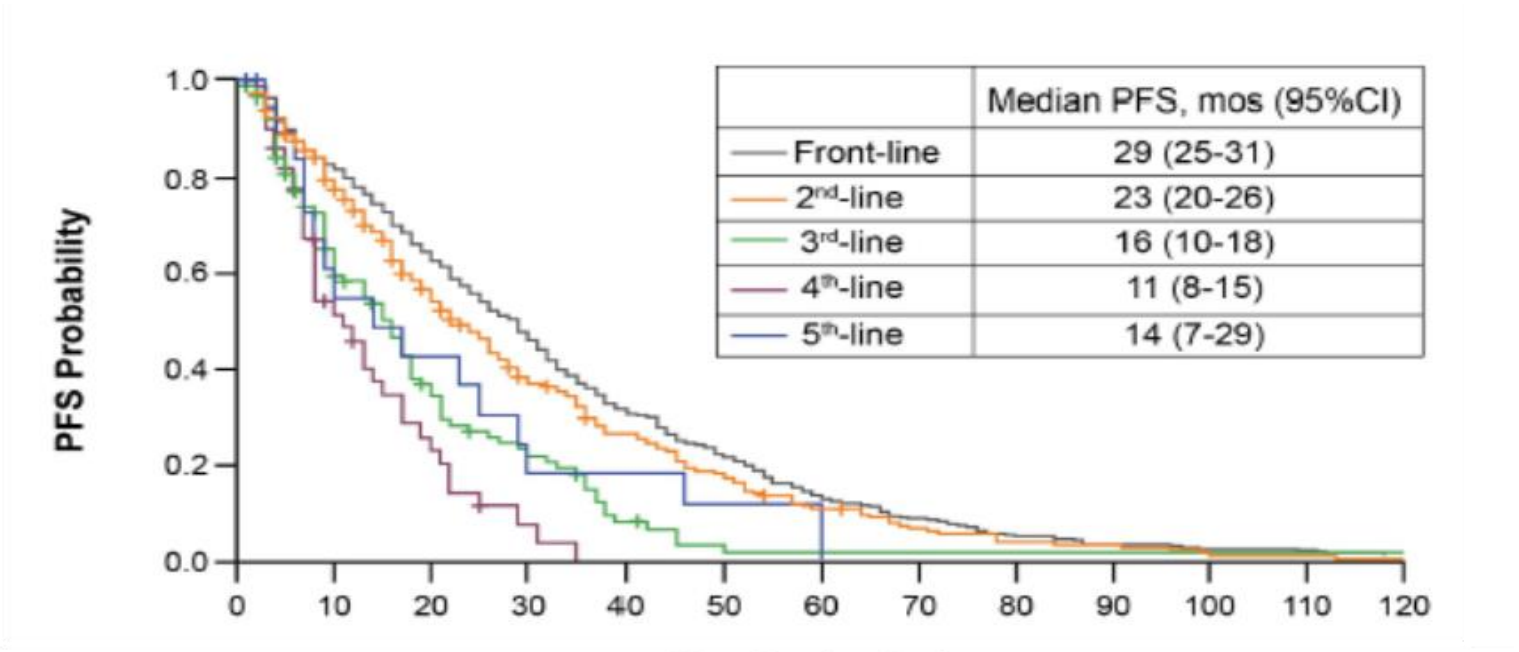
Median PFS in 1L, 2L and 3L settings EU-overall and by country

Country	Number of cases	Median PFS, months (95% CI)		
		1L	2L	3L
EU-overall	454	29 (25-31)	23 (20-26)	16 (10-18)
UK	72	32 (25-36)	20 (11-35)	13 (9-33)

Table 19, Company submission

Indirect comparison: Pan-European chart review study (3)

Kaplan-Meier PFS estimates by line of treatment



	Median PFS, mos (95%CI)
Front-line	29 (25-31)
2nd-line	23 (20-26)
3rd-line	16 (10-18)
4th-line	11 (8-15)
5th-line	14 (7-29)

Number at risk													
Front-line	454	376	293	218	145	101	63	40	25	16	12	11	6
2nd-line	387	189	118	76	51	35	20	12	7	6	3	12	1
3rd-line	160	58	30	18	6	2	1	1	1	1	1	1	1
4th-line	61	20	9	2	0	0	0	0	0	0	0	0	0
5th-line	26	10	7	4	3	2	2	0	0	0	0	0	0

Source: Figure 13, Company submission

Indirect comparison: Pan-European chart review study (4)

Comparing with Study 1118E

- A “matched” cohort was created by selecting a subset of the overall pan-European chart review cohort that had received similar prior lines of therapy as Study 1118E (175 of the 454 patients were selected)
- The analysis excluded patients from Study 1118E who had 5 or more prior lines of therapy because patients selected from the chart review had a maximum of 4 prior treatments (47 of the 63 patients from Study 1118E were therefore included)
- The company’s multivariable Cox proportional hazards model produced an estimated hazard ratio (HR) for PFS for ibrutinib versus standard therapies of [redacted]

Indirect comparison: Pan-European chart review study (5)

Figure 14: PFS curves of ibrutinib vs. matched chart review cohort

Figure 14, Company submission

Adverse events

- The company presented adverse events (AEs) based on Study 1118E and from other disease areas in which ibrutinib has a marketing authorisation
- AEs of any grade were very frequent in all trials, with almost all patients experiencing an AEs of any grade
- 51% f patients in Study 1118E experienced a grade 3/4 AE
- Diarrhoea, neutropenia, fatigue and nausea were the most common AEs experienced
- Of the 19% of patients who stopped treatment, 6% discontinued as a result of toxicity
- The CHMP considered that the overall safety profile in these subjects was consistent with the safety profile observed in subjects with other B-cell malignancies such CLL and MCL

ERG comments: Study 1118E

- Study 1118E is a well-reported single-arm study
- Includes patients with relapsed/refractory (R/R) WM only
- Patients enrolled into the study were not based in the UK, were generally younger and had less severe disease than patients with R/R WM who might routinely present in practice in England
- High risk of bias due to the absence of a control group
- High risk of selection bias because of the absence of randomisation
- High risk of performance and detection bias because of the absence of blinding
- Outcome measures were generally valid and reliable but the response criteria (the primary outcome) were “modified”
- Inadequate reporting of methods used to assess response (including whether response was assessed by investigator or independent central committee)

ERG comments: indirect comparison

Acknowledges the absence of RCTs in this patient population and that a conventional network meta-analysis is not possible, but noted a number of concerns with the company's approach:

1. The indirect comparison method may not adjust for all potential confounders
   - There was considerable variation in PFS between the countries included in the European chart review. The matching process was based on matching the number of lines of therapy received by the cohort to Study 1118E and the multivariable Cox model does not include line of treatment as a factor. The ERG considered that other confounders may remain and that not all sources of uncertainty have been considered
2. The matched cohort
   - The methods used to select patients in the European chart review cohort are not clear. The criteria applied does not define a unique sample of patients, and sensitivity analysis from an alternative match cohort produced an hazard ratio of [redacted]. Raises concerns regarding the reliability of the estimated treatment effect

ERG comments: indirect comparison (2)

3. Different definitions of disease progression were used in Study 1118E and the European chart review. Impact on estimated treatment effect is unclear
4. Analysis excluded the 16 patients in Study 1118E who received 5 or more lines of treatment
5. Proportional hazards assumption
   - Company's Cox model assumes that the PFS hazard in the ibrutinib group is proportional to that in the matched European chart review cohort
   - Company stated that all statistical tests visual inspections showed that the proportionality assumption should not be rejected
   - ERG notes that an absence of evidence against the proportionality assumption is not the same as evidence to support it. A consequence of making this assumption is to assume that the treatment effect is maintained for the lifetime of patients
6. Treatment effect estimated only for PFS
   - Unclear whether the company's approach could have been used to estimate the relative benefits of ibrutinib versus standard therapies on OS

Key clinical effectiveness issues

- **What is the clinical need for this treatment?**
- The 1 ibrutinib study is a single arm, open label study of 63 patients who had received at least 1 prior therapy. The ERG considered the study to contain a high risk of bias

  What is the committee's view of the strength of the clinical evidence?
- Study 1118E was a US based study, and patients may have been younger with less severe disease than those who might routinely present in practice

  Are the results of Study 1118E generalisable to the UK clinical setting?
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