NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ibrutinib for treating Waldenström's macroglobulinaemia [ID884]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ibrutinib for treating Waldenström's macroglobulinaemia [ID884]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Contains AIC, CIC

Pre-meeting briefing
Ibrutinib for treating Waldenstrom's Macroglobulinaemia [ID884]

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting.

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 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?

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Further detail and discussion on the company's CDF proposal can be found in the company submission page 19

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
- Symptoms include severe fatigue, night sweats, lack of concentration, frequent/persistent infections, breathlessness, sinus problems, and unexplained weight loss
- WM 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)
- Approximately 330 people are diagnosed with WM in England annually
- It is more common in men and mainly affects people 70 years and older

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Further detail and discussion on the background can be found:

- Company submission pages 12 to 14 and 27 to 30
- ERG report pages 1 and 2

To note

- Recent studies have suggested that autoimmune and chronic inflammatory conditions may play an important role in the pathophysiology of WM
- Known risk factors for WM include the presence of pre-existing IgM monoclonal gammopathy of undetermined significance (MGUS), family history of WM or other B-cell malignancies, and immunological factors
- There is some evidence to suggest that individuals have a genetic predisposition to the disease
- Company submission page12

Disease background (2)

- 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

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Further detail and discussion on the background can be found:

- Company submission pages 12 to 14 and 27 to 30
- ERG report pages 1 and 2

To note

- WM is a rare disorder and accounts for about 1-2% of all non-Hodgkin lymphomas
- Due to the rarity of the condition, data on the incidence and prevalence are limited
- Despite being a malignancy associated with a relatively long survival at diagnosis (see slides above), WM remains an incurable disease with variability in outcomes

Company submission page 28

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

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Further detail and discussion on the current management of the condition can be found:

- Company submission pages 30 to 33
- ERG report pages 30 to 34

To note

- Treatment options currently used in WM were originally developed for other lymphoproliferative diseases including multiple myeloma and chronic lymphocytic leukaemia (CLL) and include both monotherapies and combination therapies such as:
  - orally administered alkylating agents (e.g., cyclophosphamide),
  - nucleoside analogues (cladribine or fludarabine) in monotherapy or in combination therapies,
  - rituximab monotherapy, or rituximab in combination with cyclophosphamide-based therapy,
  - bortezomib-based therapy, thalidomide, or bendamustine have also been investigated as treatment options

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)	

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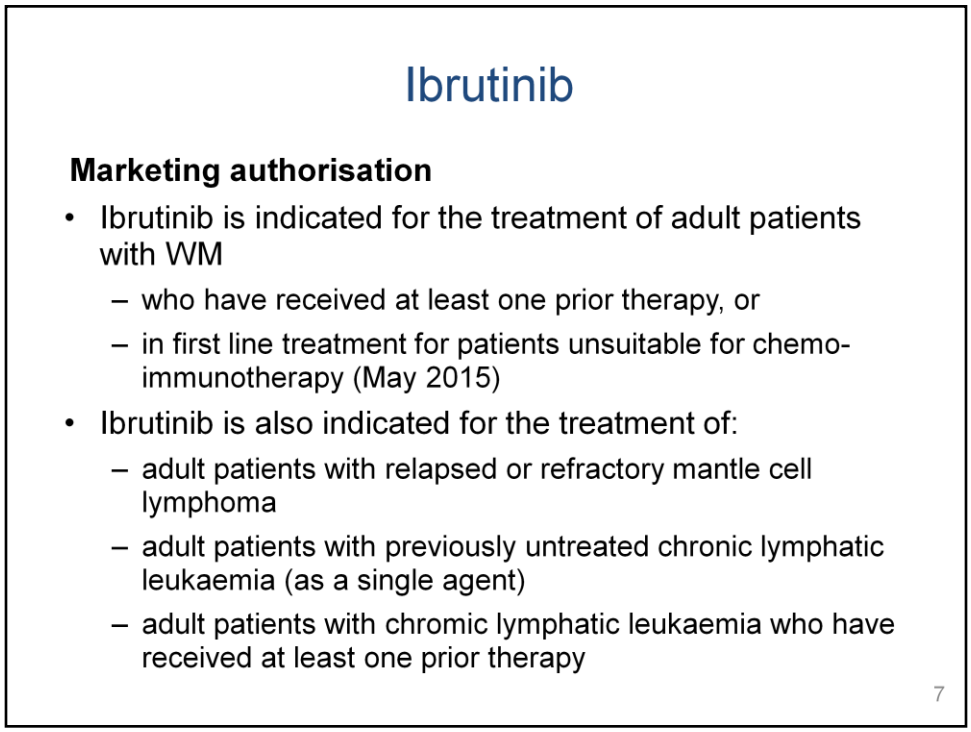
For consideration

- What proportion of patients are considered to be unfit for 1st line treatment with chemo-immunotherapy?
- What proportion of patients are eligible for stem cell transplantation?

Clinical guidelines

- Details on the BCSH guidelines are available pages 31 to 33 of the company submission and on the BCSH website at: http://www.bcshguidelines.com/documents/waldenstroms_151106.pdf
- Details on the ESMO guidelines are available pages 33 to 34 of the company submission and on the ESMO website at: https://annonc.oxfordjournals.org/content/24/suppl_6/vi155.full.pdf+html



Further detail ibrutinib can be found in the Company submission pages 20 to 26.

To note

There are two ongoing appraisal of ibrutinib:

- 'Ibrutinib for treating relapsed or refractory mantle cell lymphoma' [ID753} Expected date of publication January 2017
- 'Ibrutinib for treating chronic lymphocytic leukaemia' [ID749] Expected date of publication December 2016

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

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Please be aware the notes section contains AIC and CIC

To note

Company has agreed a patient access scheme with the department of health (simple discount of [redacted]). The agreement is commercial in confidence

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
- 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

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Comments from consultees

This section summaries comments from:

- Leukaemia CARE
- Waldenström's Macroglobulinaemia UK
- Bloodwise
- Lymphoma Association
- International Waldenström's Macroglobulinaemia Foundation
- Waldenström's Macroglobulinaemia UK Doctors Forum

Full details of the consultee comments can be found in the committee papers

The Patient's Perspective (2)

Treatment being appraised:

- 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 patient support to see ibrutinib as a treatment option

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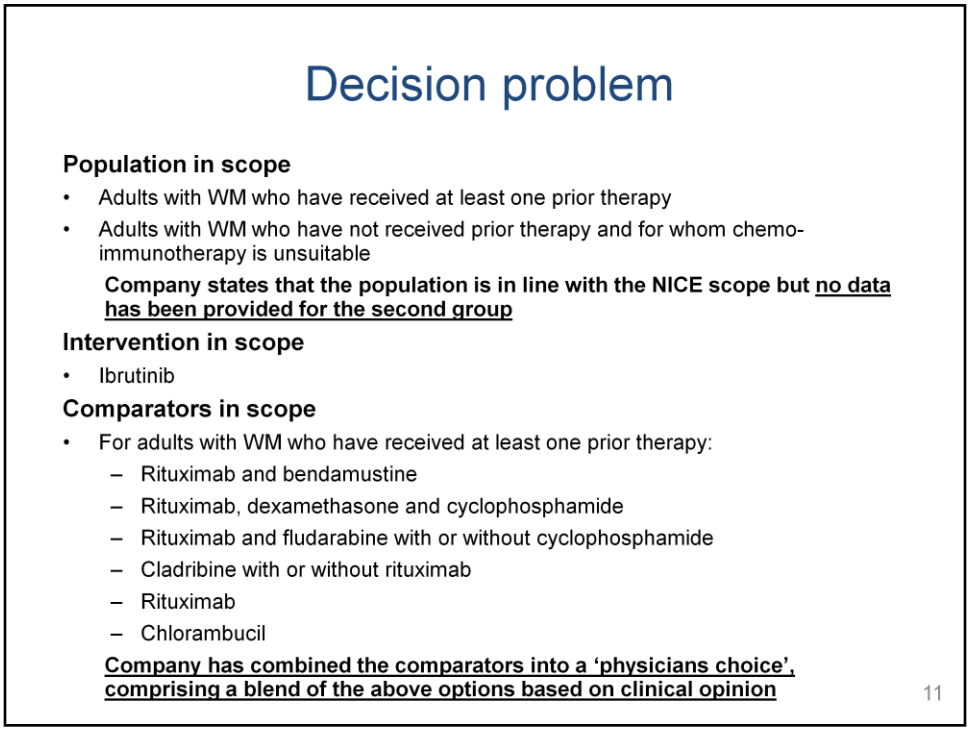

Further detail of the company's decision problem can be found:

- Company submission pages 10 and 11
- ERG report pages 7 to 13

ERG comments to note

- The CS does not contain any clinical or economic evidence for ibrutinib in adults with WM who have not received prior therapy and for whom chemo-immunotherapy is unsuitable
- The comparator are broadly in line with the final NICE scope, with the exceptions that rituximab and fludarabine (without cyclophosphamide) is not considered and chlorambucil is assumed to be given either in combination with rituximab or as monotherapy (rather than only as monotherapy).

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 but no data has been provided for this subgroup

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

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Clinical effectiveness

- No randomised-controlled trials identified
- One single-arm, open-label study of ibrutinib - Study PCYC-1118E
  - 63 adult patients with WM who had received at least one prior therapy
- No studies of ibrutinib in people with WM who have not received prior therapy and in whom chemo-immunotherapy is unsuitable

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- The company presents the clinical effectiveness evidence in chapter 4 of the company submission
- The ERG discusses the clinical effectiveness evidence in chapter 4 of the ERG report

Further detail on the clinical effectiveness literature search can be found:

- Company submission pages 35 to 40
- ERG report pages 14 to 20

PCYC-1118E study

Parameter	Description
Location	United States (n=63)
Trial design	Prospective, multicentre, phase 2 trial (non-randomised)
Trial drugs	Ibrutinib 420 mg (three 140-mg capsules) daily for 26 four-week cycles Treatment continued until the disease progressed or unacceptable toxic effects developed Patients without disease progression could provide a second informed consent and continue therapy 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

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Further detail on the PCYC-1118E study can be found in the Company submission pages 41 and 52

Summary of trial design of Study 1118E can be found in Table 12 of the company submission, page 42

Response definition

- The response outcomes, and their definitions, taken from the company submission and the original publications.
- With the exception of complete response, the definitions of response applied in Study 1118E appear to differ from the internationally recognised criteria.
- The IWWM criteria are not limited to serum IgM level only, but also include the presence or absence of clinically significant findings or symptoms.
- The ERG notes that IgM response alone is insufficient as an outcome for WM because clinical benefit might be seen in patients without IgM response, or IgM reduction alone might not result in an improvement of symptoms.

Further detail on the definitions can be found in Table 8 of the ERG report, page 24

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

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Results from PCYC-1118E are discussed in the:

- Company submission pages 59 to 61
- ERG report pages 29 to 38

To note

- Response data are based on the serum IgM level at the time of best response
- In terms of loss to follow-up, 20 of the 63 patients (32%) had discontinued treatment within the study period (maximum of 29.7 months) by the December 2014 DCO

ERG page 32

Progression free survival

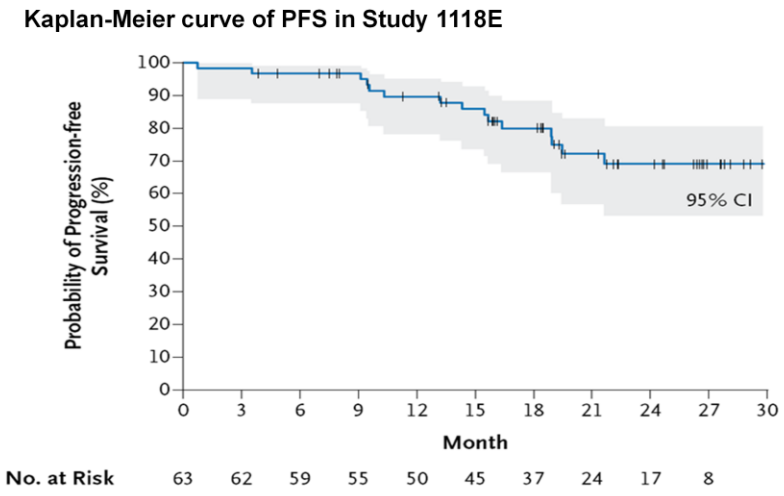

Figure 11, Company submission

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Results from PCYC-1118E are discussed in the:

- Company submission pages 59 to 61
- ERG report pages 29 to 38

To note

- By the end of data collection (December 2014), 60 of the 63 patients were still alive.
- The Kaplan-Meier curve for PFS show that at 24 months, the estimated rate of PFS was 69.1% (95% CI: 53.2%, 80.5%)

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

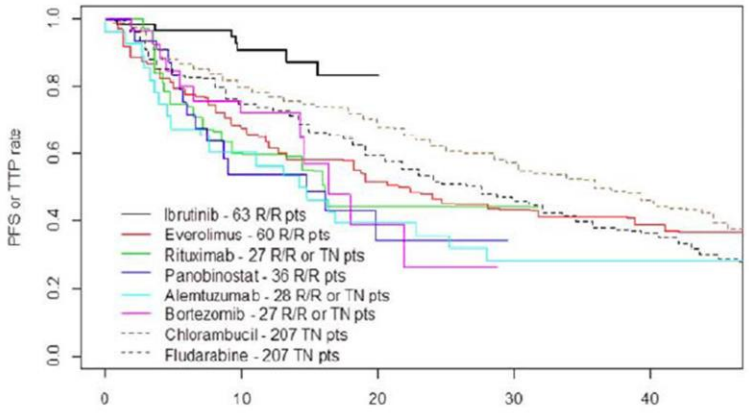

Figure 11, Company submission

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Further detail can be found:

- Company submission pages 51 to 52
- ERG report pages 20 and 21

To note

- Given the absence of comparative evidence for the second indication specified in the NICE scope, that is, first-line treatment for adult patients with WM for whom chemo-immunotherapy is unsuitable, the company submitted a figure which presents the results of a naïve unadjusted comparison of PFS outcomes (see above slide).
- This includes data from Study 1118E and selected trials of other monotherapies in previously treated and treatment-naïve WM populations.
- The company submission argues that this naïve comparison demonstrates how ibrutinib might perform relative to other treatments in the treatment-naïve subgroup specified in the final NICE scope.
- The ERG commented that no evidence was submitted to substantiate this claim, and it is unclear how the trial evidence presented in the figure was identified and selected (e.g. inclusion/exclusion criteria, definitions of PFS used).

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

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Further detail on the indirect comparison can be found in the Company submission pages 52 and 66

Inclusion criteria:

- WM diagnosis was confirmed according to International Workshop on WM (IWWM)-2 criteria;
- Patient was symptomatic when treatment was initiated;
- Diagnosis and initiation of therapy occurred between January 2000 and January 2014;
- Treated with ≥1 salvage regimen;
- Clinical and biochemical data (retrieved at the time of initial diagnosis and during treatment) included a minimum of:
    - baseline complete blood count; levels of β-2 microglobulin, serum albumin, IgM, serum monoclonal protein; immunofixation electrophoresis; and assessment of lymphadenopathy, splenomegaly, and bone marrow infiltration.

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

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To note

- A total of 454 patient records were reviewed and summarised across first-, second, third-, fourth and fifth line of treatment.
- Data were summarised across these five lines of treatment for 454, 397, 160, 61, and 26 patients, respectively.
- Patients were from France (n=92), the United Kingdom (UK; n=72), Germany (n=66), Spain (n=60), Italy (n=56), Greece (n=25), the Netherlands (n=25), Poland (n=21), Austria (n=19), and the Czech Republic (n=16).

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

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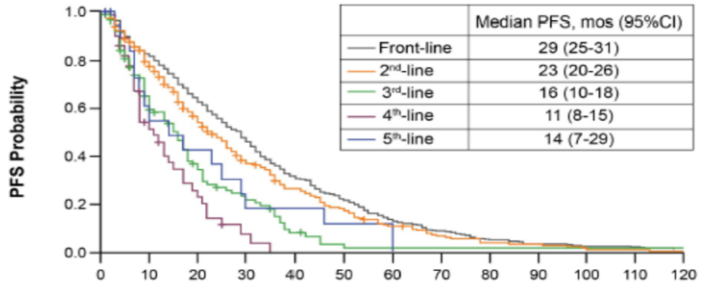
To note

- Median OS was 123 months,
    - but significantly lower in patients ≥75 years of age (75 months) or with high-risk International Prognostic Scoring System for WM (IPSSWM) risk score (91 months) and similar for patients with low/intermediate risk groups.
- Considerable country-specific OS differences were noted. Other malignancies were reported in 12% of the population after diagnosis of WM.

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

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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] (95% CI: [redacted])

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Please be aware the notes section contains AIC and CIC

Pan-European

- Each patient from the chart review was randomly sampled following two constraints: i) the same patient from the chart review was not allowed to be in two lines at the same time, and ii) the distribution across lines of therapy of the final subset of patients selected from the chart review matched the distribution of patients from Study 1118E as follows: [redacted] with 1 prior line, [redacted] with 2 prior lines, [redacted] with 3 prior lines and [redacted] with 4 prior lines.

Study 1118E

- Those that had 5 or more lines or prior therapy were excluded, therefore n=47

Patient characteristics

- Table 21 in the company submission provides the patient baseline characteristics: overall chart review matched, vs. Study 1118E vs. UK chart review cohorts

Sensitivity Analyses

- The company submission also presents two sensitivity analyses using the Cox model based on alternative imputation approaches: (i) no imputation (n=89), and; (ii) imputation, no individual clinical measurement. These two sensitivity analyses produced slightly more favourable HRs of [redacted] and [redacted].

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

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

Figure 14, Company submission

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To note

- The Kaplan-Meier estimates from the subset of 47 patients from Study 1118E who had received less than five prior lines of therapy and from the 175 matched European chart review cohort (presented in the above figure).

Adverse events

- The company presented adverse events based on Study 1118E and from other disease areas in which ibrutinib has a marketing authorisation
- Study 1118E indicates that ibrutinib is generally well tolerated in the treatment of WM patients
- The majority of adverse events were mild to moderate, easily manageable, with [redacted] of patients having grade 3/4 adverse events
- 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

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Further detail on the adverse events can be found:

Company submission pages 61 and 66

To note

- The company's model includes common grade 3/4 AEs which occurred in ≥5% of patients
- No adverse events data was presented from the European chart review

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)

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Further details can be found in the ERG report: pages 26, 27, 43 and 62

Modified response criteria

- The ERG considered the outcome measures used were generally valid and reliable.
- However, with the exception of complete response, the definitions of minor, partial very good partial response applied in Study 1118E, appear to differ from internationally recognised response criteria.
- International standards require the presence or absence of clinically significant findings or symptoms, not just serum IgM levels, as used in Study 1118E
- The ERG notes because clinical benefit might be seen in patients without IgM response, or IgM reduction might not see an improvement of symptoms.

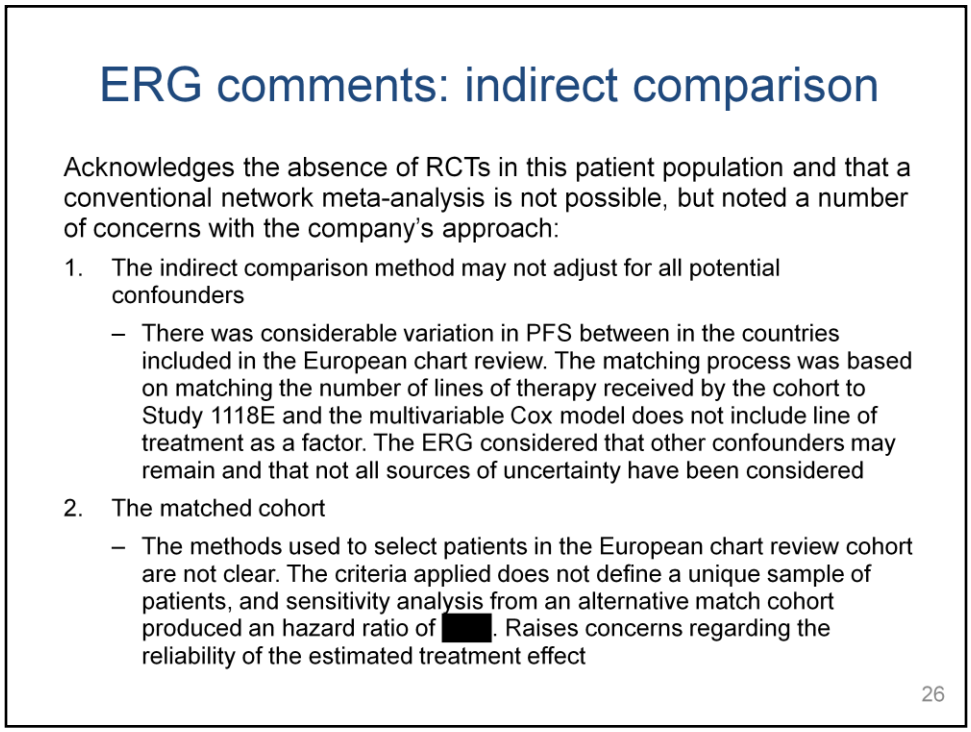
ERG report page 62

Inadequate reporting

- The ERG noted that inadequate reporting could be an issue because the methods that were used to measure outcomes were not specified
- Different methods of assessment for response can produce different values and the assessments must be conducted in a single laboratory.

- The company did acknowledged that, *"the phase 2 non-comparative nature of the study may not meet the rigour of evidence generally expected"* (Company submission, page 66).

ERG report page 43



Further details can be found in the ERG report: page 44

To note

- Progression in the chart review was defined as: *"25% increase in serum IgM from lowest nadir; progression or re-appearance of clinical features; progression or reappearance of hematopoietic insufficiency"* (Company Submission, Table 20, page 56).
- This was stated in the company submission to be comparable to the definition of progression in Study 1118E *"> 25% increase in serum IgM level occurs from the lowest attained response value or progression of clinically significant disease related symptom(s); based on the consensus panel criteria of IgM response."*
- The ERG noted that is unclear whether the differences between these definitions of progression between the two studies introduce bias into the indirect comparison.

ERG report page 41

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

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Further details can be found in the ERG report: pages 43 to 45

Key issues: clinical effectiveness

- The one 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?**

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Cost effectiveness evidence

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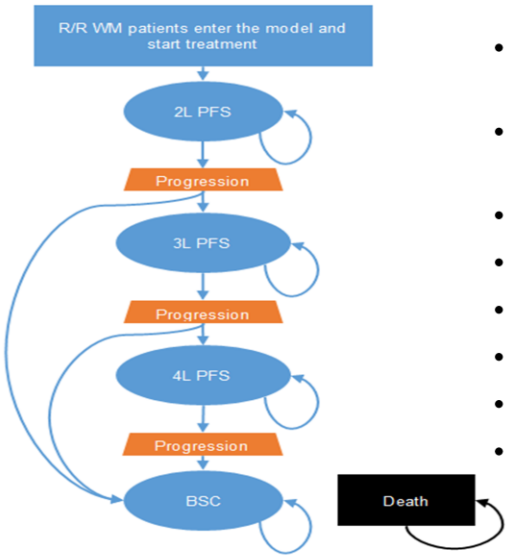
- The company presents the cost effectiveness evidence in chapter 5 of the company submission
- The ERG discusses the clinical effectiveness evidence in chapter 5 of the ERG report

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

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Further detail can be found in the company submission pages 74 to 80

To note

- Second line (2L) treatment: patients enter the model here and initiate either ibrutinib or the comparator, PC. Patients can remain progression-free in this state, progress and initiate the next line of treatment (which can either be 3L active treatment or BSC), or die.
- Third line (3L) treatment: a proportion of patients who progress following 2L treatment, enter this state and initiate 3L (active) treatment. Patients can remain progression-free in this state, progress and initiate the next line of treatment (which can either be 4L active treatment or BSC), or die.
- Fourth line (4L) treatment: a proportion of patients who progress following 3L treatment, enter this state and initiate 4L (active) treatment. Patients can remain progression-free in this state, progress and initiate BSC, or die.
- BSC: a proportion of patients will initiate BSC following progression from 2L, 3L, or 4L because they may not be eligible for further active treatment. Patients can remain progression-free in this state or die.
- Death: patients can enter this absorbing state from any of the four other health states.

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.

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Further detail can be found in the company submission pages 74 to 80

To note

- Two lines of subsequent treatment (i.e. 3L and 4L) were included in the model to maintain face validity because clinical expert opinion and the chart review indicated that WM patients tend to receive multiple lines of treatment during their lifetimes. Treatments received in these two HS are assumed to be active treatments for WM.
- The "other treatments" component of PC was created as it was difficult for clinicians to provide exact estimates for the uptake of a few individual treatments and, overall, these treatments are rarely used in clinical practice[2, 60]. As such, these were grouped to ensure they are captured and the cost of each component was given equal weight within the group.
- BSC refers to a non-interventional form of treatment with the intent of symptom management. This was assumed to consist of no active therapy and four annual haematologist visits.

Company submission, page 76

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

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Further detail can be found in the company submission pages 80 to 83

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

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Progression free survival

Progression free survival parametric fitting

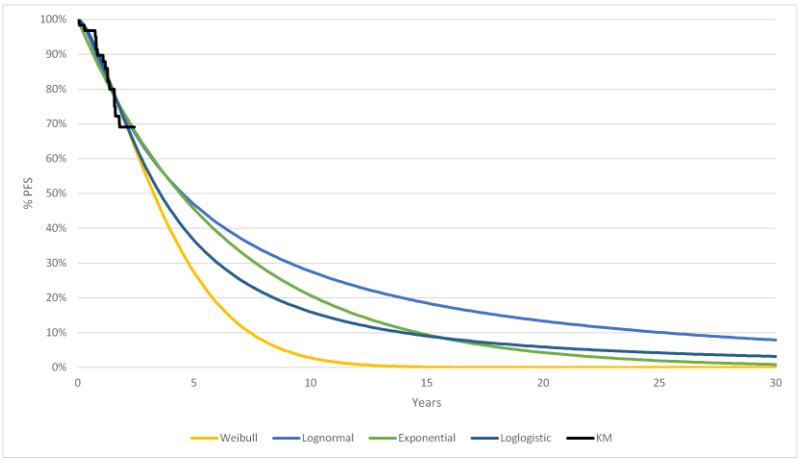

Figure 20, Company's submission

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To note:

- Within the ibrutinib group, the probability of remaining alive and progression-free in the second-line progression-free state during each model cycle was estimated by fitting parametric survivor functions to the PFS data from Study 1118E (n=63).
- Exponential, Weibull, log normal, and log logistic models were fitted to the available PFS time-to-event data (presented in the above slide)
- The ERG noted that there is a high level of censoring in the available data from Study 1118E; at the last available observation, the probability of PFS is around 0.69
- The ERG further noted that the Weibull model has the lowest mean PFS duration; however, given that treatment is assumed to be continued until progression, this is the most favourable function to use in terms of incremental costs for ibrutinib versus rituximab/chemotherapy

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

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Further detail can be found in the company submission pages 89 to 92

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

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To note

- Patients who remained progression-free in each health state were assigned a utility value of 0.799, based on the weighted average of “on treatment” utility over time from RESONATE. This value was derived as the weighted average EQ-5D-5L score for patients who remained in the PFS health state from weeks 4 to 60 in the RESONATE CLL trial .
- After progressing within the WM model and entering BSC HS, patients were assigned a utility value of 0.665. This value was calculated by applying a utility decrement of 12.8% to the baseline utility of 0.763 generated from the RESONATE EQ-5D-5L data for R/R CLL. This percentage utility decrement was derived from Beusterien et al. (2010), a time trade-off QoL study carried out to ascertain CLL utilities in the UK.
- Utility decrements associated with AEs (ranging from 0.123 to 0.195) were applied to patients as they experienced AEs in the model. The utility decrements associated with progression and adverse events were based on published literature, as analysis of RESONATE EQ-5D-5L data did not identify differences for these events.
- A summary of the utility values applied in the model is provided in Table 43 of the company submission.

Company submission, page 92

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

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Further detail can be found in the Company submission pages102 to 112

- All the results presented include the confidential patient access scheme agreed with the Department of Health.

To note

- The deterministic sensitivity analysis suggest that the 5 most influential parameters were:
    - the discount rate for health benefits
    - the discount rate for costs
    - the utility value associated with PFS in the second-line progression-free state
    - the hazard of death during BSC
    - the dose intensity for ibrutinib are the five most influential parameters.
- The ERG highlight that the model is not sensitive to the HR for PFS

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)

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Further detail can be found in the Company submission pages 112 to 113

All the results presented include the confidential patient access scheme agreed with the Department of Health.

To note:

- Across all four scenarios, the ICER for ibrutinib were greater than £56,000 per QALY gained

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

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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

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Further detail can be found in the ERG report page 98

To note

- Given that the company's HR for PFS has been estimated using outcomes for patients who have received multiple prior lines of therapy, but is applied only in the second-line progression-free state, this seems to imply an underlying assumption that the number of prior lines of therapy received is not a treatment effect modifier. This assumption is however inconsistent with the evidence used to populate the transition probabilities for the third- and fourth-line progression-free health states whereby different progression rates and distributions are employed compared with the second-line progression-free health state (see ERG report, Table 34).
- The ERG also notes that the evidence used to inform progression and death event rates throughout the subsequent states of the model is inconsistent with the definition of health states within the model
- Consequently, the ERG does not consider that the evidence available justifies the sequence-based model structure developed by the company.

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)

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Further detail can be found in the ERG report pages 99 and 100

To note:

- The PFS curve determines the probability of leaving the state, whilst the pre-progression curve mortality determines the proportion of those patients leaving the state who move to the dead state

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

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Further detail can be found in the ERG report pages 100 and 101

To note:

- Logical inconsistency of 2nd line pre-progression mortality and post-progression
  - clinical advice suggests that survival prognosis would decrease following progression from each consecutive line of treatment – the model suggests the opposite
- ERG is unable to judge whether an alternative survivor function may be more appropriate as the fitted Kaplan-Meier plots were not presented

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

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Further detail can be found in the ERG report pages 100 to 104

To note:

Pre-progression mortality for the comparison

- Following clarification, the ERG is unclear whether the model uses data on all deaths or only those occurring before progression to model pre-progression mortality for the rituximab/chemotherapy group.

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

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Further detail can be found in the ERG report pages 113 to 116

To note:

- With the exception of the disutilities associated with adverse events experienced during second-line treatment, the company's model does not account for any of these HRQoL effects.
- The ERG noted that clinical advice suggested that the utility score applied in the BSC state was lower than might be expected.

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

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Further detail can be found in the ERG report pages 117 to 124

All the results presented include the confidential patient access scheme agreed with the Department of Health.

To note:

- EA1 – Re-estimation of drug acquisition and administration costs
    - The ERG noted concerns regarding the accuracy and consistency of the drug acquisition and administration costs in the comparator.
    - Using clinical advisors the ERG re-estimated each of them using the British National Formulary
- EA2 – Correction of apparent errors surrounding follow-up costs
    - The ERG amended the model such that the costs of follow-up by year are the same irrespective of line of therapy
- EA3 – Use of ibrutinib pre-progression mortality rate from Study 1118E
    - The company's model uses age- and sex-adjusted general population mortality rates to describe the proportion of patients

leaving the progression-free state who die during each cycle.

- The ERG noted that the mortality rate observed within Study 1118E was consistently higher than the age- and sex-adjusted general population life table estimate.

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)

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Further detail can be found in the ERG report pages 124 to 126

To note

- The results of the model were not sensitive to the hazard ratio assumed for PFS for ibrutinib versus rituximab/chemotherapy.
- The ERG considers it unlikely that further data collection will lead to a more favourable cost-effectiveness profile for ibrutinib.

Threshold analysis

- Within this exploratory analysis, the HR for PFS for ibrutinib versus rituximab/chemotherapy was varied within the range 0.01 to 1.00. (available in the company submission, Figure 21)
- The ERG's threshold analysis around the HR for PFS suggests that under the ERG's base case assumptions, the lowest possible deterministic ICER for ibrutinib versus rituximab/chemotherapy is estimated to be £59,620 per QALY gained (HR~[redacted]).
- Under the company's scenario which is based on general population pre-progression mortality rates, the lowest possible deterministic ICER for ibrutinib versus rituximab/chemotherapy is estimated to be £56,917 per QALY gained

(HR~[redacted]).

- The ERG therefore considers it unlikely that further data collection will lead to a more favourable cost-effectiveness profile for ibrutinib.

ERG report page 126

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

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Further detail can be found in the Company's submission, page 24

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

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Further detail can be found in the Company's submission, page 35

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

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Further detail can be found in the Company's submission page 19

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

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Key issues: cost effectiveness

- 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?**

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Key issues: cost effectiveness (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?**

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Authors

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- with input from the Lead Team (**Rachel Hobson**, **Brian Shine** and **Pam Rees**)

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Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Single Technology Appraisal

Ibrutinib for treating Waldenström's macroglobulinaemia [ID884]

Provisional matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • Janssen (ibrutinib) Patient/carer groups • African Caribbean Leukaemia Trust • Anthony Nolan • Black Health Agency • Cancer Black Care • Cancer Equality • Cancer52 • Delete Blood Cancer • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Leukaemia Cancer Society • Leukaemia CARE • Lymphoma Association • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • Muslim Council of Britain • Rarer Cancers Foundation • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Cancer Care • WMUK Professional groups • Association of Cancer Physicians • British Committee for Standards in Haematology • British Geriatrics Society • British Institute of Radiology • British Psychosocial Oncology Society • British Society for Haematology • Cancer Research UK • Royal College of General Practitioners	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Blood and Transplant • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Possible comparator companies • Accord Healthcare (fludarabine) • Actavis UK (fludarabine) • Aspen (chlorambucil) • Baxter Healthcare (cyclophosphamide) • Hospira UK (fludarabine) • LIPOMED (cladribine) • Napp (bendamustine) • Roche Products (rituximab) • Sandoz (cyclophosphamide, fludarabine) • Sanofi (fludarabine) • Teva UK (fludarabine) Relevant research groups • Bloodwise • Cochrane Haematological Malignancies Group

Consultees	**Commentators (no right to submit or appeal)**
• Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiology • UK Clinical Pharmacy Association • UK Health Forum • UK Oncology Nursing Society <u>Others</u> • Department of Health • NHS Darlington CCG • NHS England • NHS Wyre Forest CCG • Welsh Government	• Institute of Cancer Research • Leuka • Leukaemia Busters • MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies;
Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ibrutinib for treating Waldenström's macroglobulinaemia

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of ibrutinib within its marketing authorisation for treating Waldenström's macroglobulinaemia.

Background

Waldenström's macroglobulinaemia is a type of non-Hodgkin's lymphoma. Lymphomas are cancers of the lymphatic system, which is a part of the immune system. Lymphomas are divided into two types: Hodgkin's lymphoma and non-Hodgkin's lymphoma. Non-Hodgkin's lymphomas can be categorised according to their grade (how fast they grow) or cell type affected (B-cell or T-cell), as well as by their clinical features. Lymphoplasmacytic lymphomas are a group of rare low grade (slow growing or indolent) non-Hodgkin's lymphomas. The most common of these is Waldenström's macroglobulinaemia. Waldenström's macroglobulinaemia 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. Symptoms are highly variable, but the most common ones include severe fatigue, night sweats, lack of concentration, frequent/persistent infections, breathlessness, sinus problems, and unexplained weight loss.

Approximately 330 people are diagnosed with Waldenström's macroglobulinaemia in England annually.[1] It is more common in men and mainly affects people 70 years and older.[2] Because Waldenström's macroglobulinaemia develops slowly, most people have no symptoms until they are diagnosed. As a result, most people are diagnosed in the advanced stages of the disease.

There is currently no NICE guidance on treating Waldenström's macroglobulinaemia. The British Committee for Standards in Haematology (BCSH) guidelines recommends treatment with a combination regimen with rituximab and either cladribine, bendamustine, dexamethasone (plus cyclophosphamide) or fludarabine (with or without cyclophosphamide). Chlorambucil monotherapy is also recommended for those people who cannot tolerate other treatments. Choice of treatment depends on a variety of clinical factors including grade of disease, kidney function, co-morbidities and whether a person is able to have stem cell transplantation. Patients treated with existing treatments generally have a partial response which lasts for a time before the disease relapses.

The technology

Ibrutinib (Imbruvica, Janssen) is an inhibitor of a protein called Bruton's tyrosine kinase, which stops B-cell (lymphocyte) proliferation and promotes cell death.

Ibrutinib has a marketing authorisation in the UK for treating adult patients with Waldenström's macroglobulinaemia who have received at least one prior therapy, or as first line treatment for patients in whom chemo-immunotherapy is unsuitable.

Intervention(s)	Ibrutinib
Population(s)	Adults with Waldenström's macroglobulinaemia who have received at least one prior therapy Adults with Waldenström's macroglobulinaemia who have not received prior therapy and in whom chemo-immunotherapy is unsuitable
Comparators	For people 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 For people who have not received prior therapy and in whom chemo-immunotherapy is not suitable: • chlorambucil • rituximab • best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • duration of response/remission • adverse effects of treatment • health-related quality of life

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Guidelines: Cancer Service Guidance, Improving outcomes in haemato-oncology cancers, October 2003 (Update in development, anticipated publication date: September 2019): http://www.nice.org.uk/guidance/indevelopment/gid-cgwave0799 Clinical Guideline in Preparation, 'Non-Hodgkin's lymphoma: diagnosis and management of non-Hodgkin's lymphoma'. Anticipated date of publication January 2018. Related NICE Pathways: NICE Pathway: Blood and bone marrow cancers, Pathway created: Updated 2016. http://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers/blood-and-bone-marrow-cancers-overview
Related National Policy	Department of Health, Dec 2014, 'Improving Outcomes: A Strategy for Cancer - Fourth Annual Report' Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf

References

1. WMUK (2015), What is WM? Accessed December 2015.

2. Owen, R et al. (2014) Guidelines on the diagnosis and management of Waldenström macroglobulinaemia. British Journal of Haematology, 165:316-33.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ibrutinib for treating Waldenström's macroglobulinaemia [ID884]

Company evidence submission

April, 2016

File name	Version	Contains confidential information	Date
ID884_Janssen_ibrutinib_Submission_17jun16_ ACIC	1.0	Yes	17 June 2016

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

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List of abbreviations

1L, 2L, 3L…	First, second, third line...
AE	Adverse events
AF	Atrial fibrillation
AIC	Akaike information criteria
ASCO	American Society of Clinical Oncology
ASCT	Allogeneic stem cell transplant
ASH	American Society for Hematology
ATP	Adenosine Triphosphate
B2M	β2-microglobulin
BCR	B cell receptor
BCSH	British Committee for Standards in Haematology
BIC	Bayesian information criteria
BIA	Budget Impact Analysis
BNF	British National Formulary
BR	Bendamustine and rituximab
BSA	Body surface area
BSC	Best supportive care
BTK	Bruton's tyrosine kinase
CCo	Clinical Cut-off
CDF	Cancer Drugs Fund
CE	Cost-effectiveness
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIRS-G	Cumulative Illness Rating Scale-Geriatric
CLL	Chronic lymphocytic leukaemia
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
DH	Department of Health
DoF	Data on File
DOR	Duration of Response
DRC	Dexamethasone + Rituximab + Cyclophosphamide
ECOG	Eastern Cooperative Oncology Group
EFS	Event free survival
EHA	European Hematology Association
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESMO	European Society of Medical Oncology
FCR	Fludarabine + cyclophosphamide + rituximab
FCS	Fully Conditional Specification
FR	Fludarabine + rituximab
GE	Gastroesophageal
HCHS	Hospital and Community Health Service
HR	Hazard ratio
HRU	Health Resource Utilisation
HS	Health State
ICER	Incremental cost-effectiveness ratio
IgM	Immunoglobulin M
IPSSWM	International Prognostic Staging System for Waldenström's Macroglobulinaemia
IRRC	Independent Response Review Committee
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
IV	Intravenous
IWWM	International Workshop on Waldenström's Macroglobulinaemia

KM	Kaplan Meier
LPL	Lymphoplasmacytic Lymphoma
LY	Life year
LYG	Life years gained
MAIC	Matching adjusted treatment comparison
MCL	Mantle cell lymphoma
MEA	Managed Entry Agreements
MGUS	Monoclonal Gammopathy of Undetermined Significance
MICE	Multiple Imputations by Chained Equations
MRR	Major response rate
MRU	Medical resource use
NCCN	National Comprehensive Cancer Network
NHL	Non-Hodgkin's lymphoma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
Od	Once daily
ONS	Office of National Statistics
OR	Odds ratios
ORR	Overall response rate
OS	Overall survival
PAS	Patient access scheme
PC	Physician's choice
PD	Progressive disease
PFS	Progression free survival
PICOS	Population Intervention Comparators Outcomes, Study
PPS	Post-progression survival
PSS	Personal social services
PR	Partial response
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
QOL	Quality of life
R/R	Relapsed/refractory
RCT	Randomised controlled trial
SACT	Systemic Anti-Cancer Therapies
SC	Subcutaneous
SCT	SCT - stem cell transplantation
SE	Standard Error
SLR	Systematic literature review
SSL	Small lymphocytic leukaemia
STA	Single Technology Appraisal
TA	Technology Appraisal
TEAE	Treatment-Emergent Adverse Event
TTF	Time to treatment failure
TTFR	Time to first response
TTP	Time to progression
ULN	Upper Limit of Normal
UTI	Urinary Tract Infection
VGPR	Very Good Partial Response
WHO	World Health Organisation
WM	Waldenström's macroglobulinaemia

1. Executive summary

1.1. *Statement of decision problem*

This submission addresses the clinical and cost-effectiveness of ibrutinib for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, and in first line treatment for patients unsuitable for chemo-immunotherapy. The scope of this submission is therefore in line with both the marketing authorisation of ibrutinib[1] and the final scope for this appraisal.

Further details of the decision problem and how it has been addressed in this submission are presented in Table 1 on the following pages.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	• 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.		N/A – the decision problem addressed is in line with the final scope.
Intervention	• Ibrutinib.		N/A – the decision problem addressed is in line with the final scope.
Comparator (s)	<u>For adults with WM who have received at least one prior therapy:</u> • rituximab and bendamustine • rituximab, dexamethasone and cyclophosphamide • rituximab and fludarabine with or without cyclophosphamide • cladribine with or without rituximab • rituximab • chlorambucil	<u>For adults with WM who have received at least one prior therapy:</u> A physician's choice (PC) comparator encompassed the following treatments: • rituximab and bendamustine • rituximab, dexamethasone and cyclophosphamide • rituximab and fludarabine *with* cyclophosphamide • cladribine with or without rituximab • rituximab • chlorambucil with or without rituximab	<u>For adults with WM who have received at least one prior therapy:</u> The PC comparator aims to accurately reflect the fact that there is currently no licensed (other than ibrutinib) or funded treatment for these patients, and there is no clear standard of care for patients with WM. PC is comprised of the comparators listed within the final NICE scope with the exception of rituximab in combination with fludarabine and without cyclophosphamide based on clinical opinion. Furthermore, chlorambucil with

	<u>For adults with WM who have not received prior therapy and for whom chemoimmunotherapy is not suitable:</u> • chlorambucil • rituximab • best supportive care (BSC)	<u>For adults with WM who have not received prior therapy and for whom chemoimmunotherapy is not suitable:</u> • chlorambucil • rituximab • BSC	rituximab was included within the PC composition. The selection of PC as the key comparator, as well as its composition, was validated by UK clinical opinion [2, 3]. <u>For adults with WM who have not received prior therapy and for whom chemoimmunotherapy is not suitable:</u> As per scope.
Outcomes	As per 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).		
Economic analysis	As per scope: • The cost-effectiveness of treatments is expressed in terms of incremental cost per quality-adjusted life year (QALY) • The time horizon for estimating clinical and cost effectiveness is sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs are considered from a National Health Service (NHS) and Personal Social Services (PSS) perspective.		
Subgroups to be considered	None detailed.	No subgroup is considered in this submission.	N/A – the decision problem addressed is in line with the final scope.
Special considerations including issues related to equity or equality	The population targeted by this submission is in line with that for which the European Medicines Agency (EMA) granted ibrutinib a license and for which ibrutinib has been scoped, i.e. WM patients who have received prior therapy, and have not received prior therapy and for whom chemo-immunotherapy is unsuitable. As such, the targeted population is broader than the one studied in the pivotal trial (Study 1118E), and includes patients with relapsed or refractory (R/R) WM.		Given that there is no treatment licensed and/or funded for WM patients, the addition of ibrutinib to the treatment pathway will address equity issues regarding the lack of effective treatments for patients with WM.

1.2. *Description of the technology being appraised*

A summary of the technology being appraised is provided in Table 2 below.

Table 2: Technology being appraised

UK approved name and brand name	Ibrutinib (Imbruvica®).
Marketing authorisation/CE mark status	Ibrutinib received a positive opinion for WM from the Committee for Medicinal Products for Human Use (CHMP) on the 21st of May 2015[4]. The marketing authorisation was subsequently granted by the European Commission (EC) on the 3rd of July 2015 [5].
Indications and any restriction(s) as described in the summary of product characteristics	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. Ibrutinib is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients. The use of preparations containing St. John's Wort is contraindicated in patients treated with ibrutinib.
Method of administration and dosage	The WM dose is three 140 mg capsules (420 mg in total) once daily (od). Ibrutinib is administered as an oral monotherapy and is taken until disease progression or until the treatment is no longer tolerated by the patient.

1.3. *Summary of the clinical effectiveness analysis*

Disease overview and burden

WM natural history and pathophysiology

WM is a lymphoproliferative B-cell disorder characterised by infiltration of lymphoplasmacytic cells into the bone marrow and immunoglobulin M (IgM) monoclonal gammopathy [6]. While the exact aetiology of WM is still not fully understood, the disease is thought to originate from memory-like B-cells that have not completed terminal differentiation into IgM-secreting plasma cells. These WM cells differentiate into lymphoplasmacytic cells and plasma cells in the bone marrow [6, 7].

Recent studies have suggested that autoimmune and chronic inflammatory conditions may play an important role in the pathophysiology of WM [7]. Known risk factors for WM include the presence of pre-existing IgM monoclonal gammopathy of undetermined significance (MGUS), family history of WM or other B-cell malignancies, and immunological factors [6]. There is also evidence that some individuals have a genetic predisposition to the disease [7].

Despite being a malignancy associated with a relatively long survival at diagnosis, WM remains an incurable disease with variability in outcomes.

Early stage WM is asymptomatic and typically indolent, progressing slowly to symptomatic disease. It is estimated that approximately a quarter of patients with WM are asymptomatic

at diagnosis [8]. The symptoms and signs of WM may vary but are usually related to signs of bone marrow infiltration by lymphoplasmacytic cells and IgM paraprotein-related symptoms such as cryoglobulinaemia (cold agglutinin syndrome), demyelinating neuropathy, and symptomatic hyperviscosity, anaemia or cytopenias. A recent study demonstrated that the median progression time from asymptomatic to symptomatic disease was 6.9 years, but was as long as 10 years in patients with no adverse risk factors[6].

WM constitutes 1% to 2% of haematologic malignancies; with an overall age-adjusted incidence in the European Union (EU) of 3.8 per million persons per year, WM meets European Medicines Agency (EMA) criteria for rare diseases. One study of patients in the UK estimated an age-standardised annual incidence of WM at 5.5 per million persons per year[9]. This translates to 300 to 400 new WM cases each year in the UK.

Diagnosis of WM

Diagnosis of WM requires demonstration of an IgM monoclonal protein and histological evidence of bone marrow infiltration by lymphoplasmacytic cells [6, 8, 10-12]. International and UK guidelines)[10, 11] recommend that the presence of lymphoplasmacytic cells in the bone marrow should be documented by trephine biopsy and aspirate followed by confirmation by immunophenotyping. Assessment of plasma viscosity is also recommended when signs and symptoms of hyperviscosity syndrome, such as oronasal or retinal bleeding or peripheral neuropathy, are present or when IgM levels are above 4 g/dL[6, 10, 12, 13].

The International Prognostic Staging System for Waldenström's Macroglobulinaemia (IPSSWM) is used to assess the likelihood of disease progression, and to guide treatment once patients have developed signs and symptoms of WM, i.e. once they are deemed to have active, symptomatic disease. It is recommended that all patients are assessed at diagnosis, although this does not directly impact treatment choices [10].

Survival in WM patients

Median OS in WM ranges from less than 4 years to 12 years, depending upon IPSSWM risk category. A recent pan-European observational study estimated a median overall survival (OS) of 10 years (n = 454) but considerable country-specific variation is reported with UK-specific analysis (n = 72) estimating a median OS of 5 years.[14] The relatively late age of diagnosis combined with the fact that WM generally follows an indolent disease course, means that nearly half of patients diagnosed with WM die from causes unrelated to the disorder [13] but, for those patients with higher risk or more advanced disease, survival is curtailed.

Burden of disease

Although WM is an indolent disease, once a patient becomes symptomatic and/or whilst on standard treatments, quality of life (QoL) is diminished and management of sequelae and adverse events becomes crucial.

While evidence quantifying the disease-related QoL impact on patients with WM is scarce, it is apparent that the clinical features experienced by many patients with WM, including generalised weakness (asthenia) and cachexia, impact patients' ability to carry out activities of daily living.

Key morbidities associated with WM include cytopenias resulting from bone marrow infiltration by lymphoplasmacytic cells and the adverse effects of immunoglobulins, which can cause the occurrence of painful complications such as neuropathy and

cryoglobulinaemia. Patients with WM may experience irreversible vision loss resulting from retinal haemorrhaging secondary to hyperviscosity [15], which further reduces patient QoL.

Patients with hyperviscosity are treated with plasmapheresis to temporarily reduce IgM levels [6], which is invasive and time-consuming and provides only symptom management without addressing the underlying pathophysiology of the disease. Plasmapheresis can result in hypocalcaemia, leading to painful muscle spasms and numbness and tingling, and requiring treatment with calcium [16].

With a median age at diagnosis of 68 years, WM disproportionately affects the elderly population who may have comorbidities, limited mobility, limited biological capacity to tolerate chemotherapy, and a limited ability to tolerate AEs, which also have a negative impact on health-related QoL [17, 18].

Current management of WM patients

To date, there is no established standard of care for the treatment of WM in the UK. The lack of randomised clinical trials (RCT) has impeded the development of an evidence-based algorithm for WM. The majority of published studies are non-randomised, often single institution-based, and phase 2 studies that typically include both newly diagnosed and relapsed patients [10]. Evidence-based guidelines for the treatment of first line and R/R WM are available from the British Committee for Standards in Haematology (BCSH) and the European Society of Medical Oncology (ESMO) [10, 12]. In the absence of a gold standard treatment for WM, the guidelines generally recommend "physician's choice" from among the many available agents, although no drugs have been licensed or are funded by the NHS for WM. Treatment options currently used in WM were originally developed for other lymphoproliferative diseases including multiple myeloma and chronic lymphocytic leukaemia (CLL) and include both monotherapies and combination therapies such as:

- orally administered alkylating agents (e.g., cyclophosphamide),
- nucleoside analogues (cladribine or fludarabine) in monotherapy or in combination therapies,
- rituximab monotherapy, or rituximab in combination with cyclophosphamide-based therapy,
- bortezomib-based therapy, thalidomide, or bendamustine have also been investigated as treatment options[10].

WM patients are therefore currently managed with off-label treatments that do not target disease-specific abnormalities and are generally aimed at managing disease symptoms. These can lead to treatment-related side effects that may be life-threatening, particularly in older adults.

Off-label treatment with traditional agents is associated with limited clinical benefit and significant disadvantages, primarily high toxicity. For example, with chemo-immunotherapy (often used for first line treatment), further depletion of bone marrow reserve and may lead to development of thrombocytopenia, neutropenia and anaemia; treatment with rituximab may result in an abrupt increase in serum IgM levels (IgM flare), which may require supportive plasmapheresis; and treatment with nucleoside analogues is linked to malignant transformation.

As stated by the CHMP in its Variation assessment report dated 21 May 2015[19], there is a high unmet need for the treatment of WM patients, especially "[…] *in the first line setting for*

the group of patients unsuitable for chemo or immunotherapy for whom no satisfactory treatment options are currently available".

Ibrutinib in WM

Ibrutinib, a first-in-class BTK inhibitor

Ibrutinib is the first product to be granted marketing authorisation by the EMA for the treatment of WM. It is a potent, targeted, non-chemotherapeutic agent and the first-in-class inhibitor of Bruton's tyrosine kinase (BTK), which is a critical signalling kinase in the B cell receptor (BCR) pathway and whose activity is essential for tumour cell survival and proliferation.

BTK inhibition therefore represents a step-change in the therapeutic armamentarium of clinicians treating WM. Inhibition of BTK by ibrutinib leads to sustained inhibition of multiple key signalling pathways that regulate growth, differentiation, homing and proliferation in both normal and, more importantly, malignant B-cells. The pharmacological activity of ibrutinib has been shown to translate into unprecedented efficacy in several difficult-to-treat B-cell malignancies, namely CLL/small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL) and WM [20-25].

Furthermore, ibrutinib is conveniently administered once-daily as monotherapy and therefore represents an attractive treatment option for all patients, ranging from younger professionally active patients for whom hospital-based treatment significantly disrupts work-related activities to elderly patients for whom transport to the hospital can add a significant burden to the disease itself. Lastly, the benign toxicity profile of ibrutinib means that it does not require pre-medication or prophylactic treatment to prevent side effects.

Ibrutinib efficacy and safety in WM

No RCT relevant to this appraisal was identified by the systematic literature review (SLR), which was conducted to identify prospective WM clinical studies of monotherapy ibrutinib or potential comparator therapies, as defined in the NICE Final Scope.

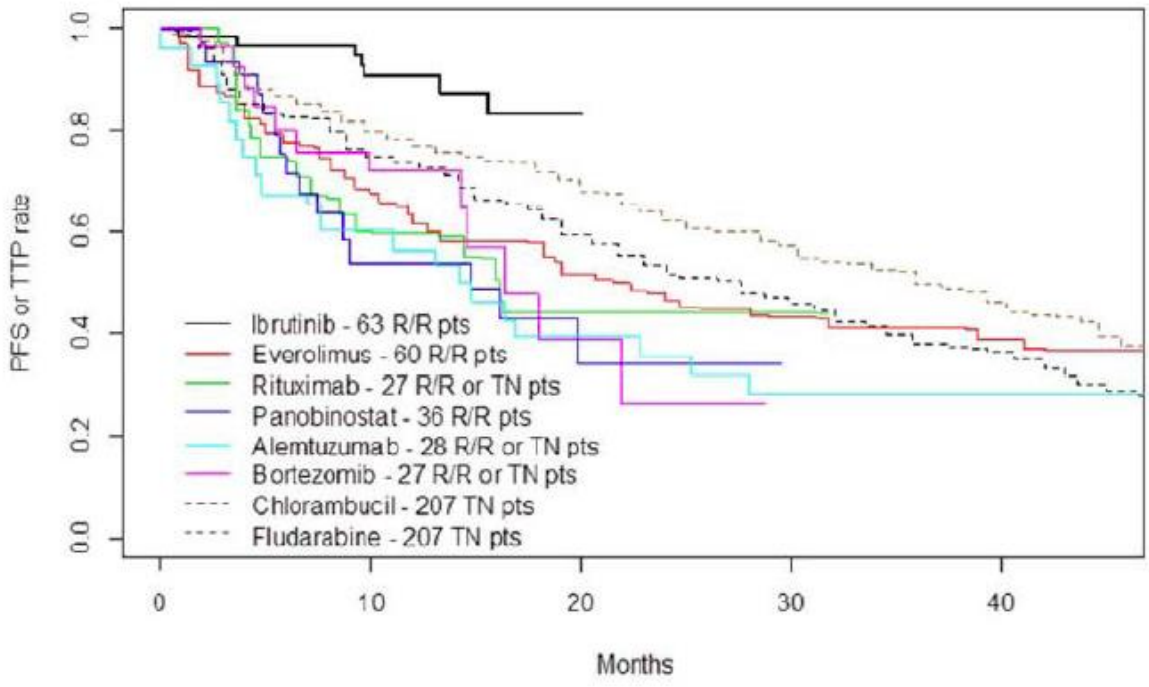
The pivotal study upon which ibrutinib monotherapy was granted EMA approval for the treatment of WM was a phase 2, investigator-initiated study of 63 patients with R/R WM (Study 1118E) [23] Not only was the primary endpoint (overall response rate [ORR]) considered appropriate by the CHMP for a single arm trial in this setting, but the CHMP also deemed the Study 1118E study population to be representative of the general WM population with previously-treated disease [19]. Findings based on the latest available data (database lock December 2014, with a median duration of follow up of 24 months) for Study 1118E were published in Treon et al. 2015 [23].

Study 1118E demonstrated the significant clinical benefit of ibrutinib: the level of response observed was robust and durable, with a high ORR (90.5%) and a high major response rate (61.9% by the Independent Response Review Committee [IRRC]); durable remissions can be inferred as median duration of response (DOR) was not reached by the end of the study. Median PFS was not reached at a median follow up of 24 months, showing prolonged clinical benefit (the rate of PFS was 69.1% at 24 months). In addition, only 3 deaths were reported during trial follow-up (median OS was 95.2% at 24 months). Treatment with ibrutinib also resulted in rapid reduction in serum IgM and improvement in haemoglobin, addressing the principal underlying causes of disease-related comorbidities.

Regarding the generalizability of Study 1118E efficacy results to first line patients, the CHMP relied on historical comparisons of PFS in patients with WM presented below in Figure 1 and concluded that:

"*the observed ORR of 87.3%, as reported in the 1118E study, is reassuring in terms of activity, and numerically superior in inter-study comparisons with most published studies investigating other monotherapy agents in previously treated and/or naive patients.*"

Figure 1: Naïve comparison of progression-free survival in patients with WM (single-agent use)



Source: CHMP variation report dated 21 May 2015

It is important to note that the above figure was not developed from a formal indirect comparison and, as such, represents a naïve unadjusted comparison of various WM treatment options.

Study 1118E also supported the generally benign safety profile of ibrutinib in the treatment of WM patients. The majority of treatment-emergent adverse events (TEAEs) were mild to moderate, easily manageable, and there was a low incidence of grade 3/4 AEs. Of the 19% of patients who stopped treatment, only 6% discontinued as a result of toxicity.

As the safety profile of ibrutinib in patients with WM is consistent overall with what is already known in ibrutinib-treated patients with CLL/SLL or MCL, the CHMP determined that ibrutinib has "*an acceptable safety profile to support the extension of the indication to include WM*". This decision was reached on the ground that "*no new safety signal has been evoked. No significant tolerability issues in the WM population as compared to the overall integrated dataset including CLL/SLL and MCL patient populations have been identified. In addition, data from the long-term safety population is not indicative of any cumulative toxicity*."

Comparative clinical effectiveness

There is a paucity of data in WM. An SLR was conducted and found no RCT relevant to this appraisal. Consequently, a conventional indirect comparison to Study 1118E could not be conducted. The availability of a large and robust pan-European observational study of WM patients, the first of its kind, allowed for the comparative clinical effectiveness of ibrutinib in the R/R setting to be derived. These data inform the cost-effectiveness analysis of ibrutinib.

Place of ibrutinib in the management of WM patients

WM is a serious, life-threatening condition due to morbidities resulting from cytopenias and excess immunoglobulins. Available treatment options are limited and may not be suitable for older patients who are unable to tolerate aggressive therapies [10, 18] Most therapies that are available for WM were originally developed to treat patients with other lymphoproliferative diseases, including multiple myeloma and CLL [26]. Given its clinical profile as well as its convenient mode of administration, ibrutinib represents a unique treatment opportunity given the current unmet need for patients with WM.

In historical naïve cross-study comparisons, patients experienced longer PFS with ibrutinib than when treated with other single agents, irrespective of the population (i.e., R/R or first line), as shown in Figure 1 in Section 1.3 below [27-31].

AE-related discontinuation or dose reduction was infrequent. In combination with the ease of once-daily, oral therapy and low rates of grade 3/4 AEs, ibrutinib provides compelling clinical value to patients who otherwise have limited treatment options. In addition, the efficacy and safety profile of ibrutinib will reduce costs associated with treatment-related AEs, inpatient treatment, and less effective palliative therapies, and reduce the need for blood products and leukopheresis for patients with R/R WM.

Summary of the cost-effectiveness analysis

Methods and inputs

A *de novo* cost-effectiveness model was developed to estimate the benefits, consequences, and costs of treating WM patients with ibrutinib compared with a physician's choice (PC) comparator. In the absence of a standard of care for the treatment of R/R WM patients, a PC comparator was selected that reflects the scope and distribution of therapies currently used in routine UK clinical practice, in line with clinical opinion. The population addressed by the economic model reflects the characteristics of the patients that were enrolled in Study 1118E.

Ibrutinib efficacy was modelled using the PFS Kaplan-Meier (KM) data from the phase 2 pivotal trial. In the absence of long-term data, PFS was extrapolated directly from the KM data. Only 3 deaths occurred in Study 1118E; therefore, as the OS KM-based mortality rate was comparable to the UK general population mortality rate, the latter was used to inform mortality of ibrutinib patients within the model.

In the absence of comparative trial-based clinical data and no relevant RCT in WM, a conventional indirect treatment comparison (ITC) could not be conducted to estimate efficacy in the comparator arm. Comparative efficacy (PFS) for the PC comparator was derived based on patient-level data collected in the European observational study (n = 454)[32]. A hazard ratio (HR) for ibrutinib vs. PC was estimated based on data from the pan-European chart review.

A total of 175 patients from the chart review were included in this pooled analysis and as such represents a relatively large and robust dataset in a rare condition such as WM. Given that the maximum number of prior treatments in the chart review was four, patients with five or more prior treatment lines in the Study 1118E study were excluded from the analyses (n = 47) were included in the pooled analysis). The baseline characteristics of these populations were broadly aligned. The mortality rate for the PC comparator arm was derived from the chart review study. Both ibrutinib and PC were assumed to have the same subsequent treatment options.

The model considered grade 3 and 4 AEs that occurred in ≥5% of patients in at least one of the treatments, based on published clinical trial studies for ibrutinib and each of the treatments included in the comparator arm. These included anaemia, leukopenia, neutropenia, thrombocytopenia, lymphocytopenia, infection (non-pneumonia), neuropathy, lung toxicity, diarrhoea and constipation.

Due to the lack of utility data for the WM population, utility estimates obtained from a study in an R/R CLL population were used as a proxy on the basis that the two diseases have similar age of patient population and treatment paradigm. This assumption was supported by clinical opinion [2].

Costs were obtained from standard UK sources; the British National Formulary was used for drug costs and NHS reference costs for resource use. Medical resource use (e.g., for the frequency of visits to the haematologist and routine monitoring tests) was primarily informed by UK clinical opinion [2].

Base case results

Based upon the economic analysis, treatment with ibrutinib in R/R WM is estimated to a deliver substantial survival benefit. Ibrutinib generated an additional [redacted] ([redacted] vs. [redacted]) life years and [redacted] ([redacted] vs. [redacted]) quality-adjusted life years (QALYs) vs. PC, respectively (Table 3).

The resulting incremental cost-effectiveness ratio (ICER) for ibrutinib vs. PC based upon the list price of ibrutinib is £78,647. When taking into consideration the currently approved discount for ibrutinib, the ICER falls to £58,630. [redacted]

Table 3: Incremental cost-effectiveness results in R/R WM (at list price)

Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	78,647
PC	[redacted]	[redacted]	[redacted]				
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; PC, Physician's choice							

Table 4: Incremental cost-effectiveness results in R/R WM (with PAS)

Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	58,630
PC	[redacted]	[redacted]	[redacted]				
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; PC, Physician's choice							

1.4. *Proposal for inclusion in the Cancer Drug Fund*

The ibrutinib efficacy data in WM and the long-term safety data across all licenced indications show a considerable positive impact of ibrutinib on patients with WM. Janssen recognises that, whilst the data are promising, the phase 2 non-comparative nature of Study 1118E may not meet the evidence standards required for a recommendation from the NICE Committee, and thus there is a need for further data collection to substantiate the clinical data and to address a number of uncertainties.

Janssen believes that the opportunity to collect real-world clinical data will help to confirm the key assumptions used in the health economic model and address the concerns which may be raised in relation to the clinical and safety evidence during the appraisal. Importantly, data collection will capture QoL data specific to WM and, if greater benefits with ibrutinib are observed in clinical practice (e.g., in reducing fatigue) compared with the proxy CLL utility data currently being used, this will only improve the estimate of cost-effectiveness.

Janssen proposes to use a WM UK registry currently under development by University College London and is confident that the additional research required is feasible, should NICE recommend ibrutinib for inclusion within the Cancer Drugs Fund (CDF).

1.5. *Concluding remarks*

In a disease with such high unmet clinical need and such limited data, Janssen have made every effort to estimate comparative efficacy and present as robust an analysis of the cost-effectiveness of ibrutinib as possible. The modelling results consistently suggest a substantial clinical benefit from ibrutinib over PC, as evidenced by the incremental QALY gain. Sensitivity analyses show some variation around the point estimate of the ICER; however, this variation is relatively small considering the evidence base is not yet complete. With further evidence, Janssen is confident that it can robustly be demonstrated that ibrutinib offers value for money in the treatment of patients with WM.

Inclusion in the CDF would allow for the collection of further evidence and, most importantly, in the interim would allow patients access to an effective, innovative treatment in an environment where none such options currently exist.

2. The technology

2.1. *Description of the technology*

Ibrutinib is a first-in-class inhibitor of the intracellular signalling molecule, Bruton's tyrosine kinase (BTK), a critical signalling kinase in the B-cell receptor (BCR) pathway for tumour cell survival and proliferation [33-35].

A summary of the technology is provided in Table 5 below followed by a full description of the innovative and targeted mechanism of action.

Table 5: Details of ibrutinib

Approved name	Ibrutinib
Brand name	Imbruvica®
Therapeutic class	Anti-neoplastic agents, protein kinase inhibitors
ATC code	L01XE27
Pharmaceutical form(s)	Capsule
Strengths available	140 mg
Route of administration	Oral
Pack/Package size	90 hard capsules 120 hard capsules
Manufacturer	Janssen

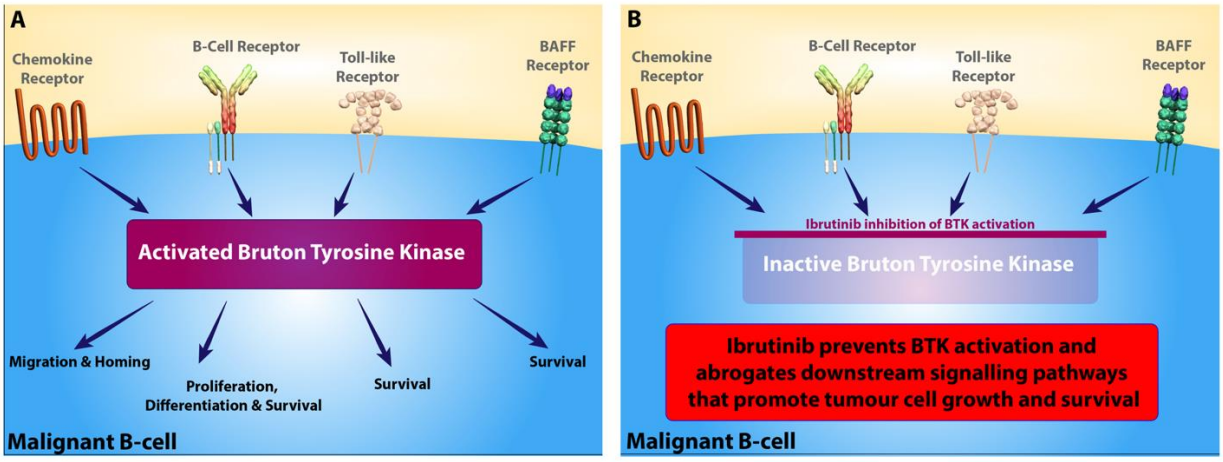
Ibrutinib mechanism of action

B-cells are an essential component of the adaptive immune system; their regulated ability to traffic between the blood and lymphatic circulatory systems and to home to lymphoid tissue is central to their function. In addition, close regulation of survival, differentiation and proliferation is required to provide appropriately rapid but self-limited immune responses. Bruton Tyrosine Kinase (BTK) is a critically important intracellular signalling molecule that plays a pivotal role in the multiple signalling pathways that govern survival, homing, adhesion, differentiation and proliferation in both normal and malignant B-cells [34, 35]. BTK has been shown to be intimately involved in the pathogenesis of several B-cell malignancies, including chronic lymphocytic leukaemia (CLL), mantle cell lymphoma (MCL) and Waldenström's macroglobulinaemia (WM) [36, 37]. Because of its selective expression in B-cells (it is absent from T-cells), BTK represents an attractive therapeutic target in B-cell malignancies [35, 38-40].

Ibrutinib is a potent, orally bioavailable, highly specific inhibitor of BTK [35, 37, 41]. Sustained inhibition of BTK activation and function is accomplished when ibrutinib binds to a critical cysteine residue (Cys-481), forming a stable, covalent bond and blocking entry to the

adenosine triphosphate (ATP) binding domain of BTK. Ibrutinib mechanism of action is illustrated in Figure 2 below.

Figure 2: Mechanism of action of ibrutinib

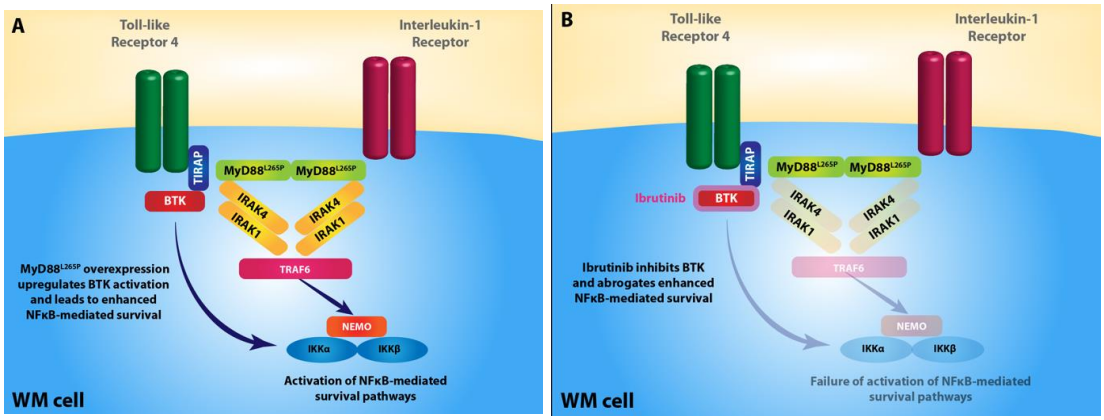


A – Role of BTK in malignant B-cell migration, proliferation, differentiation and survival; B - Abrogation of signalling pathways by ibrutinib

WM patients have a high frequency of certain somatic mutations that are associated with specific biological and clinical features. The most common of these mutations, $MyD88^{L265P}$, is present in 90-95% of WM patients and is seldom seen in other B-cell malignancies [23, 42]. Another class of WM-specific mutations that affect the CXCR4 gene, designated $CXCR4^{WHIM}$ are reported in around 29% of WM cases.

WM cells with the $MyD88^{L265P}$ mutation overexpress the signalling adapter molecule MyD88, which enhances BTK phosphorylation and consequently promotes WM cell survival. This aberrant survival pathway is unique to WM [23, 42]. Ibrutinib targets this upregulated survival pathway by inhibiting BTK activation, leading to increased WM cell death. Mechanism of action of ibrutinib in WM in specific is illustrated in Figure 3 below:

Figure 3: Mechanism of action of ibrutinib Specific to WM



BTK=Bruton's tyrosine kinase; IKK=Iκβ kinase complex; IκBα=inhibitor of nuclear factor kappa-light chain-enhancer of activated B cells (NF-κB); IRAK=IL1R-associated kinase; NEMO=NF-κB essential modulator; TIRAP=toll-interleukin 1 receptor domain-containing adaptor protein; TRAF6=tumour necrosis factor receptor-associated factor 6;

A – Role of BTK in the upregulation of NF-κB-mediated survival pathways in MyD88^{L265P} WM. B - Abrogation of upregulated pro-survival signalling by ibrutinib.

2.2. *Marketing authorisation/CE marking and health technology assessment*

The European Medicines Agency (EMA) has granted approval for ibrutinib in the following indications [1]:

- adult patients with relapsed or refractory MCL;
- adult patients with previously untreated CLL (as a single agent);
- adult patients with CLL who have received at least one prior therapy;
- adult patients with WM who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy

In the EMEA EPAR Variation assessment report dated 21st May 2015, the CHMP stated[19]:

"*Based on historical comparisons of results obtained with ibrutinib in the R/R (Refractory/Relapsed) setting with efficacy and safety/tolerability for single drugs and combination therapies in the first line setting, the indication has been revised to include adult patients with WM who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy. The restricted indication was considered acceptable as* ***there is no reason to expect inferior efficacy or a worse safety profile in the first line setting, and for the group of patients unsuitable for chemo-immunotherapy, limited treatment options are currently available****. …****Study 1118E provided convincing evidence*** *of clinical efficacy of ibrutinib in terms of the primary endpoint with support of secondary outcomes in adult patients with WM who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy*."

Therefore, while the pivotal Study 1118E enrolled R/R WM patients only, the EMA approved ibrutinib for the treatment of WM patients both in the R/Rand in the 1L setting, provided that 1L line patients are ineligible for chemo-immunotherapy.

2.3. *Administration and costs of the technology*

Ibrutinib is administered orally once daily at the patient's home, and does not require any pre-medication or associated treatment administration. No administration cost is therefore associated with the use of ibrutinib.

With respect to the acquisition cost of ibrutinib, a Department of Health (DH)-approved confidential simple Patient Access Scheme (PAS) is currently in place. Details of this scheme and of the cost-effectiveness results reflecting the arrangements agreed in this scheme are provided in Appendix 9. Importantly, however, discussions between NHS England and Janssen remain ongoing as to the final price of ibrutinib, as it is a CDF-transition drug across various indications. Consequently, the currently-DH approved price does not represent the final price of ibrutinib for this indication. Table 6 below summarises the anticipated costs of treatment with ibrutinib at list price.

Table 6: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	140 mg capsule, administered as monotherapy	SmPC[1]
Acquisition cost (excl VAT)	£51.10 per capsule	British National Formulary[43]
Method of administration	Oral	SmPC[1]
Doses	Three 140 mg capsules per day	SmPC[1]
Dosing frequency	Once daily (od)	SmPC[1]
Average length of a course of treatment	Treatment is until disease progression or unacceptable toxicity. Data from Study 1118E showed PFS was 69.1%, and OS was 95.2% at median follow-up of 24 months. Median treatment duration was 19.1 months (range, 0.5-29.7).	SmPC[1] Treon *et al*. 2015[23]
Average cost of a course of treatment	The cost per year of treatment is £55,954.50, estimated based on list price and dosing regimen.	Calculated based on list price and dosing regimen.
Anticipated average interval between courses of treatments	Ibrutinib is administered continuously until disease progression or unacceptable toxicity. Patients may discontinue treatment briefly in specific circumstances; for example, treatment should be held for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.	SmPC[1]
Anticipated no of repeat courses of treatments	Ibrutinib is administered continuously until disease progression or unacceptable toxicity.	SmPC[1]
Dose adjustments	Ibrutinib dose should be lowered to 140 mg od (one capsule) when used concomitantly with moderate CYP3A4 inhibitors. Ibrutinib dose should be reduced to 140 mg od (one capsule) or withheld for up to 7 days when it is used concomitantly with strong CYP3A4 inhibitors. Ibrutinib therapy should be withheld for any new onset or worsening grade ≥ 3 non-haematological toxicity, ≥ grade 3 neutropenia with infection or fever or grade 4 haematological toxicities. Once the symptoms of the toxicity have resolved to grade 1 or baseline (recovery), treatment may be reinitiated at the starting dose. If the toxicity reoccurs, the dose should be reduced by one capsule (140 mg). A second dose reduction of 140 mg may be considered as needed. For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 280 mg od (two capsules). For patients with moderate liver impairment (Child-Pugh class B), the recommended dose is 140 mg od (one capsule).	SmPC[1]

Anticipated care setting	The anticipated setting of care would be secondary care as WM, a haematological malignancy, is managed in this setting. Treatment with ibrutinib should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.	SmPC[1]
SmPC – summary of product characteristics; PFS – progression free survival; OS – overall survival		

2.4. *Changes in service provision and management*

Ibrutinib's pharmacological properties, together with its efficacy and its safety profile, will have a noticeable positive impact on service provision and management.

Ibrutinib is self-administered by the patient at home as it is an oral monotherapy. There are no concomitant therapies specified in the marketing authorisation or used in the key clinical trials [23, 44, 45]. As explained above in Section 2.3, ibrutinib has no further administration requirements and does not require any premedication, unlike the majority of existing treatments for WM.

Current treatment guidelines recommend rituximab-containing combination chemotherapy regimens such as dexamethasone + rituximab + cyclophosphamide (DRC), bendamustine + rituximab (BR), fludarabine + rituximab (FR), fludarabine + cyclophosphamide + rituximab (FCR) and cladribine + rituximab (Clad-R)[10]. Use of these regimens requires hospital-based infusion and chemotherapy facilities, and the toxicity burden of these regimens can be significant, particularly given the advanced age of most WM patients.

It is therefore reasonable to assume a steep reduction in infusion service requirements for patients on ibrutinib. No additional infrastructure, no change to the current standard of care testing and no further monitoring over and above current clinical practice is anticipated with this application.

A full evaluation of the resource use and costs associated with treatment can be found in Section 5 and 6.

2.5. *Innovation*

Ibrutinib is a first-in-class, oral, highly selective BTK inhibitor that offers a substantial step-change in the management of WM.

Ibrutinib significantly and 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. Treatment options currently used in WM, mainly rituximab-based chemotherapy regimens, were originally developed for other lymphoproliferative diseases including multiple myeloma and CLL. Moreover, they tend not to target disease-specific abnormalities and are generally aimed at managing treatment-related side effects that may be life-threatening, particularly in older adults. 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.

The National Comprehensive Cancer Network (NCCN) WM guidelines have recently been updated and recognise the innovative nature of ibrutinib and now recommend ibrutinib as non-stem cell toxic treatment option in both first line and salvage settings [11]. BCSH and ESMO guidelines have not been updated since ibrutinib was granted EMA approval for the treatment of WM in 2015.

Section 3 presents the current treatment landscape in WM and describes in greater detail the significant impact that the addition of ibrutinib is anticipated to have on the treatment pathway.

Ibrutinib's mode and mechanism of action alleviates the patient and NHS burden associated with current WM treatments

Ibrutinib is a potent, novel therapeutic target and a critical signalling kinase in the BCR pathway for tumour cell survival and proliferation [34, 35, 46, 47].

Ibrutinib is administered orally, once daily which provides an ease of administration to patients and has the added benefit of avoidance of chemotherapy. As a result, the time and logistical challenges for patients and carers related to repeated hospital visits for infusions is eliminated and the significant side-effects and psychological impact of chemotherapy are reduced, thereby freeing up NHS resources.

Unlike other targeted agents, ibrutinib is administered as monotherapy and does not require an associated intravenous (IV) monoclonal antibody administration. It also does not require premedication or prophylactic treatment to prevent side effects. There are no other WM treatments either licensed or recommended by NICE in the UK.

As discussed throughout this section, ibrutinib's pharmacological properties (e.g., oral bioavailability, potency, high specificity with reduced off-target effects, ideal elimination kinetic) lead to an unprecedented efficacy combined with a highly acceptable safety profile, representing a true step-change in the treatment of B-cell malignancies, including WM.

Ibrutinib demonstrates a well-tolerated safety profile which allows patients to continue therapy

The safety profile of ibrutinib has been well characterised in the broader ibrutinib clinical programme and the drug has similar tolerability in WM patients, even in a heavily pre-treated and/or elderly population with baseline comorbidities. There appear to be no unexpected safety signals associated with use in WM patients[23].

The safety data for ibrutinib have been derived from phase 2 and 3 studies in CLL, MCL and WM [21, 23, 24, 48]. AEs are generally predictable, of low grade and can be effectively managed with supportive therapy. The incidence of AEs appear to decrease over time and rarely result in need for discontinuation (7% in the 16-months follow-up RESONATE trial) or dose reduction [21, 24, 48].

Ibrutinib's manageable and predictable safety profile allows patients to remain on therapy, which supports maintaining target dose and ongoing treatment. This is in contrast to other chemo-immunotherapy agents commonly used in this setting [10, 49].

Section 4 reports the detailed safety data associated with ibrutinib.

Benefits of ibrutinib may not be fully captured by the quality adjusted life year (QALY) metric

WM is a debilitating condition associated with significant morbidity. It is therefore anticipated that WM will also impact on carers and the wider society as a result of patients with WM and their carers taking time off work. The social impact is likely to increase as the disease progresses. Such indirect benefits will not be captured in the QALY calculation.

Oral administration brings the advantage of ease of administration and the ability for patients to return to work and/or to resume normal daily activities, without the need for repeated hospital visits. This has obvious social, psychological and general well-being benefits and reduces costs for patients, carers and the NHS.

3. Health condition and position of the technology in the treatment pathway

3.1. *Overview of the disease*

WM is a lymphoproliferative B-cell disorder characterised by infiltration of lymphoplasmacytic cells into the bone marrow and IgM monoclonal gammopathy [6]. It is considered to be a lymphoplasmacytic lymphoma (LPL) by the World Health Organization (WHO) classification system [13, 50, 51].

Epidemiology

WM is a rare disorder that accounts for just 1-2% of all non-Hodgkin lymphomas [51]. With a median age at diagnosis of 68 years, WM disproportionately affects the elderly population [17, 18]. WM tends to me more common in men and the incidence appears to be lower in non-Caucasians [9].

The rarity of the condition and evolving criteria for classification and diagnosis means that only limited incidence and prevalence data are available. The British Committee for Standards in Haematology (BCSH) guidelines state that the age standardised incidence rate of WM is 0.55 per 100,000 persons per year in the UK [10]. Assuming a UK population of 64 million, this equates to an estimated 352 new cases each year, which is similar to the statement on the WMUK website which estimates that approximately 400 cases are diagnosed in the UK each year [52].

While prevalence data for WM in the European Union (EU) are not available, the incidence appears to be similar to the US where the overall incidence of WM is approximately 3 per million persons per year [6, 7]. To estimate WM EU prevalence, we took the 5-year prevalence of NHL in the EU of 210,509 persons, and applied the highest reported proportion of 2% of NHL as a conservative estimate. This provides an estimated prevalence of 4,210 persons. The total population in the EU-27, Norway, Iceland, and Lichtenstein is approximately 507,809,710 [53]. The EU prevalence of WM would, therefore, can be estimated as 0.08 per 10,000.

WM meets the EMA prevalence criteria for rare disease (EU prevalence of the condition must be ≤ 5 in 10,000) and ibrutinib has been granted orphan designation by the EMA in this indication.

Natural history and pathophysiology

While the aetiology of WM is still not fully understood, the disease is thought to originate from memory-like B-cells that have not completed terminal differentiation into IgM-secreting plasma cells. These WM cells differentiate into lymphoplasmacytic cells and plasma cells in the bone marrow [6, 7].

Recent studies have suggested that autoimmune and chronic inflammatory conditions may play an important role in the pathophysiology of WM [7]. There is also evidence that some individuals have a genetic predisposition to the disease [7]. Familial clustering of LPL/WM has been documented in several studies, with one large study involving 1,539 patients showing that patients with first-degree relatives with WM had a significantly higher risk of developing the condition themselves [7]. Allelic variants of IL6, BCL2, IL10, and TNFSF10 have been identified as candidate genes that increase the risk of WM [7].

In most cases WM is preceded by IgM-MGUS, a pre-malignant condition with a similar immunophenotype. IgM-MGUS can be differentiated from WM by the extent of bone marrow involvement and the absence of symptomatic disease [8]. The natural history of IgM-MGUS is not well characterised, but it is estimated that it progresses to frank WM or a related B-cell malignancy at an annual rate of 1-1.5% [7, 54 6].

Clinical presentation

Early stage WM is asymptomatic and typically indolent, progressing slowly to symptomatic disease. It is estimated that approximately 25% of patients with WM are asymptomatic at diagnosis[8]. The symptoms and signs of WM may vary but are usually related the tumour infiltration and monoclonal IgM accumulation that characterise this disease [7].

Proliferation of tumour cells in the bone marrow suppresses maturation of blood cells, resulting in cytopenias and progressive anaemia which is a common symptom in newly-diagnosed patients. Haemolytic anaemia and immune thrombocytopenia can also occur in some patients with WM [6]. WM cells can also infiltrate the tumour, liver and spleen. Lymphadenopathy and organomegaly are reported to occur in approximately 15-20% of patients with WM. Tissue infiltration of other organs is less common, but involvement of the lungs and the gastrointestinal system has been reported in WM.

Approximately 15% of WM patients present with symptoms of hyperviscosity due to the presence of elevated serum IgM levels. Common symptoms also include headache, blurred vision, and oronasal bleeding.

Additional symptoms associated with the presence of monoclonal IgM include cryoglobulinaemia, peripheral neuropathy and cold agglutinin haemolytic anaemia.

Diagnosis and prognosis

Diagnosis

Diagnosis of WM requires demonstration of an IgM monoclonal protein and histological evidence of bone marrow infiltration by lymphoplasmacytic cells [6, 8, 10-12]. International and UK guidelines recommend that the presence of lymphoplasmacytic cells in the bone marrow should be documented by trephine biopsy and aspirate followed by confirmation by immonophenotyping (flow cytometry and/or immunohistochemistry)[10, 11]. Expression of CD19, CD20, CD22 and CD79a are normally increased in patients with active WM [6, 10, 12].

Serum protein electrophoresis and immunofixation should be used to confirm the presence of IgM monoclonal protein, while quantification of IgM levels can be done either by densitometry or total serum IgM quantification by nephelometry [10, 12]. Assessment of plasma viscosity is also recommended when signs and symptoms of hyperviscosity syndrome, such as oronasal or retinal bleeding or peripheral neuropathy, are present or when IgM levels are above 4 g/dL [6, 10, 12, 13].

Conventional karyotyping is of limited application in WM because of the low rate of cell proliferation and is not required as part of the standard diagnostic workup [10, 12].

Staging and prognosis

The International Prognostic Staging System for Waldenström's Macroglobulinaemia (IPSSWM) is used to assess the likelihood of disease progression, and to guide treatment once patients have developed signs and symptoms of WM, i.e., once they are deemed to have active, symptomatic disease. It is recommended that all patients are assessed at

diagnosis, although this does not directly impact treatment choices [10]. The IPSSWM uses a combination of characteristics that are known to adversely impact survival in WM to create low-risk, intermediate-risk, and high-risk groups. These factors include [17]:

- advanced age (>65 years)
- β2-microglobulin (B2M) >3 mg/L
- anaemia (haemoglobin ≤11.5 g/dL)
- thrombocytopenia (platelet count ≤100 x 10^9/L)
- IgM monoclonal gammopathy (IgM >7.0 g/dL).

While WM generally follows an indolent course, it remains an incurable disease and there are some significant variations in clinical course and outcome. Median OS in WM ranges from just under 4 years to 12 years depending upon risk category [17], with longer survival (median: 11 years) observed in patients diagnosed with symptomatic WM[6]. A summary of the IPSSWM risk categories and the corresponding survival estimates expressed in terms of median survival (months) and 5-year survival is provided in Table 7 below:

Table 7: IPSSWM risk categories and survival [17]

Risk category	Definition	Median survival (months)	5-year survival* (%)
Low risk	Aged ≤65 years plus not more than 1 adverse characteristic	142.5	87
Intermediate risk	2 adverse characteristics or aged >65 years	98.6	68
High risk	3 or more adverse characteristics	43.5	36

Adverse characteristics are aged >65 years; platelet count ≤100 X 10^9/L; ß2-microglobulin >3 mg/L; haemoglobin ≤11.5 g/dL; monoclonal IgM concentration >7.0 g/dL; granulocytes ≤1.5 X 10^9/L; albumin ≤3.5 g/dL.
* *P*<0.001.
IPSSWM=International Prognostic Staging System for Waldenström's Macroglobulinaemia.

Treatment-associated morbidity also has an impact on survival. Patients undergoing treatment for symptomatic WM are at prolonged risk of secondary infections with monoclonal antibodies and purine analogues and risk of myelodysplasia from fludarabine. Patients with WM are also at increased risk for second malignancies such as transformation to diffuse large B-cell lymphoma[51].

Advances in treatment prior to the arrival of novel agents such as ibrutinib have only resulted in small gains in survival. One study that used data from the SEER database to investigate trends in survival in patients with WM between 1980 and 2010 found only modest improvements in the median OS (+1.7 years, from 5.6 to 7.3 years), and 5-year rates of OS (+9 %-points, from 56% to 65%) in patients treated from 2001 to 2010 compared with those treated from 1980 to 2010[55, 56].

3.2. *Effects of the disease or condition on patients, carers and society*

There is a lack of evidence quantifying the impact of WM and its treatment on patient quality-of-life (QoL). This is compounded by a paucity of clinical trials and the lack of a specific QoL instrument for this disease.

Nearly half of WM patients have an associated IgG and IgA hypogammaglobulinaemia, which increases the risk of infection and there is no evidence that immunoglobulin replacement therapy is beneficial[51].

Other common co-morbidities include cytopenias resulting from bone marrow infiltration by lymphoplasmacytic cells and the adverse effects of immunoglobulins, which can cause the occurrence of painful complications such as cryoglobulinaemia and neuropathy. Central nervous system and peripheral neuropathy has been reported in as many as 47% of WM patients [57]. WM cells may also infiltrate the meninges, brain cells, and the cerebrospinal fluid (Bing-Neel syndrome

Patients with WM that experience hyperviscosity will be treated with plasmapheresis, which is invasive, time-consuming and provides only symptomatic management to temporarily reduce IgM levels [6]. Patients may also face catastrophic sequelae including irreversible vision loss secondary to hyperviscosity, with severe impact on QoL for both the patient and carers [15].

In a patient survey [60] by the WMUK patient association of [redacted] patients (of which, [redacted] of respondents to the question on stage of disease had R/R WM), respondents reported that the symptoms that most impacted their QoL were as follows:

- Tiredness or lack of energy
- Weakness
- Frequent infections
- Tingling or numbness in feet or legs
- Shortness of breath

Treatment-associated morbidity can be serious, including prolonged risk of secondary infections with monoclonal antibodies and purine analogues, risk of myelodysplasia from fludarabine, and worsening of peripheral neuropathy related to bortezomib[51]. Patients with WM are also at increased risk of thrombosis and second malignancies, including transformation to diffuse large B-cell lymphoma, myelodysplastic syndrome, acute myeloid leukaemia, and solid cancers [51].

The WMUK patient survey [60] reported that, in patients' opinions, the most tolerable treatment options were watch and wait, ibrutinib followed by rtx maintenance. The least tolerable were ASC, R-ESHAP followed by bortezomib + rituximab.

WM disproportionately affects the elderly population who may have other comorbidities, limited mobility, limited biological capacity to tolerate chemotherapy, and a limited ability to tolerate adverse events, which also have a negative impact on health-related QoL [17].

3.3. *Current treatment landscape and anticipated positioning of ibrutinib*

This submission addresses the following two patient populations which are included within ibrutinib's marketing authorisation [1]:

- adult first line WM patients unsuitable for chemo-immunotherapy and
- adult WM patients who have received at least one prior therapy.

There is general agreement in current guidelines for WM that treatment should only be initiated in the presence of symptoms e.g. hyperviscosity, neuropathy, symptomatic

adenopathy [10-12]. Patients with asymptomatic disease do not require treatment and should be subject to a "watch and wait" strategy [11, 12, 51].

The goals of treatment, once started, are to reduce the tumour mass, provide symptomatic relief and reduce the risk of organ damage [11, 13]. Plasmapheresis is recommended initially for immediate disease control for patients with symptomatic hyperviscosity (which can be fatal).

NICE Guidance

There currently is no NICE guidance for the treatment of WM.

Clinical Guidelines

The lack of randomised data has complicated and held back the development of evidence-based algorithms in WM. The majority of published studies are non-randomised, often single institution-based, phase 2 studies that typically include both newly diagnosed and relapsed patients[10].

Evidence-based guidelines for the treatment of frontline and R/R WM are available from the British Committee for Standards in Haematology (BCSH) and the European Society of Medical Oncology (ESMO) [10, 12]. As, at the time these guidelines were published, no treatment was licensed or was funded by the NHS for WM (i.e. these were published before ibrutinib EC approval in WM in July 2015), the guidelines generally recommend a "physician's choice" from among the many available agents. These guidelines are discussed in further details below by line of therapy.

First line therapy

The main BCSH guideline recommendations for the treatment of first line WM are summarised in Table 8 below:

Table 8 BCSH treatment algorithm for first line WM[10]

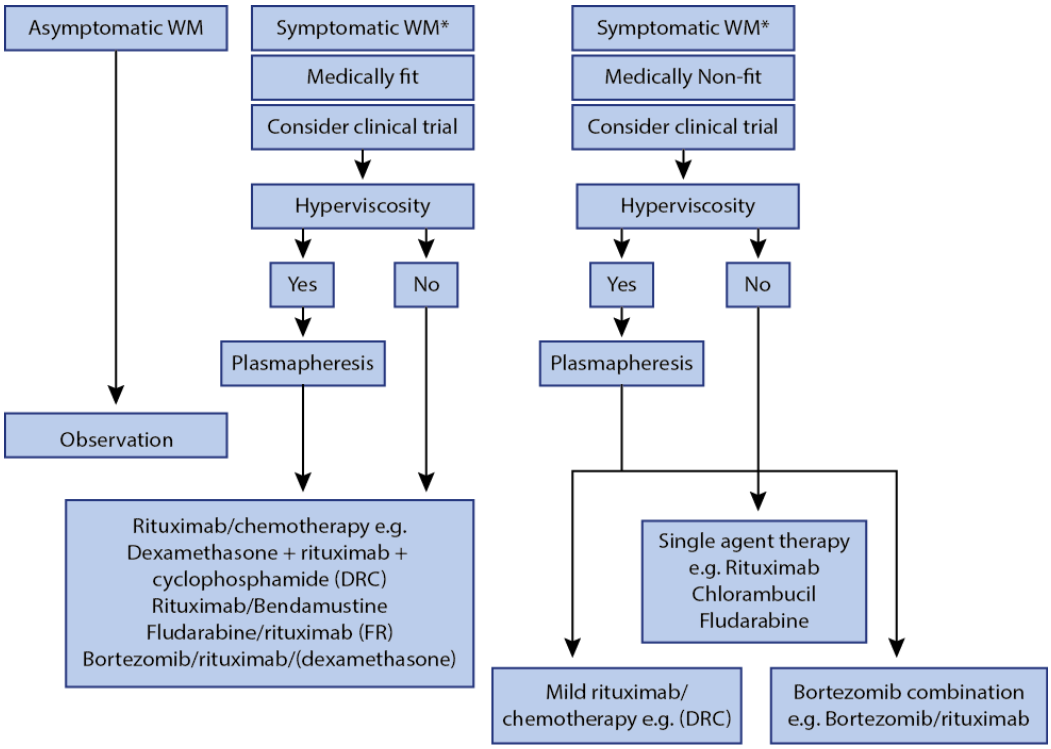
BCSH guidelines for treatment of first line WM
Patients with symptomatic WM should receive a rituximab-containing regimen, e.g. RCD, BR, FR, FCR or Clad-R. The choice of regimen in individual patients will take into consideration performance status, clinical features including renal function, co-morbidities and potential candidacy for SCT.
Given the risk of IgM flare, careful monitoring of all patients receiving rituximab is required. Rituximab should be deferred in patients at high risk of hyperviscosity.
R-CHOP should not be used as primary therapy in WM.
Chlorambucil remains suitable therapy in elderly frail patients.
Bortezomib is not recommended as primary therapy outside the context of a clinical trial.
There is insufficient evidence to support the use of maintenance rituximab.

RCD - rituximab + cyclophosphamide + dexamethasone, BR - bendamustine + rituximab, FR - fludarabine + rituximab, FCR - fludarabine + cyclophosphamide + rituximab, Clad-R - cladribine + rituximab, SCT - stem cell transplantation, R-CHOP - Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisolone

ESMO has also issued guidelines for treatment of patients with newly diagnosed WM. Recommended first line therapies include alkylating agents (chlorambucil), nucleoside analogues (cladribine or fludarabine), bortezomib, and rituximab. The choice of therapy

should be guided by the patient's age, clinical presentation, and level of fitness. Although 'fitness' is not specifically defined in the guidelines, it is broadly implied to mean free of comorbidities that are not associated with WM [12].

Figure 4: ESMO treatment algorithm for first line WM[12]



DRC=dexamethasone+rituximab+cyclophosphamide; FR=fludarabine+rituximab; WM=Waldenström's macroglobulinaemia

Relapsed or refractory therapy

As WM is an incurable disease, most patients will eventually relapse after first line therapy. Treatment choice for R/R patients will depend on factors such as length of prior treatment, mechanisms of action of prior therapies, and patient characteristics [11, 12]. Bortezomib-based therapy and purine analogue-based therapy with fludarabine are treatments that have been investigated in R/R WM [11]. Bendamustine + rituximab (BR) is also widely used in this setting.

The BCSH criteria for reintroduction of treatment at relapse are broadly similar to those used at frontline. Treatment should only be initiated when clinical symptoms develop and not at time of progression. Decisions around treatment at relapse should depend on patient wishes, availability of clinical trials, duration of previous responses, tolerability to previous treatment, performance status, comorbidities and potential for stem cell transplantation [10]. The key BCSH recommendations for the management of R/R patients are summarised below [10]:

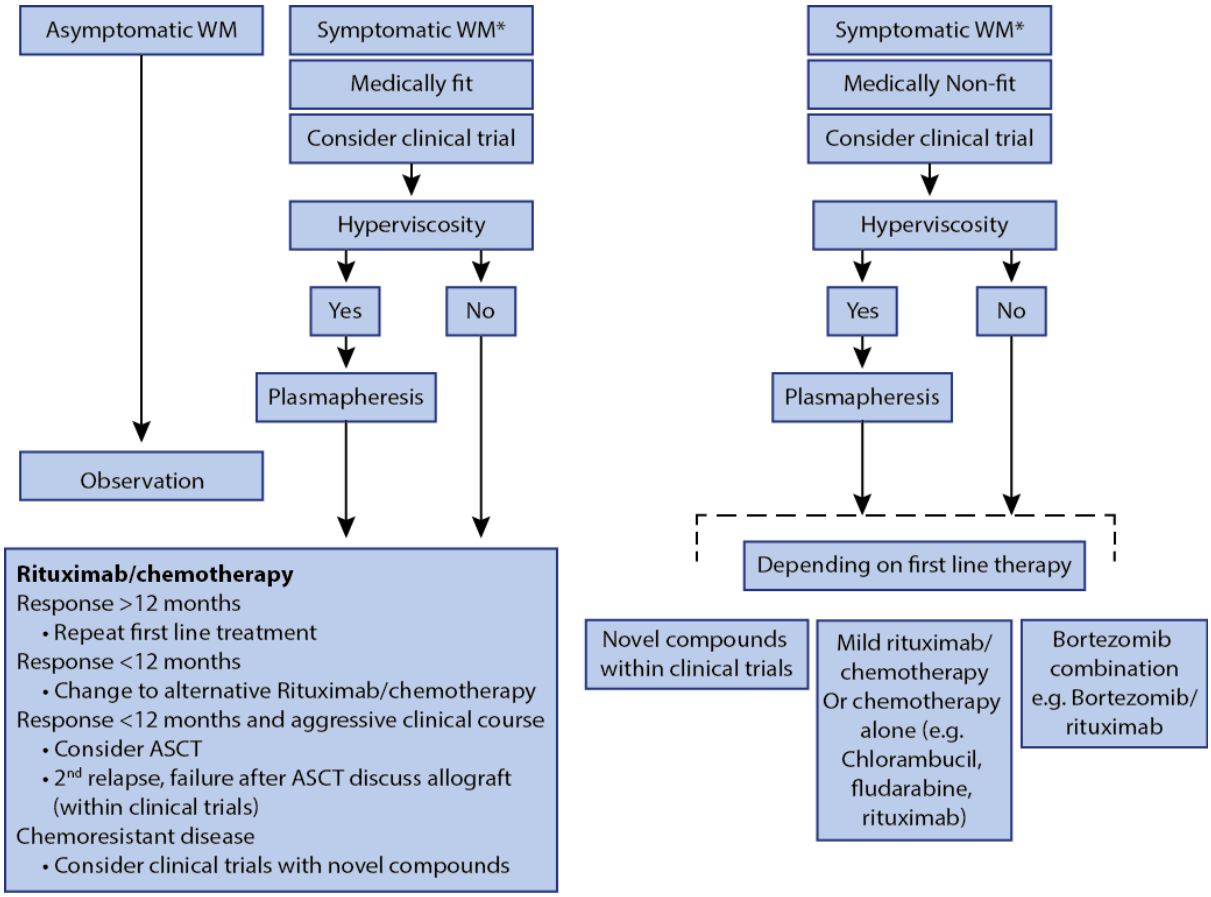
Table 9: BCSH treatment algorithm for R/R WM[10]

BCSH guidelines for treatment of R/R WM
Repeat bone marrow aspirate and trephine assessment and CT scanning should be performed prior to the reintroduction of treatment.
Patients who remain asymptomatic despite serological evidence of progression can be observed until clinical symptoms occur.
Patients should receive a rituximab-containing regimen if CD20 is expressed. Appropriate regimens include FR, FCR, Clad-R, BR and DRC. The choice of regimen in individual patients will take into consideration performance status, clinical features including renal function, co-morbidities and potential candidacy for SCT.
Retreatment with primary therapy may be appropriate in some patients.
Bortezomib-containing regimens are suitable in the relapse setting. Weekly regimens are preferable, given the neurological toxicity associated with the biweekly schedules. Prophylaxis against herpes zoster virus (HZV) reactivation is recommended.
Alemtuzumab is a potential option in refractory disease* Surveillance for CMV reactivation is recommended.

BR - bendamustine + rituximab, FR - fludarabine + rituximab, FCR - fludarabine + cyclophosphamide + rituximab, Clad-R - cladribine + rituximab, SCT - stem cell transplantation, DRC: dexamethasone + rituximab
* Alemtuzumab is now only available on a named-patient basis

The ESMO guidelines for relapsed WM recommend that an alternative rituximab/chemotherapy regimen should be used if the relapse occurs within the first year, with the choice of therapy depending on the prior regimen. If the initial treatment was with rituximab plus alkylating agents, the salvage regimen may be switched to rituximab in combination with nucleoside analogues, rituximab / bendamustine or bortezomib and vice versa. The ESMO treatment algorithm for relapsed patients is illustrated in Figure 5 below:

Figure 5: ESMO treatment algorithm for relapsed WM [12]



Unmet needs in WM

There is no established standard of care for the treatment of WM in the UK[13, 51]. CDF delisting of bortezomib in 2015 (after the BCSH and EMSO guidelines were published) has further limited treatment options for WM patients.

Treatment options currently used in WM were originally developed for other lymphoproliferative diseases including multiple myeloma and chronic lymphocytic leukaemia (CLL). WM patients are therefore currently managed with off-label treatments that do not target disease-specific abnormalities and are generally aimed at managing disease symptoms[26]. These can lead to treatment-related side effects that may be life-threatening, particularly in older adults. Other limitations associated with current treatments for WM are summarised in Table 10:

Table 10 Limitations associated with current treatments for WM

Treatment	Limitation
Rituximab	Serious, life-threatening risk of a spike or flare in IgM levels when rituximab is used as monotherapy or in combination with other agents [15]. Patients unsuitable for chemoimmunotherapy have limited alternative therapies [19]

Bendamustine	Possible stem cell toxicity and/or risk of transformation [11]
Traditional chemotherapy	Higher rates of cytopenias and myelosuppression [58]
Fludarabine	Potentially toxic to stem cells; increased risk of transformation, myelodysplasia and AML [11]

The development of ibrutinib as a new, targeted therapy will help to address many of these needs. Indeed, within the WMUK patient survey [60], [redacted] of respondents felt there is unmet need for more drug therapy options for patients with WM.

3.4. *Equality of opportunity/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.

4. Clinical effectiveness

4.1. *Identification and selection of relevant studies*

A clinical systematic literature review (SLR) was conducted in order to identify and select studies relevant for consideration within this submission.

Search strategy

The search strategy was developed to identify published relevant clinical studies that enrolled patients with WM. An initial literature search was conducted on 06 February 2015 and then updated on 03 May 2016. The search algorithms used were generated under the PICOS framework (Population, Intervention, Comparators, Outcomes, Study design) and in line with the research question (Appendix 1).

The same syntax and search settings were used for both the initial and the updated searches. A summary of the search strings and the rationale for their design is in Appendix 1.

The databases searched without date limits were as follows:

- MEDLINE (via PubMed) and MEDLINE In-Process (via PubMed)
- Embase (via Embase.com) and Embase In-Process (via Embase.com)
- Cochrane Collaboration Central Register of Clinical Trials (CENTRAL, via the Cochrane Library).

To capture new trials that were not yet indexed, PubMed and Embase.com searches were run without limitations (i.e., no limitations such as title-abstract designations, Medical Subject Headings [MeSH] terminology, etc.) to identify new publications from December 2014 through to June 2015.

Searches were also performed via the Cochrane Library and the other databases noted above to identify any high-quality, recently conducted SLRs (published from 2011 to 2015) to serve as supplemental data sources. Bibliographies of relevant systematic review articles published since 2011 and the bibliographies of accepted studies were also reviewed to identify any additional, relevant publications.

In addition to the databases listed above, ‘grey’ literature (i.e., material that can be referenced but is not typically published in peer-reviewed, database-indexed medical journals) was also searched for meeting abstracts or conference posters presenting any relevant information on the outcomes of interest. Proceedings from the past three years (if available) for the following key conferences were screened for relevant abstracts:

- American Society of Clinical Oncology (ASCO) 2013–2015 (via Embase)
- American Society of Hematology (ASH) 2013–2015 (via Embase)
- European Hematology Association (EHA) 2013–2015 (via Embase)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 2013–2015 (international and European meetings): http://www.ispor.org/
- International WM workshop (IWWM) 2012 and 2014: http://www.wmworkshop.org/
- Clinicaltrials.gov (only studies for which results are available were searched)

Study selection

The SLR focussed on trials of WM patients reporting efficacy outcomes (OS, PFS, response to treatment, response duration, time to first response, event-free survival [EFS], time to treatment failure [TTF], time to progression [TTP]), and safety outcomes (AEs, discontinuations of interest).

The search was not limited by date or language; however, all non-English-language publications with English abstracts were reviewed at the abstract level, and those that met the abstract inclusion criteria were noted separately (rejected as "Language other than English") and were not assessed further in the review. Publications without titles and abstracts in English were title screened and categorised according to the available information. All publications identified provided English-translated titles.

All randomised trials and non-randomised trials reporting on a comparator of interest were assessed for their study design, patient population (in order to be sufficiently comparable to the ibrutinib trial), and how the outcome of interest was reported.

The pre-specified inclusion and exclusion criteria used to identify studies relevant for inclusion in this review (along with their rationale) are described in Appendix 1.

After the initial removal of duplicate citations, abstracts were screened by two independent investigators using the pre-specified inclusion and exclusion criteria. Any discrepancies between the two investigators were reviewed and resolved by a third investigator before proceeding to full-text article retrieval. In this initial screening phase, studies were not excluded based on intervention/comparators of interest.

Full-text articles were reviewed by a single investigator and all articles rejected at the full-text screening level were independently verified by a second, senior-level investigator based on the reason for rejection and whether the rejection was correct. Accepted full-text articles were further validated for inclusion during data extraction. The inclusion/exclusion criteria for the interventions/comparators of interest were applied during full-text screening.

Flow diagram

After the initial removal of duplicate citations, 1,595 abstracts were retained (across the initial and updated searches) and screened according to the pre-specified inclusion and exclusion criteria. A table presenting the total number of references yielded from each database as well as a breakdown by search cut-off date (06 February 2015 and 03 May 2016 for the initial and updated searches, respectively) is provided in Appendix 2.

Of the 1595 abstracts screened, 1377 studies were excluded at the abstract level. Among the 218 studies retrieved, when screening them again on the basis of complete manuscript – rather than abstract only, 130 citations were rejected and 88 citations reporting the findings of 64 trials were accepted, including:

- 23 reported outcomes for first line (i.e. treatment naïve) patients – 3 of them included comparators covered by the NICE Final scope[31, 61, 62]

- 32 reported outcomes for R/R (i.e. previously treated) patients – 9 [23, 45, 63-68] of them included comparators covered by the NICE Final scope;
- and 33 reported outcomes for mixed treatment naïve and previously treated patients

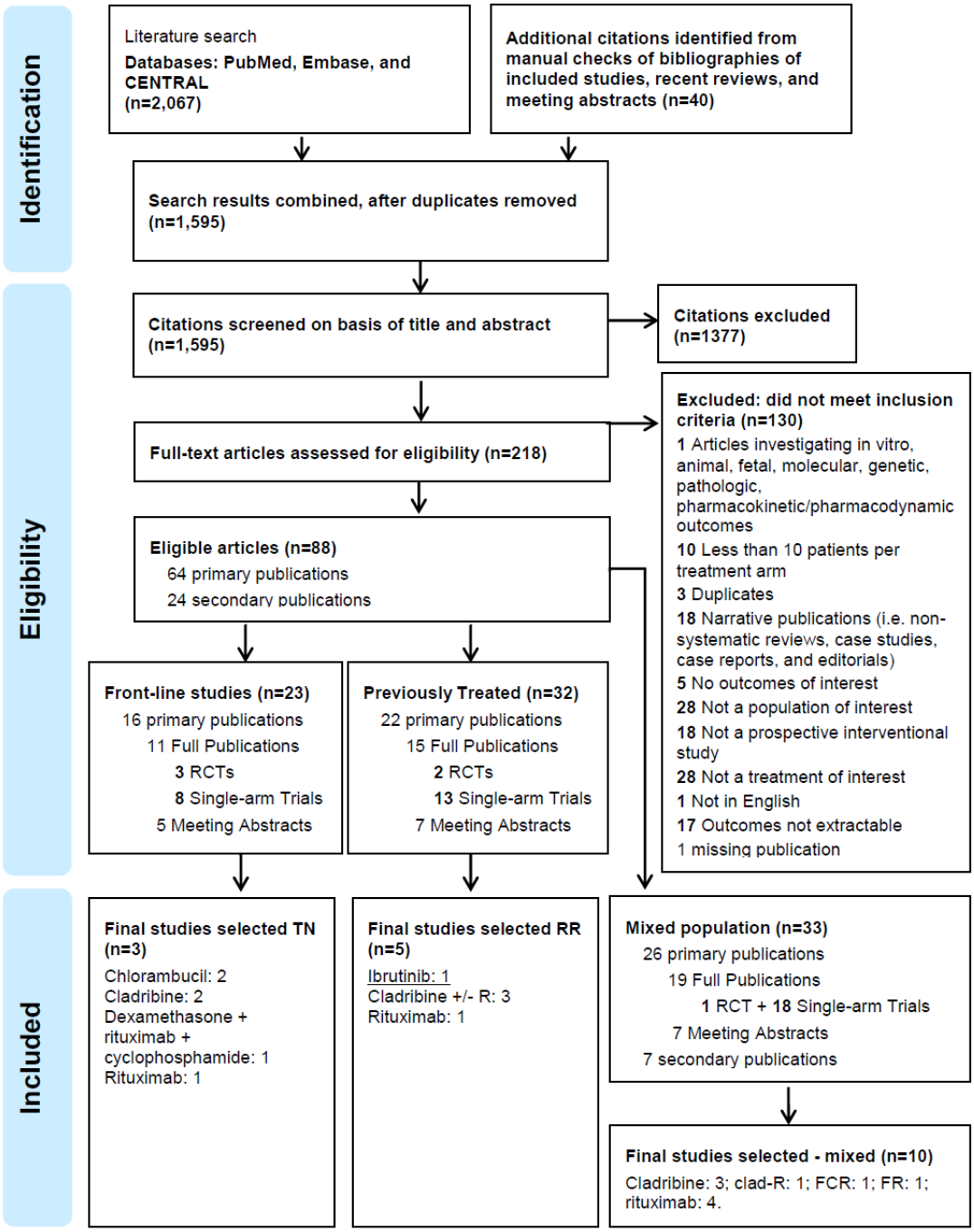
Among the 64 accepted trials (including 4 trials with ibrutinib), 19 trials (including 3 trials with ibrutinib were only available in abstract format without accompanying full-text publications and were discarded from the review, leaving 45 selected trials:

- 11 trials focused on front-line WM patients including 3 RCTs;
- 15 trials including 2 RCTs and 13 single-arm studies focused on previously treated WM patients;
- 19 trials reported on mixed populations both front-line and previously treated patients.

As described in Appendix 2, a final step of the updated SLR consisted in removing trials that included comparators that were not included in the NICE Final scope. A total of 27 trials were therefore removed from the final list of studies retained for this review (a list of excluded trials is provided in Appendix 2), leaving 18 studies, including 3 in the TN [31, 61, 62], 5 in the R/R[23, 64-67] and 10 in the mixed TN and R/R[69-78] settings respectively. Over, of the 3 RCTs that were retained, none involved patients treated with ibrutinib. The only trial with patients treated with ibrutinib was the phase 2 pivotal trial, Study 1118E, Treon et al. 2015 [23] on which ibrutinib was granted approval by the European Medicines Agency for the WM indication. Further details of the selected studies are provided in Appendix 2)

The process of eliminating references based on the systematic review protocol and the subsequent exclusion of studies from the present consideration of clinical evidence for ibrutinib is presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram template in Figure 6 below:

Figure 6: PRISMA Flow Diagram of Clinical Efficacy and Safety Studies



Multiple publications from one study

When any particular study or trial had multiple publications associated with it, this was identified during study linking/related-publication identification and taken into account in the

review trial flow (as shown in Figure 6) where a clear distinction has been made between numbers of included *studies* and numbers of included *publications* at the relevant stages).

In order to avoid double-counting of data, when data from a single study presented in this clinical effectiveness section were drawn from more than one source or publications, or when studies were linked, the relevant publications associated with the actual study itself are shown.

4.2. *List of relevant randomised controlled trials*

No RCT relevant to this appraisal, i.e. no RCT that included ibrutinib monotherapy as an intervention or a comparator, was identified by the literature search. This is not a surprise, as the EMA approval of ibrutinib in the treatment of WM was based on the findings of a single-arm phase 2 study presented in Section 4.10 below[19].

4.3. *Summary of methodology of the relevant randomised controlled trials*

As per Section 4.2, no RCT relevant to this appraisal was identified and therefore a summary of methodology of relevant RCTs cannot be provided.

4.4. *Statistical analysis and definition of study groups in the relevant randomised controlled trials*

As per Section 4.2, no RCT relevant to this appraisal was identified and therefore a statistical analysis and definition of study groups in the relevant RCTs cannot be provided.

4.5. *Participant flow in the relevant randomised controlled trials*

As per Section 4.2, as no RCT relevant to this appraisal was identified, a participant flow in the relevant RCTs cannot be provided.

4.6. *Quality assessment of the relevant randomised controlled trials*

As per Section 4.2, as no RCT relevant to this appraisal was identified, a quality assessment of the relevant RCTs cannot be provided.

4.7. *Clinical effectiveness results of the relevant randomised controlled trials*

As per Section 4.2, since no RCT relevant to this appraisal was identified, clinical effectiveness results of the relevant RCTs cannot be provided.

4.8. *Subgroup analysis*

As per Section 4.2, no relevant RCT was identified and therefore no information on subgroup analysis can be provided.

4.9. *Meta-analysis*

As per Section 4.2, no relevant RCTs were identified and therefore a meta-analysis cannot be conducted.

4.10. *Non-randomised and non-controlled evidence*

Non-randomised and non-controlled evidence relevant for this submission include the phase 2 pivotal study (Study 1118E).

WM is considered a rare disease by the EMA given the small number of patients with this condition; clinical research is therefore limited in this disease area. The EMA approved ibrutinib for the treatment of WM patients, both in the first line (in patients for whom chemo-immunotherapy is unsuitable) and in the R/R settings based on the findings of Study 1118E, which enrolled R/R patients only (n = 63) [19]. In its Variation assessment report dated 21 May 2015, the CHMP stated:

"*During the assessment the CHMP raised a major objection about the indication needing to be further discussed, with reference to first line setting. Based on historical comparisons of results obtained with ibrutinib in the R/R (Refractory/Relapsed) setting with efficacy and safety/tolerability for single drugs and combination therapies in the first line setting, the indication has been revised to include adult patients with WM who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy. The restricted indication was considered acceptable as* ***there is no reason to expect inferior efficacy or a worse safety profile in the first line setting, and for the group of patients unsuitable for chemo-immunotherapy, limited treatment options are currently available****... Study PCYC-1118E provided* ***convincing evidence*** *of clinical efficacy of ibrutinib in terms of the primary endpoint with support of secondary outcomes in adult patients with WM who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.*"

The small sample size of Study 1118E therefore needs to be assessed in light of the broader clinical context to fully appreciate the strength of the evidence generated by this study and specifically that [23]:

- Ibrutinib demonstrates single agent activity in WM patients, as evidenced by high response rates and PFS;
- Ibrutinib provides durable remissions and is well tolerated (with low rates of grade 3/4 adverse events) in this patient population.

An overview of Study 1118E is provided in Table 11 below:

Table 11: List of relevant non-RCTs

Trial no./ title	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
PCYC-1118E (Clinicaltrials.gov *NCT01614821)*	Ibrutinib	WM adults with at least one prior line of therapy	Efficacy and safety	Treon et al. 2015[23]	This phase 2 study (n = 63) is the only completed trial for ibrutinib in WM and is the pivotal study on which ibrutinib was granted EMA approval.

WM=Waldenström's macroglobulinaemia; EMA=European Medicines Agency

PCYC-1118E

Trial

PCYC-1118E (Study 1118E), a prospective multi-centre, open-label, phase 2 trial of single-agent ibrutinib, was conducted in adult WM patients who have received one prior line of therapy. It was led by Professor Treon across three sites in the United States (US). A total of 63 patients were enrolled in the study. An overview of key features of Study 1118E design is provided in Table 12 below [23].

Data sources

Data in this section are predominantly drawn from the published paper (Treon *et al.* 2015) and the clinical study report (CSR) [23, 79]. The published paper, which was based on a 19th December 2014 data clinical cut-off (CCO) date, is used wherever possible, with additional information drawn from the CSR (based on 28th February 2014 CCO date).

Table 12: Summary of trial design of Study 1118E [23, 79]

Parameter	Description
Location	United States
Trial design	Prospective, multicentre, phase 2 trial.
Enrolment	63 patients were enrolled from May 23, 2012 to June 13, 2013.
Key Eligibility criteria	• Age ≥18 years. • Measurable disease, defined as the presence of serum IgM with a minimum IgM level >2 times the institutional upper limit of normal (ULN). • Clinicopathological diagnosis of WM. • Necessity of treatment based on IWWM guidelines. • At least 1 prior therapy for WM. • ECOG performance status of ≤2. • Adequate hematologic, renal, and hepatic function. • No active therapy for other malignancies with the exception of topical therapy for basal cell or squamous cell skin cancers.
Exclusion criteria	• Warfarin anticoagulation therapy. • Diagnosed lymphoma of the central nervous system.
Trial drugs	Ibrutinib was administered orally (PO) at 420 mg (three 140-mg capsules) daily (QD) for 26 four-week cycles until the disease progressed or unacceptable toxic effects developed. Patients without disease progression could provide a second informed consent and continue therapy beyond 26 cycles.

Primary outcomes	• ORR (≥25% reduction in serum IgM levels) including:
	  ○ Major response (≥25% reduction in serum IgM levels)
	  ○ PR (≥50% reduction in serum IgM levels)
	  ○ VGPR rate (≥90% reduction in serum IgM levels)
	• CR major response rate (≥50% reduction in serum IgM levels).

Secondary outcomes	• PFS • Safety and tolerability

CR, complete response; ECOG, Eastern Cooperative Oncology Group; ORR, overall response rate; PFS, progression free survival; VGPR, very good partial response.

Methods

Patients enrolled in Study 1118E were symptomatic adult patients with previously-treated WM. The full eligibility criteria are presented in Table 12 above. The CHMP, in its Variation report, deemed the study population to be representative for the general WM population with previously treated disease[19].

Ibrutinib was administered orally at 420 mg (three 140-mg capsules) daily for 26 four-week cycles [23]. Patients were evaluated for response and tolerance to ibrutinib on Day 1 of Cycles 2 and 3, then every 3 cycles for up to a total of 26 four-week cycles or until disease progression. In patients with no disease progression, treatment with ibrutinib could be extended past 26 cycles [23]. Investigator response assessments were performed per protocol and confirmed by an Independent Response Review Committee (IRRC) [23].

The primary endpoint was two-fold: i) to determine the overall response rate (ORR), which included the rate of minor response (MR), partial response (PR), very good partial response (VGPR) and complete response (CR), and ii) to determine the rate of major response (MR) according to criteria adopted from the 3rd International Workshop on Waldenström's Macroglobulinaemia (IWMM) [23, 79, 80]. The CHMP considered that both the primary endpoint (ORR per investigator assessment utilising response criteria adopted from the 3rd IWWM) and the independent review sensitivity analysis were appropriate for a single arm trial in this setting [19]. The definitions of the various levels of response are presented in Table 13 below.

Table 13: Modified IWWM response criteria for investigator assessment of response and progression [79]

Category	Response Criteria
Complete response	Resolution of all symptoms, normalisation of serum IgM levels, required 2 consecutive measurements of IgM and negative serum immunofixation. Resolution of any adenopathy or splenomegaly by central radiology.
Very good partial response	≥90% reduction in serum IgM levels or IgM levels within normal range. Required 2 consecutive measurements of IgM.
Partial response	≥50% reduction of serum IgM from baseline. Required 2 consecutive measurements of IgM.
Minor response	≥25% reduction in serum IgM levels. Required 2 consecutive measurements of IgM.

IgM=immunoglobulin M. IWWM= International Workshop on Waldenström's Macroglobulinaemia

Secondary outcomes included PFS and safety and tolerability. PFS was defined as the duration of time from start of treatment to objective disease progression, death or last follow-up [79]. The lower boundary of the 95% CI was required to exceed 32% in order to reject the null hypothesis (i.e., to meet study success criteria) [79].

Results

A total of 63 patients were enrolled in the study from 3 sites in the US [23] and 43 patients (68%) remained on treatment after the final data were entered on 19th December 2014[23]. Treatment was administered for a median of 19.1 months (range, 0.5 to 29.7 months)[23].

Patient baseline characteristics

The median age was 63.0 years (mean age was 64.5 years); the majority of patients were male (76.2%) [23]. The median time from diagnosis of WM to study entry was 76 months (range: 6 to 340 months) [23]. The median number of prior regimens was 2 (range: 1 to 9) [23]. Baseline demographics and clinical characteristics are reported in Table 14 [23] below:

Table 14: Baseline demographic and clinical characteristics in Study 1118E[23, 88]

Characteristic	Ibrutinib (N=63) n (%)
Demographic characteristic	
Age Median (range), years Mean (SD), years	 63.0 (44 to 86) 64.5 (10.7)
Gender Male, no. Female, no.	 48 (76.2) 15 (23.8)
Race White, no. Other, no.	 60 (95.2) 3 (4.8)
Clinical characteristics	
Time since initial diagnosis Median (range), months	 76 (6 to 340)
IPSSWM risk* at baseline, no. (%) Low Intermediate High	 14 (22) 27 (43) 22 (35)
Serum IgM (mg/dL) Median (range) >4,000, no. (%)	 3,520 (724 to 8,390) 26 (41)
Haemoglobin level Median (range), g/dL	 10.5 (8.2 to 13.8)
Median haematocrit (range), %	30.8 (24.5 to 41.5)
ß$_2$-microglobulin level, no. (%) Median (range), mg/L >3 mg/L, no. (%) >3.5 mg/L, no. (%)	 3.9 (1.3 to 14.2) 45 (71) 35 (56)
Prior WM treatment	
Time (days) from last treatment Median (range)	 170 (1 to 3,276)

Characteristic	Ibrutinib (N=63) n (%)
Number of regimens Median (range)	2 (1 to 9†)
Number of regimens, no. (%) 1 2 3 4 ≥5	 18 (28.6) 14 (22.2) 8 (12.7) 7 (11.1) 16 (25.4)
Previous therapy, no. (%) Monoclonal antibody Glucocorticoid Proteasome inhibitor Alkylating agent Nucleoside analogue mTOR inhibitor Immunomodulator Anthracyclines Autologous SCT Other, including experimental therapy	 57 (90) 42 (67) 33 (52) 32 (51) 15 (24) 13 (21) 7 (11) 7 (11) 4 (6) 13 (21)
Refractory to most recent therapy, no (%)	25 (40)

IgM=immunoglobulin M; mTOR=mammalian target or rapamycin; IPSSWM=International Prognostic Scoring System for Waldenström's Macroglobulinemia; SCT=stem cell transplantation; SD= standard deviation; WM=Waldenström's macroglobulinaemia.
*IPSSWM assesses the following 5 adverse factors: age >65 years; haemoglobin ≤11.5 g/dL; platelets ≤100 x 10^9/L; β-2 microglobulin >3 mg/L; and serum IgM monoclonal protein concentration >70 g/L. Risk at baseline categories are defined as follows: low risk, if ≤1 adverse factor except age; intermediate risk, if 2 adverse characteristics or age >65 years; high risk, if >2 adverse characteristics

Overview of primary endpoint results

The key results from Study 1118E are shown in Table 15 below and demonstrate that ibrutinib showed high rates of overall and major response in patients with previously treated WM; the responses were rapid and durable, improved over time and were associated with sustained improvements in haemoglobin and IgM levels.

Results also show that ORR and major responses continue to improve across genomic subgroups with extended therapy (i.e., >6 cycles). These findings further support the importance of continued dosing of ibrutinib in patients with WM [23].

Table 15: Key results from Study 1118E [23]

Variable	Ibrutinib 420 mg (n=63)
ORR	90.5% (95% CI: 80.4 – 96.4)
MRR	MRR: 73.0% (95% CI: 60.3 – 83.4)
PFS	Median PFS has not been reached. At 24 months, the estimated rate of PFS was 69.1% (95% CI: 53.2 – 80.5).
OS	Median OS has not been reached.

	At 24 months, the estimated rate of OS was 95.2% (95% CI: 86.0 – 98.4).
DOR	Not reached

ORR, overall response rate; CI, confidence interval; OS, overall survival; MRR, major response rate; PFS, progression free survival; DOR, duration of response.

Response

The ORR was 90.5% (95% CI: 80.4, 96.4), meeting the primary endpoint success criteria of the study. Responders were categorised as follows [23]:

- Very good partial response (VGPR): n=10
- Partial response (PR): n=36
- Minor response (MR): n=11

The major response rate (defined as rate of complete response or ≥50% decrease in serum IgM levels) was 73% (95% CI: 60.3, 83.4). Both ORR and major response rate were consistent across most subgroups, showing a consistent treatment effect across the variables studied (Figure 7 and Figure 8).

Figure 7: Sub-analysis of overall response rate in Study 1118E[23]

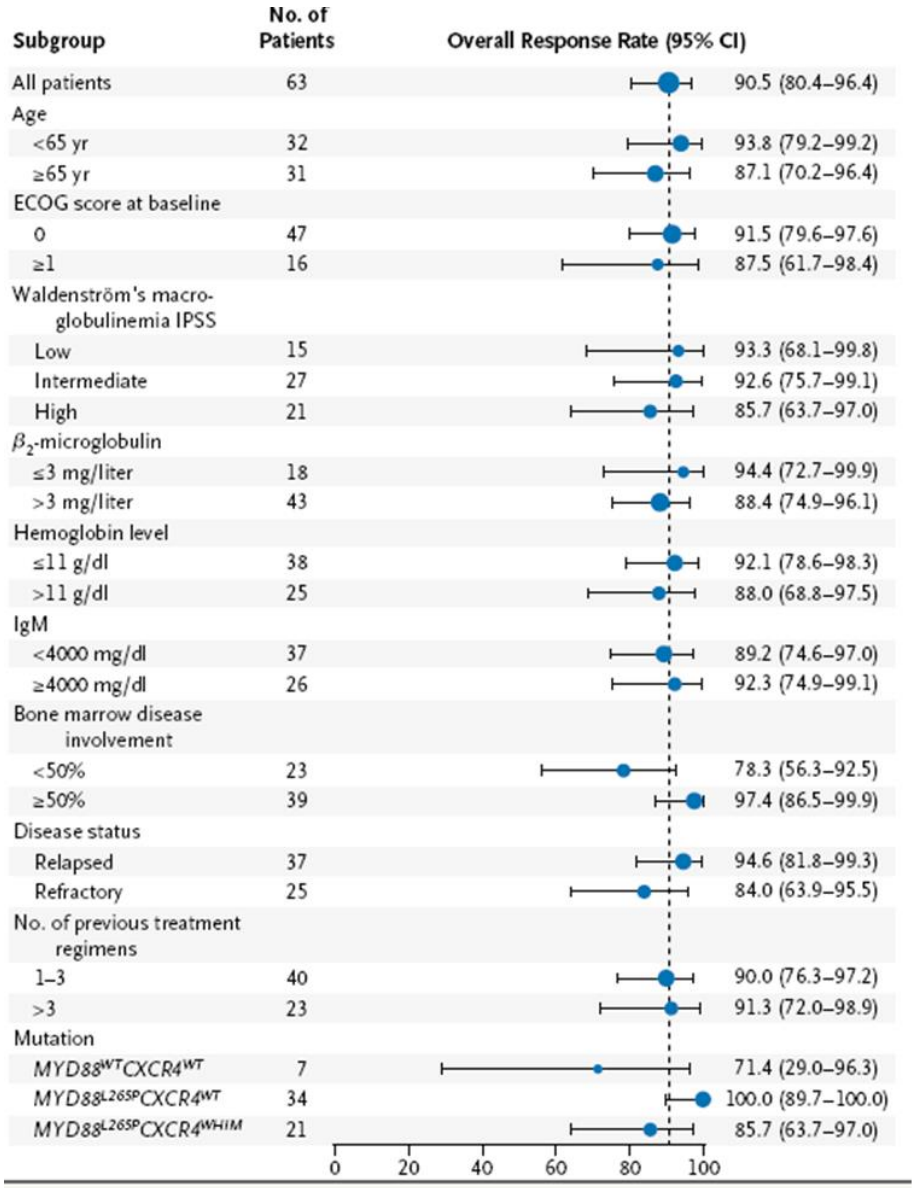
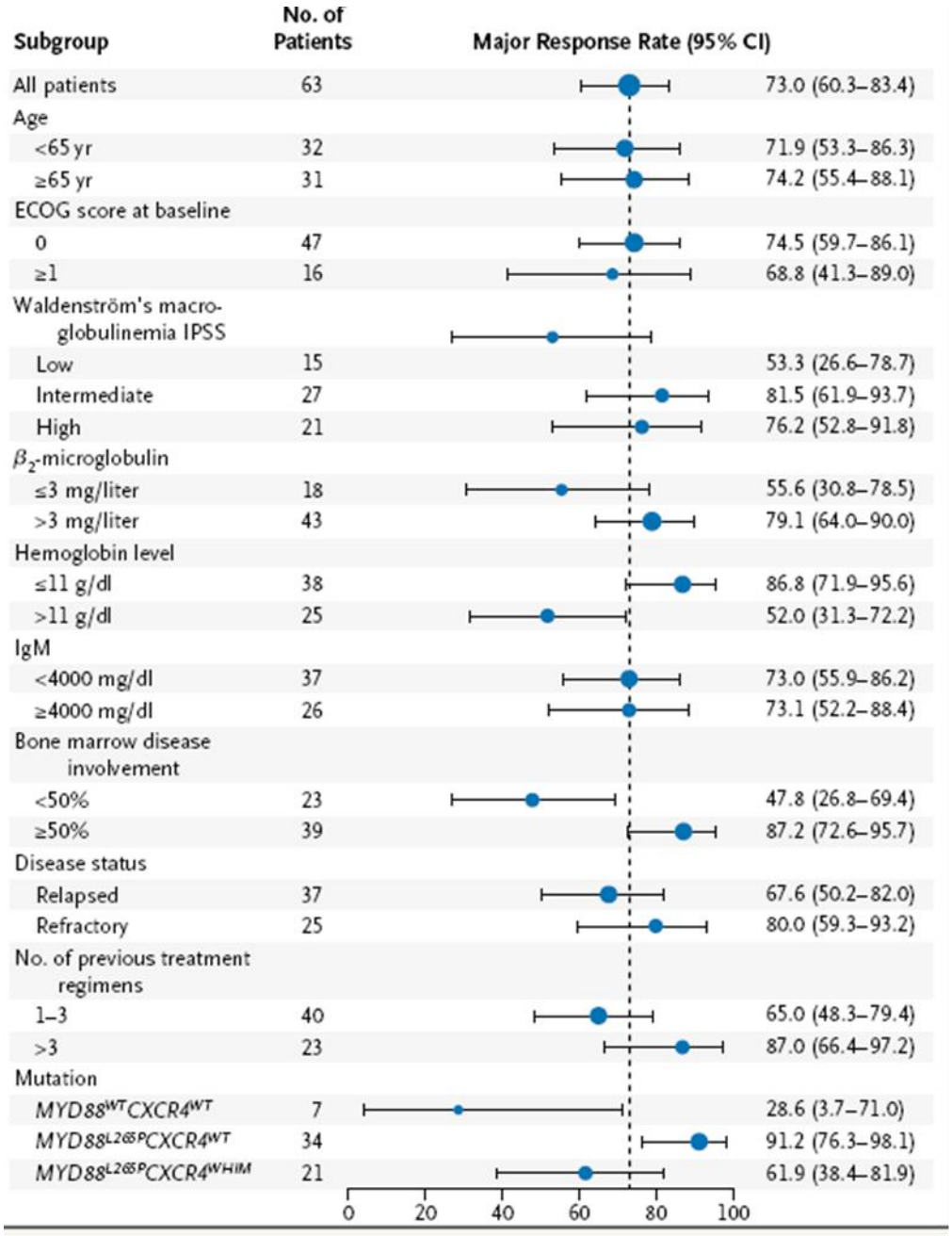


Figure 8: Subgroup analysis of major response rate in Study 1118E[23]



Responses were durable [23, 79]. At 18 months, the Kaplan-Meier estimate for event-free rate for all responders was 80.9% (95% CI: 64.9%, 90.2%), and the corresponding value for major responders was 86.7% (95% CI: 67.9%, 94.9%). Median duration of overall response had not been reached by the data CCO of December 19, 2014.

Responses were also rapid, with a median time to response of 4 weeks [23, 79] The median times to at least minor response or partial response were 4 weeks and 8 weeks, respectively.

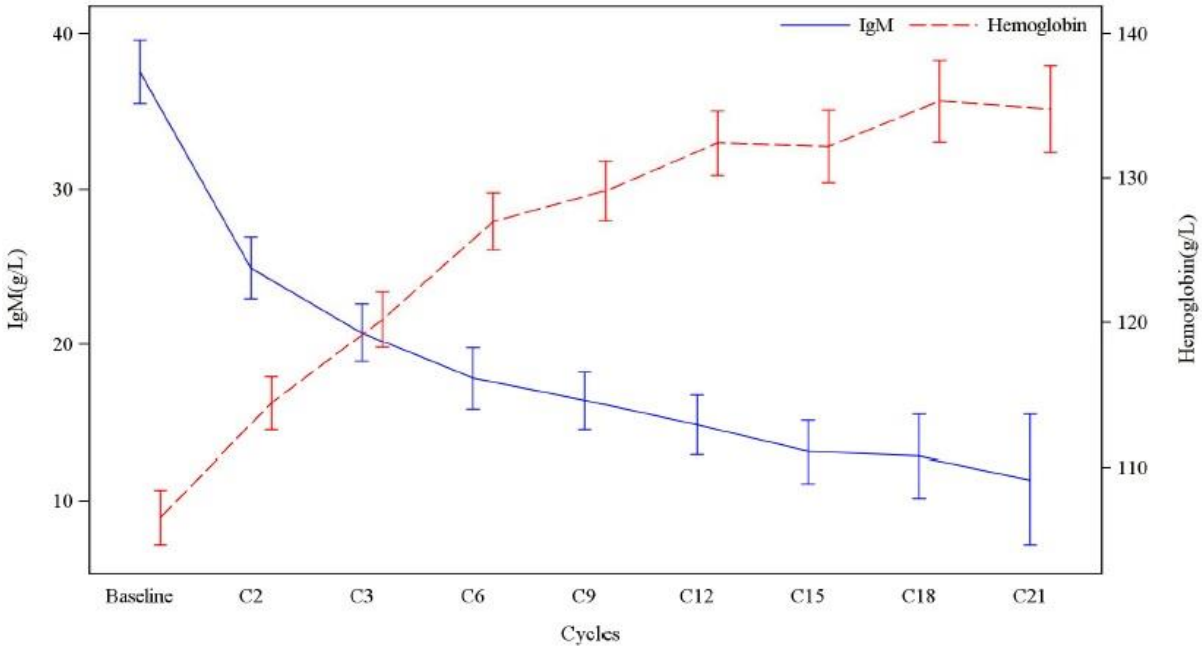
The median absolute serum IgM concentration at baseline for subjects treated with ibrutinib was 3,520 mg/dL (range: 724 mg/dL to 8,390 mg/dL)[23]. Additional information on serum antibody levels is shown in Table 16 below.

Table 16: Serum antibody levels [23, 79, 88]

Characteristic	Value
Median Serum IgM level over time — mg/dL	
Baseline	3,520
8 weeks	2,350
Time of best response	880
Patients with a serum IgM level ≥3,000 mg/dL,, %(n)	
Baseline	73 (46)
After therapy	10 (6)
Median haemoglobin level among respondent patients — g/dL	
Baseline	10.5
8 weeks	12.0
Time of best response	13.8

IgM: immunoglobulin M, mg/dL: milligrams per decilitre, g/dL: grams per decilitre
Source: [79] [23]

Figure 9: Haemoglobin levels and IgM concentrations with ibrutinib treatment



Treatment with ibrutinib resulted in a significant decline in median percentage of bone marrow infiltration from 60% to 25% (P<0.001) [23].

At baseline, lymphadenopathy and splenomegaly were identified by computed tomography (CT) in 37 (59%) and 7 (11%) of patients, respectively. Both lymphadenopathy and splenomegaly were reduced with ibrutinib treatment, as shown in Table 17 below:

Table 17: Reduction in CT-identified lymphadenopathy and splenomegaly in Study 1118E [23]

Clinical characteristic	(N=63)
Lymphadenopathy	
Baseline lymphadenopathy (>1.5 cm)	35*
Decreased	25
Remained stable	9
Increased	1
Splenomegaly	
Baseline splenomegaly (≥15 cm)	7
Decreased	4
Remained stable	2
Could not be evaluated due to elective splenectomy	1
*two patients discontinued before repeat imaging was required	

Progression free and overall survival

By the end of data collection (at CCO date 19 December 2014), 60 of the initial 63 patients were still alive. The Kaplan-Meier curves for PFS and OS are shown below in Figure 10 and Figure 11 respectively [23]. At 24 months, the estimated rate of PFS and OS were 69.1% (95% CI: 53.2%, 80.5%) and 95.2% (95% CI: 86%, 98.4%), respectively.

Figure 10: Kaplan-Meier curve of PFS in Study 1118E[23]

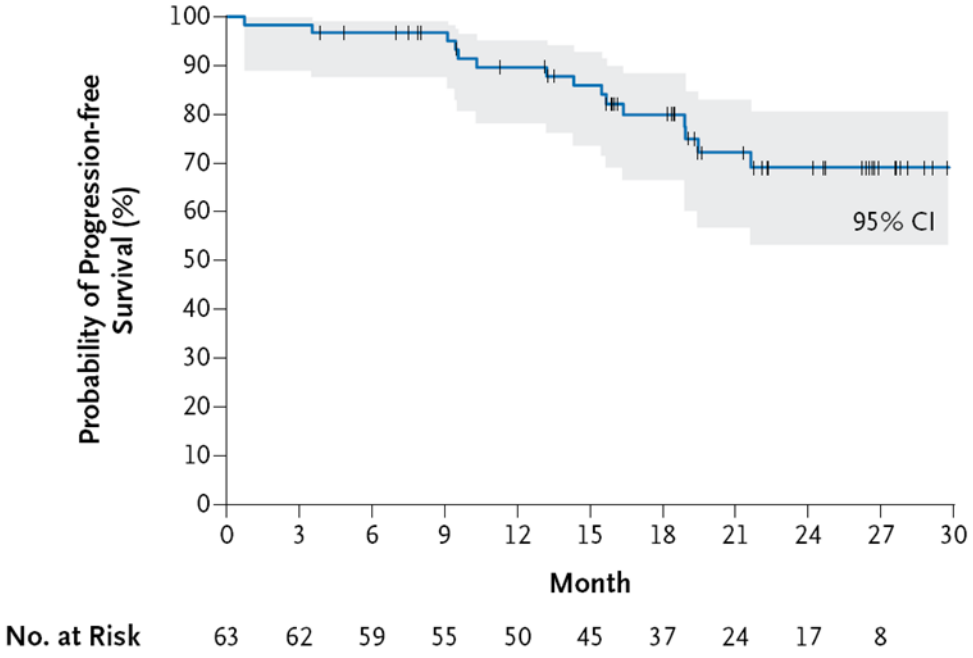
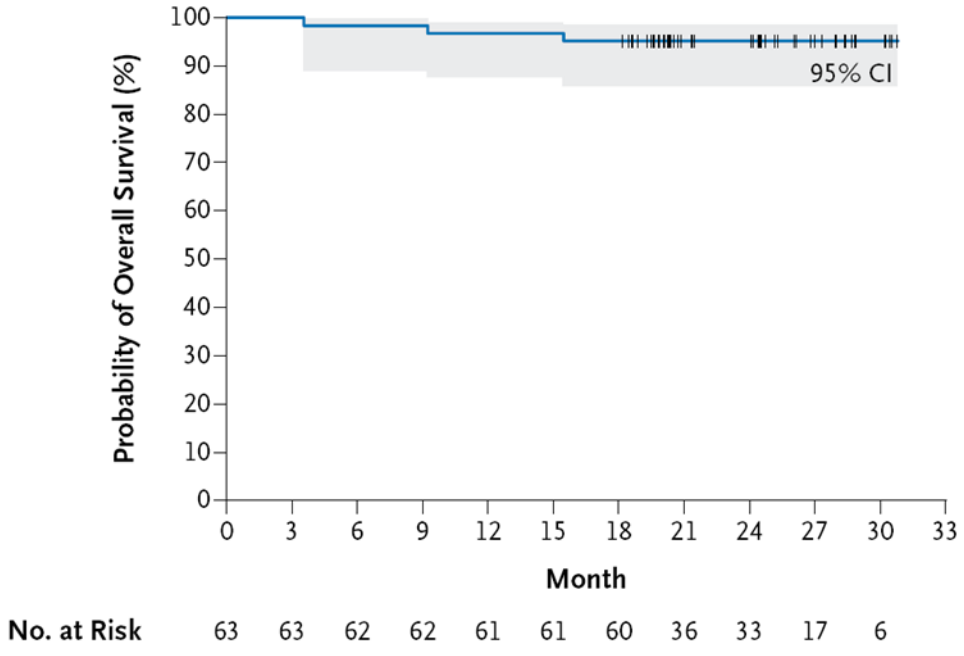


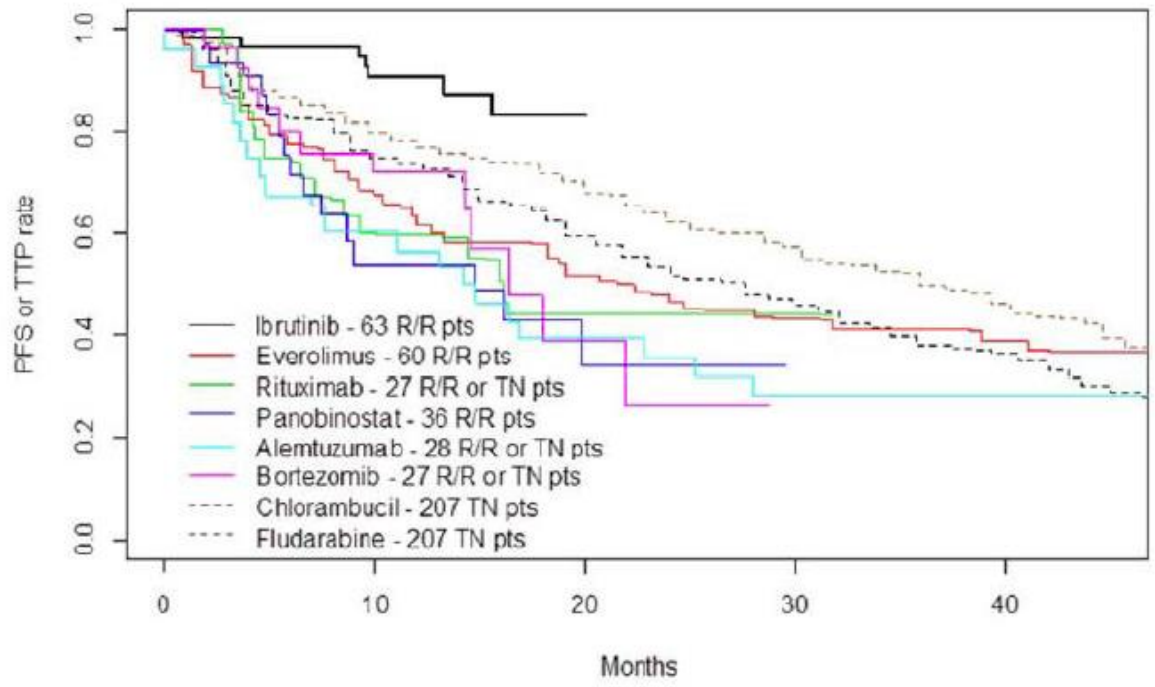
Figure 11: Kaplan-Meier curve of OS in Study 1118E [23]



Regarding the uncertainty around the generalizability of Study 1118E efficacy results to first line patients, the CHMP relied on historical comparisons of PFS in patients with WM (single

agents) presented below in Figure 1 and concluded the following: "***the observed ORR of 87.3%*** *[as per CSR - 28 February 2014 CCO date],* ***as reported in the 1118E study****,* ***is*** *reassuring in terms of activity, and* ***numerically superior in inter-study comparisons with most published studies investigating other monotherapy agents in previously treated and/or naive patients****. Furthermore, the presence of the MYD88 L265P mutation in both untreated and previously treated WM patients, supporting the mechanistic rationale for treatment with ibrutinib in the treatment-naive setting*."

Figure 12: Naïve comparison of Progression Free Survival in Patients with WM (Single-Agent Use)



Source: CHMP variation report dated 21 May 2015[19]

Of note, safety results from Study 1118E are presented in detail in Section 4.12 below.

4.11. *Indirect and mixed treatment comparisons*

Background

An SLR was conducted that concluded only five trials, all single-armed, had been published for the treatment of R/R WM patients (please refer to Section 4.1 above), including the Treon et al. 2015 publication presenting the findings of Study 1118E [23]. Of the four non-ibrutinib trials, they did not report Kaplan-Meier data for PFS, they were outdated (published in the 1990s), or they had very small sample sizes; therefore, no published trial data were available to estimate the comparative clinical benefit of ibrutinib versus current treatments and no conventional indirect treatment comparison could be conducted.

Consequently, patient-level efficacy data from the pan-European chart review study were considered. This chart review is described below and is followed by a presentation of the methods used to derive the comparative efficacy estimates relative to ibrutinib.

Pan-European chart review study

Study
A retrospective observational study based on the chart review of WM patients was conducted to generate data on epidemiologic/treatment patterns and efficacy outcomes for WM over a prolonged period of time (~10 years)[32]. This chart review (CR) study was conducted in collaboration with the European Consortium for Waldenström's Macroglobulinemia (ECWM)

Data sources
Data in this section are predominantly drawn from the abstract presented at the 2015 American Society of Hematology (ASH) annual conference and Janssen data on file (DoF). The published poster is used wherever possible, with additional information drawn from the DoF.

Methods
Data from treatment-naïve and relapsed WM patient records across ten European countries including the UK were gathered by internet survey from 3rd December 2014 to 31st January 2015. Physicians completed a retrospective electronic record for patients who met the following inclusion criteria:

- WM diagnosis was confirmed according to International Workshop on WM (IWWM)-2 criteria;
- Patient was symptomatic when treatment was initiated;
- Diagnosis and initiation of therapy occurred between January 2000 and January 2014;
- Treated with ≥1 salvage regimen;
- Clinical and biochemical data (retrieved at the time of initial diagnosis and during treatment) included a minimum of:
    - baseline complete blood count; levels of β-2 microglobulin, serum albumin, IgM, serum monoclonal protein; immunofixation electrophoresis; and assessment of lymphadenopathy, splenomegaly, and bone marrow infiltration.

Key study endpoints included initial/subsequent lines of treatment, PFS, and OS. The number of patient records per country was pre-specified to balance the distribution between European countries.

Results
A total of 454 patient records were reviewed and summarised across first-, second, third-, fourth and fifth line of treatment. Data were summarised across these five lines of treatment for 454, 397, 160, 61, and 26 patients, respectively. Patients were from France (n=92), the United Kingdom (UK; n=72), Germany (n=66), Spain (n=60), Italy (n=56), Greece (n=25), the Netherlands (n=25), Poland (n=21), Austria (n=19), and the Czech Republic (n=16).

Median age at initiation of first line treatment was 65 years (range, 29-89) for the pan-European population and 65 (range, 30-89) for the UK population. Patient baseline characteristics are provided in further detail in Table 18 below, demonstrating that the UK cohort was comparable to the overall pan-European cohort from the chart review:

Table 18: Chart review study - patient baseline characteristics at initiation on front-line treatment

Characteristic	Overall (N=454)	UK (n=72)
Age at initiation of 1L treatment		
Years, median	65	[redacted]
Years, range	29-89	[redacted]
Percent ≥65 (n)	[redacted]	[redacted]
Percent Male (n)	61 (278)	[redacted]
Median number of lines started (range)	[redacted]	[redacted]
IPSSWM risk *, % (n)		
Low	[redacted]	[redacted]
Intermediate	[redacted]	[redacted]
High	[redacted]	[redacted]
Serum antibody levels		
IgM		
Median (range) — g/L	[redacted]	[redacted]
Percent >4000 mg/dl (n)	[redacted]	[redacted]
Median β_2-microglobulin, range *	[redacted]	[redacted]
Median β_2-microglobulin-- mg/L *	[redacted]	[redacted]
Any cytopenia*, % (n)	[redacted]	[redacted]
Percent Haemoglobin ≤11 g/dL	[redacted]	[redacted]
Percent Platelets ≤100 × 109/L	[redacted]	[redacted]
*Missing data are not included in calculations.		

Source: [3]

The most common reasons for initiating treatment at diagnosis were constitutional symptoms (58%), cytopenias (72%; anaemia [69%]), and IgM-related symptoms (57%).

Choice of therapy varied with line of treatment; monotherapy fell from 31% in 1L to 20%/21% in 2L-3L. Combination therapy with antibody increased from 40% in first line to 64%/56% in 2L-3L. 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.

As illustrated by Figure 13 below, median PFS decreased with successive lines of treatment (29 vs. 23 vs. 16 months, for 1L, 2L and 3L, respectively) and varied by country (Table 17) [14, 32].

Figure 13: Kaplan-Meier PFS estimates by line of treatment

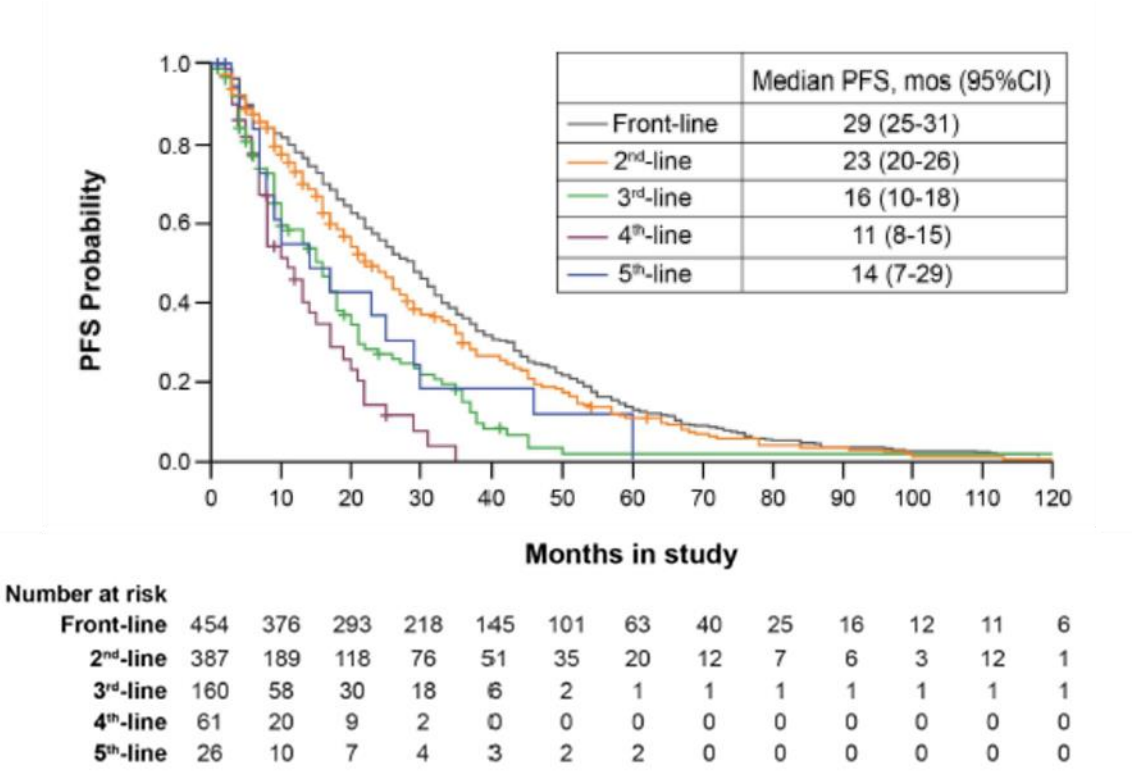


Table 19: Median PFS in 1L, 2L and 3L settings EU-overall and by country [32]

Country	Number of cases	Median PFS, months (95% CI)		
		1L	2L	3L
EU-overall	454	29 (25-31)	23 (20-26)	16 (10-18)
France	92	29 (22-32)	30 (20-37)	16 (9-32)
UK	72	32 (25-36)	20 (11-35)	13 (9-33)
Germany	66	36.5 (29-44)	24 (16-29)	8 (3-16)
Spain	60	18 (15-25)	16 (12-24)	11 (9-24)
Italy	56	31 (20-39)	30 (18-42)	17 (4-21)

Eastern European*	37	33 (26-38)	20 (16-26)	21 (4-38)
Smaller European**	71	23 (18-29)	16 (13-25)	16 (7-26)

*Includes Czech Republic and Poland
**Includes Austria, Greece, and Netherlands

Median OS was 123 months, but significantly lower in patients ≥75 years of age (75 months) or with high-risk International Prognostic Scoring System for WM (IPSSWM) risk score (91 months) and similar for patients with low/intermediate risk groups. Considerable country-specific OS differences were noted. Other malignancies were reported in 12% of the population after diagnosis of WM.

Methods

Comparability of Study 1118E and the chart review cohort
Data collected in Study 1118E and the chart review study followed comparable protocols (Table 20) and this allowed an indirect comparative analysis to be performed using patient-level data from the two studies to estimate the efficacy (PFS) of ibrutinib versus current practice, as represented by treatments captured in the chart review. Given that only three patients died in Study 1118E, it was not feasible to estimate the relative treatment effect of ibrutinib on OS.

Table 20: Comparison of Study 1118E vs. chart review: study type, key prognostic factors and definition of progression

	Study 1118E	**Chart review study**
Study type	Phase 2, single-arm trial	Chart audit of WM patients symptomatic at diagnosis from European countries. Patient records were collected from initiation of 1L treatment to up to 5 lines.
Key prognostic factors	Haemoglobin, platelet count, β2-macroglobulin, IgM reported in comparable unit measure	
Definition of progression	> 25% increase in serum IgM level occurs from the lowest attained response value or progression of clinically significant disease related symptom(s); based on the consensus panel criteria of IgM response.	25% increase in serum IgM from lowest nadir; progression or re-appearance of clinical features; progression or re-appearance of hematopoietic insufficiency

Creation of a "matched" chart review cohort
A "matched" cohort was created by selecting a subset of the overall pan-European chart review cohort (n = 454) that had received similar prior lines of therapy as Study 1118E. Given that longitudinal data were available from the chart review, each patient from the chart review was randomly sampled following two constraints: i) the same patient from the chart review was not allowed to be in two lines at the same time, and ii) the distribution across lines of therapy of the final subset of patients selected from the chart review matched the distribution of patients from Study 1118E as follows: [redacted] with 1 prior line, [redacted] with 2 prior

lines, [redacted] with 3 prior lines and [redacted] with 4 prior lines. A total of 175 patients were selected from the chart review to create this matched cohort. In addition, patients from Study 1118E that had 5 or more prior lines of therapy were excluded from the analyses given that patients from the chart review had received at most four prior treatments. Therefore, a total of 47 patients from Study 1118E were included in the analysis.

The baseline patient characteristics of the matched chart review cohort are compared with those of Study 1118E in Table 21 below. The comparison shows that overall, baseline patients characteristics were similar across the two cohorts, with perhaps a more even distribution of patients by risk status in Study 1118E than in the matched chart review cohort: For completeness, we have also reported in this table the characteristics of the UK chart review population (see Table 18 above) to support the assumption that overall, the characteristics of the patients which were included in the indirect comparison were comparable to those from UK WM patients.

Table 21: Patient baseline characteristics: overall chart review matched, vs. Study 1118E vs. UK chart review cohorts

Characteristic	Overall chart review matched (N=175)	Study 1118E (n=63)[23]	UK chart review (N=72)
Age at initiation of 1L treatment			
Years, median	[redacted]	63	[redacted]
Years, range	[redacted]	44-86	[redacted]
Percent ≥65 (n)	[redacted]	NR	[redacted]
Percent Male (n)	[redacted]	76 (48)	[redacted]
Median number of previous treatment regimen (range)	[redacted]	2 (1-9)	[redacted]
IPSSWM risk at initiation of frontline treatment*, % (n)			
Low	[redacted]	22 (14)	[redacted]
Intermediate	[redacted]	43 (27)	[redacted]
High	[redacted]	35 (2")	[redacted]
Serum antibody levels			
IgM			
Median (range) — mg/dl	[redacted]	3,520 (724-8,390)	[redacted]
Percent >4000 mg/dl (n)	[redacted]	41 (26)	[redacted]
Median IgG (range) — mg/dl	[redacted]	26 (0-125)	[redacted]
Median IgA (range) — mg/dl	[redacted]	381 (49-2,770)	[redacted]
Median β2-microglobulin, range *	[redacted]	1.3-14.2	[redacted]

Median β2-microglobulin, mg/L *	[redacted]	3.9	[redacted]
Any cytopenia*, % (n)	[redacted]	NR	[redacted]
Percent Haemoglobin ≤11 g/dL (n)	[redacted]	59(37)	[redacted]
Percent Platelets ≤100 × 109/L (n)	[redacted]	11 (7)	[redacted]
NR: not reported *Missing data are not included in calculations.			

Multivariate Cox model

A multivariate Cox proportional hazard model was developed to estimate the hazard ratio (HR) of PFS for ibrutinib versus current treatment using combined patient-level data from Study 1118E and matched chart review cohort (n = 222).

The following clinically significant patient characteristics and prognostic factors were included in the multivariate regression model to control for patient population differences between Study 1118E and the chart review study: (i) age, (ii) gender, (iii) haemoglobin ≤11 g/L, (iv) platelet ≤100x10^9/L, (v) Beta macroglobulin ≤3mg/L, (vi) M-protein (IgM) concentration <40 g/L, (vii) low risk/intermediate risk

The risk categories were defined as follows [17]:

- Low risk: presence of no more than one adverse characteristic and age ≤65 years;
- Intermediate risk: presence of two adverse characteristics or age older than 65 years.

Primary analysis & scenario analyses

Only 89 (51%) out of the matched 175 chart review subjects had complete information across all covariates in the dataset. To avoid the issue whereby including all covariates in the multivariate model would reduce the sample size, missing patient characteristics and prognostic factors were imputed to maintain the sample size and the power of the analysis (primary analysis). The primary analysis therefore, included 175 subjects.

MICE package (multiple imputations by chained equations) in R was used to impute the missing data. Of note, MICE implements fully conditional specification (FCS) to impute missing data that occurs in more than one variable. FCS specifies the multivariate imputation model on a variable-by-variable basis by a set of conditional densities, one for each incomplete variable. Starting from an initial imputation, FCS draws imputations by iterating over the conditional densities. All variables were imputed using a predictive mean matching method. Output was visually assessed for convergence and whether the distribution of the imputed values matched the distribution of the original data.

Two sensitivity analyses were conducted in addition to the primary analysis:

i. Cox regression analysis based on the matched chart review cohort that excluded patients with missing data (i.e., n = 86 patients were excluded and the remainder with complete data, n=89, were included)

ii. Cox regression analysis based on the full matched chart review cohort (n = 175), in which missing data were imputed using a subset of the covariates used in the primary analysis, i.e. using risk categories only, not individual clinical measurements (e.g., haemoglobin ≤11 g/L).

Results

Primary analysis:
The Cox regression analysis was conducted based on the full matched chart review cohort (n = 175), that included both patients with complete (n = 89) and with incomplete (n = 86) data. The HR for ibrutinib treatment versus current treatments was [redacted] (95% CI: [redacted]); note this is a univariate HR based on the Cox-model, only including treatment and all other covariates are not significant. With the exception of ibrutinib treatment effect, none of the other covariates were found to be statistically significant. This is most likely due to the relatively small number of progression/death events and short follow-up in the trial.

Table 22: Cox regression on PFS data - primary analysis

Covariates	HR	95% CI		P value
Ibrutinib treatment (versus SOC)	[redacted]	[redacted]	[redacted]	[redacted]
Beta macroglobulin ≤3mg/L	[redacted]	[redacted]	[redacted]	[redacted]
Haemoglobin ≤11 g/L	[redacted]	[redacted]	[redacted]	[redacted]
IgM <40 g/L	[redacted]	[redacted]	[redacted]	[redacted]
Platelet ≤100x10^9/L	[redacted]	[redacted]	[redacted]	[redacted]
IPSSWM: low risk	[redacted]	[redacted]	[redacted]	[redacted]
IPSSWM: intermediate risk	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	[redacted]
Age*	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI = Confidence interval; HR = Hazard ratio; IgM = Immunoglobulin m-protein; IPSSWM = International Prognostic Scoring System for WM; PFS = Progression-free survival
* Age is included as continuous variable; all other covariates as categorical (with complementary subgroup of patients as reference.

The comparison of PFS KM curves presented in Figure 14 below shows that ibrutinib is associated with superior PFS compared to current treatments.

[redacted]

Sensitivity analysis #1:
The Cox model based on the cohort with complete characteristics data (n = 89) resulted in a numerically lower HR ([redacted]) but within the 95% CI of the estimated HR of the full cohort with imputed data (Table 23).

Table 23: Cox regression on PFS data - sensitivity analysis #1 (no imputation)

Covariates	HR	95% CI		P value
Ibrutinib treatment (versus SOC)	[redacted]	[redacted]	[redacted]	[redacted]
Beta macroglobulin ≤3mg/L	[redacted]	[redacted]	[redacted]	[redacted]
Haemoglobin ≤11 g/L	[redacted]	[redacted]	[redacted]	[redacted]
IgM <40 g/L	[redacted]	[redacted]	[redacted]	[redacted]
Platelet v100x10^9/L	[redacted]	[redacted]	[redacted]	[redacted]
IPSSWM: high risk	[redacted]	[redacted]	[redacted]	[redacted]
IPSSWM: intermediate risk	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI = Confidence interval; HR = Hazard ratio; IgM = Immunoglobulin m-protein; IPSSWM = International Prognostic Scoring System for WM; PFS = Progression-free survival

Sensitivity analysis #2: The Cox model based on the full cohort (n = 175) but using risk categories only for the imputation of missing data, resulted in a HR for ibrutinib treatment versus current treatments of [redacted]).

Table 24. Cox regression on PFS data - sensitivity analysis #2 (imputation, no individual clinical measurement)

Covariates	HR	95% CI		p-value
Ibrutinib treatment (versus SOC)	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	[redacted]
IPSSWM: low risk	[redacted]	[redacted]	[redacted]	[redacted]
IPSSWM: intermediate risk	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI = Confidence interval; HR = Hazard ratio; IPSSWM = International Prognostic Scoring System for WM

In the absence of comparative trial data to estimate the clinical benefit of ibrutinib versus treatments used in current practice for WM patients, data from the pan-European chart review study can be deemed a valuable source of evidence for this submission. The similar baseline characteristics across patients in the matched chart review cohort and in Study 1118E further supports the assumption that using chart review data to estimate ibrutinib relative efficacy versus current treatments is reasonable. Furthermore, the comparison of baseline characteristics across overall pan-European and UK chart review patient cohorts suggests that the HR estimated by the Cox regression analyses described above are relevant to estimate the clinical benefit of ibrutinib in the UK WM population. The HRs presented in this section are used as clinical inputs in the economic model presented in Section 5 below.

Beyond the use of the chart review data to support this submission, the findings of the chart review can be seen as addressing the general lack of data in WM.

4.12. *Adverse reactions*

This section describes adverse reactions reported not only in WM patients (Study 1118E) but also in other diseases areas in which ibrutinib was granted EMA market authorisation, namely MCL and CLL, to demonstrate the consistency of the low toxicity profile of ibrutinib across a larger number of patients and conditions.

Data in this section are therefore predominantly drawn from the Study 1118E publication and the CSR [23, 79]. The published paper is used wherever possible, with additional information drawn from the CSR. In addition, safety data from the following trials are discussed:

- PCYC-1102/1103 phase 1b-2 study of ibrutinib in patients with CLL [21, 22].
- PCYC-1112 (RESONATE) phase 3 study of ibrutinib in patients with relapsed CLL [20].
- PCYC-1115 (RESONATE 2) phase 3 study of ibrutinib in patients with first line CLL
- PCYC-1104 phase Ib-II study of ibrutinib in patients with MCL [24, 25]

Safety from Study 1118E

The pivotal phase 2 Study 1118E supported the generally well tolerated safety profile of ibrutinib in the treatment of WM patients. The majority of TEAEs were mild to moderate, easily manageable, and with a low incidence of grade 3/4 AEs. Of the 19% of patients who stopped treatment, only 6% discontinued as a result of toxicity.

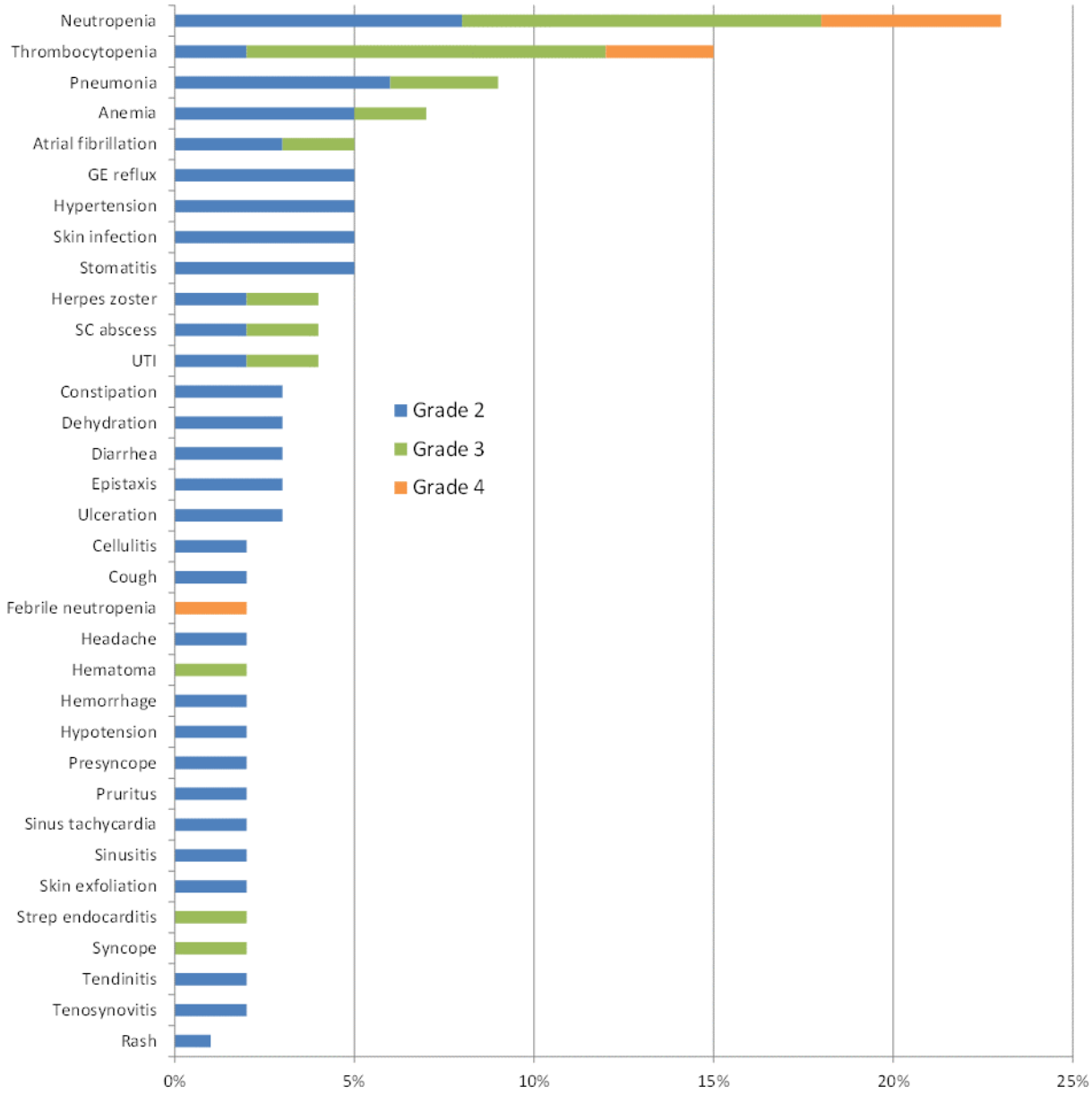
Patients with any AE resulting in dose reduction or treatment discontinuation were observed at a low incidence. Reasons for discontinuation are presented in Table 25 below:

Table 25: Reasons for discontinuing therapy[23]

Reason for discontinuation	Number of cases (n=21)
Disease progression	7
Possible treatment-related disease transformation	2
Patient choice to use commercially-obtained ibrutinib	2
Myelodysplasia and acute myeloid leukaemia related to prior treatments	2
Lack of response	1
Treatment-aggravated thrombocytopenia	1
Infection unrelated to ibrutinib	1
Haematoma post bone marrow biopsy	1
Treatment for rectal carcinoma	1
Medication incompatible with ibrutinib	1
Difficulty with travel	1
Alternative therapy	1

All patients treated with ibrutinib experienced a TEAE (any grade), the majority of which were mild to moderate. The incidence of ≥ grade 2 TEAEs is shown in Figure 15 and Table 26 below [23]:

Figure 15: Treatment-related adverse events in Study 1118E



GE, gastroesophageal; SC, subcutaneous; UTI, urinary tract infection.
Based on Treon et al (2015) [23]

Neutropenia or thrombocytopenia, each ≥ grade 3, was recorded in 9 patients (14%) and 8 patients (13%), respectively; in each case, 7 of the patients had been treated with ≥3 previous medications (P=0.05 for neutropenia, and P=0.01 for thrombocytopenia)[23]. In all cases, ibrutinib-associated neutropenia and thrombocytopenia were reversed, although reversal required dose reduction or treatment discontinuation in 3 patients and 4 patients, respectively. Three cases of atrial fibrillation (AF) were thought to be associated with ibrutinib therapy; all three patients had a history of paroxysmal AF. AF resolved, after

ibrutinib was held without cardiac intervention and protocol therapy was resumed uneventfully in all three cases [23]. Grade ≥2 bleeding events occurred in 4 patients (2 of whom had epistaxis and 2 of whom had post-procedural bleeding before the study was amended to mandate withholding times for ibrutinib). Fish-oil supplements contributed to both grade 2 epistaxis events, and these events resolved when these supplements were discontinued[23].

Table 26: Adverse events associated with ibrutinib therapy in Study 1118E[23]

Event or Abnormality	Grade 2	Grade 3	Grade 4	Grades 2-4 Total
	Number of patients (percent)			
Blood and lymphatic system disorders				
Neutropenia	5 (8)	6 (10)	3 (5)	14 (22)
Thrombocytopenia	1 (2)	6 (10)	2 (3)	9 (14)
Anaemia	3 (5)	1 (2)	0 (0)	4 (6)
Febrile neutropenia	0 (0)	0 (0)	1 (2)	1 (2)
Cardiac disorders				
Atrial fibrillation	2 (3)	1 (2)	0 (0)	3 (5)
Sinus tachycardia	1 (2)	0 (0)	0 (0)	1 (2)
Gastrointestinal disorders				
Gastroesophageal reflux	3 (5)	0 (0)	0 (0)	3 (5)
Stomatitis	3 (5)	0 (0)	0 (0)	3 (5)
Constipation	2 (3)	0 (0)	0 (0)	2 (3)
Diarrhoea	2 (3)	0 (0)	0 (0)	2 (3)
Ulceration	2 (3)	0 (0)	0 (0)	2 (3)
Infections and infestations				
Pneumonia	4 (6)	1 (2)	0 (0)	5 (8)
Skin infection	3 (5)	0 (0)	0 (0)	3 (5)
Cellulitis	1 (2)	0 (0)	0 (0)	1 (2)
Herpes zoster	1 (2)	1 (2)	0 (0)	2 (3)
Sinusitis	1 (2)	0 (0)	0 (0)	1 (2)
Streptococcal endocarditis	0 (0)	1 (2)	0 (0)	1 (2)
Subcutaneous abscess	1 (2)	1 (2)	0 (0)	1 (2)
Urinary tract infection	1 (2)	1 (2)	0 (0)	1 (2)
Post-procedural complications				
Hematoma	0 (0)	1 (2)	0 (0)	1 (2)
Haemorrhage	1 (2)	0 (0)	0 (0)	1 (2)
Dehydration	2 (3)	0 (0)	0 (0)	2 (3)

Musculoskeletal and connective-tissue disorders				
Tendinitis	1 (2)	0 (0)	0 (0)	1 (2)
Tenosynovitis	1 (2)	0 (0)	0 (0)	1 (2)
Nervous system disorders				
Headache	1 (2)	0 (0)	0 (0)	1 (2)
Pre-syncope	1 (2)	0 (0)	0 (0)	1 (2)
Syncope	0 (0)	1 (2)	0 (0)	1 (2)
Respiratory, thoracic, and mediastinal disorders				
Epistaxis	2 (3)	0 (0)	0 (0)	2 (3)
Cough	1 (2)	0 (0)	0 (0)	1 (2)
Skin and subcutaneous tissue disorders				
Pruritus	1 (2)	0 (0)	0 (0)	1 (2)
Rash	1 (2)	0 (0)	0 (0)	1 (2)
Skin exfoliation	1 (2)	0 (0)	0 (0)	1 (2)
Vascular disorders				
Hypertension	3 (5)	0 (0)	0 (0)	3 (5)
Hypotension	1 (2)	0 (0)	0 (0)	1 (2)

CHMP position on safety from Study 1118E

While the number of subjects with WM in the phase 2 study was relatively small, 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, and for which ibrutinib is also indicated (ibrutinib safety data in CLL and MCL is summarised below in this section).

The safety evaluation by the CHMP in its variation report was therefore not limited to the findings of Study 1118E, but was also based on an integrated safety dataset including 420 patients who received ibrutinib in studies PCYC-1112 (a randomised, phase 3 study comparing ibrutinib to ofatumumab in patients with CLL or SLL, N=195 (RESONATE)[20] PCYC-1102 (a non-randomised, open-label study conducted in patients with CLL/SLL, N=51) [21, 22], PCYC-1104 (a non-randomised, open-label study in MCL patients, N=111) [24, 25] and Study 1118E[19, 23].

The CHMP also considered an analysis of the long-term safety (cut-off 10 March 2014) of ibrutinib in 198 subjects who received monotherapy with the longest treatment duration and follow-up. This analysis was based on integrated data from studies PCYC-1102 [21, 22], 04753 (a phase 1, open-label, multicentre, dose-escalation study of ibrutinib in subjects with a variety of B-cell malignancies, including 4 subjects with a diagnosis of previously treated WM)[40], and 1103 (an open-label, ongoing, extension study with 119 patients already treated with ibrutinib)[21]; the long-term safety population of 198 patients includes 4 subjects with WM.

The CHMP deemed the safety profile of ibrutinib in patients with WM to be overall consistent with what is already known in ibrutinib treated patients with CLL/SLL and MCL. The CHMP stated that ibrutinib has "*an acceptable safety profile to support the extension of the*

indication to include WM"; this conclusion was reached on the ground that "*no new safety signal has been evoked. No significant tolerability issues in the WM population as compared to the overall integrated dataset including CLL/SLL and MCL patient populations have been identified. In addition, data from the long-term safety population is not indicative of any cumulative toxicity*[19]."

This led the CHMP to conclude, in its benefit-risk balance assessment, that "*the efficacy of ibrutinib in the target population is considered clinically relevant and, in the view of the safety profile, the benefits are considered to outweigh the combined risks and uncertainties. Therefore, the benefit-risk balance is considered positive*[19]."

Further safety data of ibrutinib in CLL and MCL are provided in Appendix 3.

4.13. *Interpretation of clinical effectiveness and safety evidence*

Clinical benefits and harms

Ibrutinib provides an unprecedented and consistent benefit across all WM patients
Clinical data in the phase 2 trial, Study 1118E, showed benefit with ibrutinib treatment[23]. In the 63 patients with R/RWM treated with ibrutinib, a high ORR (90.5%), with PFS at 24 months of 69%, OS at 24 months of 95%, and durable remissions (median DOR not reached at 18 months) was observed. Treatment with ibrutinib also resulted in rapid reduction in serum IgM and improvement in haemoglobin, reversing the principal underlying causes of treatment-related morbidities[23].

Ibrutinib has a manageable tolerability profile and most patients remain on treatment
In the Study 1118E, the majority of AEs were mild to moderate, with a low incidence of grade 3/4 AEs. Ibrutinib was well tolerated with a discontinuation rate of 9.5% following a median treatment duration of 19.1 months. In addition, AEs tended to be self-limiting [23]. The incidence of AEs has also been shown to decrease over time in CLL patients. Ibrutinib does not require prophylactic measures or medication, and the number of discontinuations due to AEs remains low in the most up-to-date follow up[21,24].

Strengths and limitations

Study 1118E represents one of the largest clinical trials of patients with WM to have demonstrated positive clinical activity. In addition, analysis of the demographic and baseline disease characteristics of the patients population in Study 1118E is consistent with that reported in recent epidemiological studies [17, 58, 79].

Janssen do however recognise that the phase 2 non-comparative nature of the study may not meet the rigour of evidence generally expected by the Committee and this concern is addressed in detail in Section 7.

4.14. *Ongoing studies*

There is currently one ongoing ibrutinib study within Janssen's clinical program for the treatment of WM patients, Study PCYC-1127-CA (iNNOVATE), a phase 3 trial designed to evaluate the safety and efficacy of ibrutinib in combination with rituximab in patients with WM; this study includes a third arm (Arm C) of monotherapy ibrutinib, an open label sub-

study for patients who are refractory to rituximab and therefore, not eligible for randomisation. The study design is presented in Figure 16.

Ibrutinib does not currently have a license for combination therapy in WM and therefore, only Arm C of iNNOVATE would be relevant to this current appraisal.

The study was initiated in July 2014, and the estimated completion date is January 2019. Interim results are expected in April 2017 at the earliest.

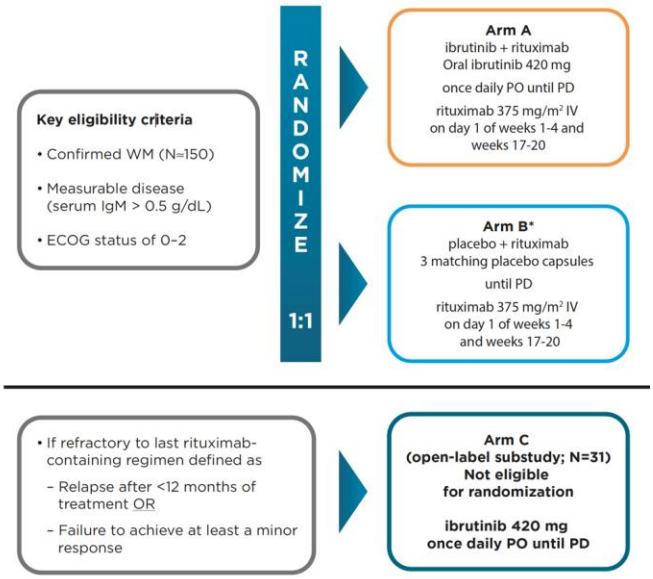
Table 27: List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
PCYC1117-CA (iNNOVATE) Clinicaltrials.gov NCT02165397	Arm A: Ibrutinib + rituximab	Arm B: Rituximab + placebo	Arm C consisted of patients with rituximab-refractory WM	Dimopoulos et al. 2015, Dimopoulos et al. 2016[44, 45]

*The iNNOVATE also includes Arm C: ibrutinib monotherapy as part as an open-label sub-study

Study methods from iNNOVATE reported in this section, including study design presented in Figure 15, were described in two posters presented at ASH in December 2015 and at BSH in April 2016 [44, 45]. No study results were presented at these conferences besides preliminary results for the Arm C sub-study. Further information around study design is provided in Table 28.

Figure 16: iNNOVATE trial design*[44, 45]



*Access to next-line ibrutinib (cross-over) for patients treated with placebo in combination with rituximab may be provided after confirmed disease progression (by IRC) and disease requiring treatment.

Table 28: Overview of iNNOVATE study design

Location	Europe (UK, France, Germany, Greece, Italy, Spain), the US, Canada and Australia
Trial design	Multicentre, randomised, double-blind, placebo-controlled, phase 3 study
Enrolment	Approximately 150 patients were randomised across arms A and B; 31 patients have been enrolled in an open label, phase 3 substudy (Arm C)
Randomisation and blinding	Randomisation was via an interactive web response system. Patients were randomised in a 1:1 ratio to each of the 2 treatment arms: • Treatment Arm A: oral ibrutinib in combination with intravenous rituximab. • Treatment Arm B: oral placebo in combination with intravenous rituximab. Central randomisation was implemented in this study. Randomisation was stratified using the following stratification factors: • WM International Prognostic Scoring System assessed at screening (low vs. intermediate vs. high) • Number of prior systemic treatment regimens (1-2 vs. ≥3) • ECOG status (0-1 vs. 2).
Trial drugs	**Treatment Arm A:** Ibrutinib: 420 mg (3 capsules) orally administered daily beginning from Day 1 in Week 1. Rituximab: 375 mg/m^2 IV per package insert weekly for four consecutive weeks, followed by a second four-weekly rituximab course after a three-month interval. Day 1 of Weeks 1-4 and Weeks 17-20 (total of 8 infusions of rituximab). **Treatment Arm B**: Placebo: 3 capsules of placebo orally administered daily beginning from Day 1 in Week 1. Rituximab: 375 mg/m^2 IV per package insert weekly for four consecutive weeks, followed by a second four-weekly rituximab course after a three-month interval. Day 1 of Weeks 1-4 and Weeks 17-20 (total of 8 infusions of rituximab). **Treatment Arm C**: Ibrutinib: 420 mg (3 capsules) orally administered daily beginning from Day 1 in Week 1.
Monitoring	Patients will continue to be monitored through either response follow-up or survival follow-up and will continue until death, lost to follow-up, consent withdrawal, or study end, whichever occurs first.
Primary outcome	PFS (up to 3 years after the final patient is randomised)
Secondary outcomes	• ORR • Improvement of haemoglobin levels • Time to next treatment • OS • Safety and tolerability

ECOG, eastern cooperative oncology group; ORR, overall response rate; OS, overall survival; PFS, progression free survival; ULN, upper limit of normal.

The primary endpoint is PFS, which is defined as duration from the date of randomisation to the date of disease progression or death, whichever is first reported. It will be assessed according to the modified 6th IWWM criteria. Secondary endpoints include ORR, improvement of haemoglobin levels, time to next treatment, OS and safety and tolerability. ORR is defined as the proportion of subjects who achieve PR or better according to the modified 6th IWWM criteria as assessed by independent review committee (IRC).

iNNOVATE open-label sub-study (n = 31)

The open-label sub-study involved 31 patients who were refractory to their last rituximab-containing regimen and were not eligible for randomisation (Arm C). Patient eligibility criteria were the following:

Table 29: iNNOVATE study - Arm C - Key eligibility criteria[44]

Inclusion criteria	• Patients with centrally confirmed diagnosis of WM and symptomatic disease requiring treatment per 2nd International Workshop on WM criteria. • Disease refractory to the last rituximab-containing therapy defined as either relapse after <12 months OR failure to achieve at least a minor response. • Haemoglobin ≥8 g/dL. • Platelet count >50,000 cells/mm3 (50 x 10^9/L). • Absolute neutrophil count >750 cells/mm3 (0.75 x 10^9/L). • Serum aspartate transaminase or alanine transaminase <3.0 x ULN. • Bilirubin ≤1.5 x ULN. • IgM ≥ 0.5 g/dL.
Exclusion criteria	• Central nervous system involvement. • Clinically significant cardiovascular disease. • Previous therapy for WM ≤30 days prior to first treatment dose.

ORR, overall response rate; OS, overall survival; PFS, progression free survival; ULN, upper limit of normal; WM: Waldenström's macroglobulinaemia

Patient characteristics at baseline are presented in Table 30 [44]. Patients were heavily pre-treated and rituximab-refractory with a median of four prior lines of therapy [44].

Table 30: iNNOVATE study - Arm C - Baseline patient characteristics [44]

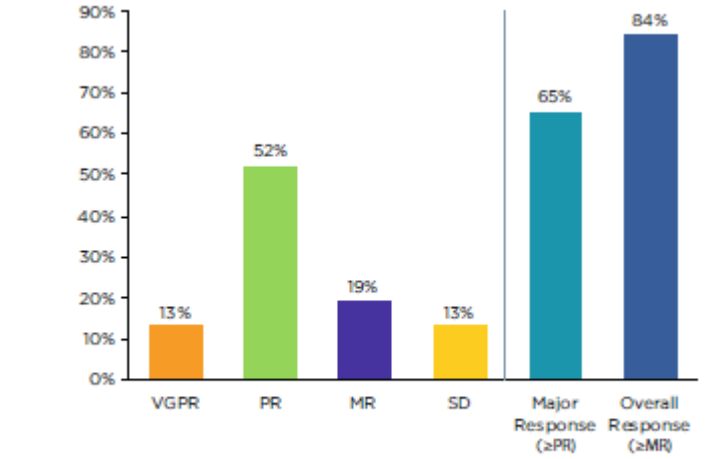
Characteristic	N=31
Median age, years (range) Age ≥70 years, n (%)	67 (47-90) 11 (35)
ECOG, n (%) 0-1 2	 25 (81) 6 (19)
IPSSWM*, n (%) Low Intermediate High	 7 (23) 11 (35) 13 (42)
Median serum IgM, mg/dL (range)	3,830 (740-10,700)
Median β2-microglobulin, mg/L (range)	3.6 (1.7-24.0)
Median haemoglobin levels, g/dL (range)	10.3 (6.4-14.6)
Median platelet count (10^9/L) (range)	218 (51-896)
Median absolute neutrophil count (10^9/L) (range)	2.9 (0.7-15.4)
Median number of prior therapies (range)	4 (1-8)

Prior autologous stem cell transplantation, n (%)	2 (6)
Types of prior therapy, n (%) Rituximab Corticosteroids Alkylating agent Vinca alkaloids Proteasome inhibitor Purine analogue[†] Anthracyclines Immunomodulating agent Nucleoside analogue[‡] Other	 31 (100) 25 (81) 25 (81) 14 (45) 14 (45) 13 (42) 8 (26) 2 (6) 2 (6) 4 (13)

IPSSWM, International Prognostic Score System for WM.
*IPSSWM was measured at the time of screening; [†]All 13 patients received fludarabine (class: purine analogue); [‡]Both patients received cytarabine (class: nucleoside analogue).

As shown in Figure 17 below, at a median follow up of 7.7 months (range: 4.7-10.7), the major response rate (≥PR) was 65% in this heavily-pretreated rituximab-refractory patient population (13% of patients had a VGPR, 52% had a PR, 19% had a MR, and 13% had stable disease) [44, 45]. The ORR was 84%.

Figure 17: iNNOVATE study - Arm C - best response to ibrutinib[44]



1 patient was non-evaluable.
CR, complete response; MR, minor response; PR, partial response; SD, stable disease; VGPR, very good partial response

Baseline median haemoglobin of 10.3 g/dL (range, 6.4-14.6) increased to 11.4 g/dL (range, 81.0-144.0) after Cycle 1 and showed improvement over time. Baseline median IgM of 3,830 mg/dL (range, 740- 10,700) declined by >50% by end of Cycle 1, with continued improvement over time. Five patients required plasmapheresis, with no additional need beyond Cycle 1 in 4 patients.

Patients achieving a best response of ≥PR showed the greatest improvement in haemoglobin. All responders (≥MR) showed an improvement in haemoglobin, as did some patients with stable disease.

No new or unexpected AEs were observed compared with previous ibrutinib trial with a manageable safety profile consistent with previous studies of single-agent ibrutinib [44, 45]. Haematological adverse events reported with ibrutinib treatment included neutropenia (the most frequently-reported event), thrombocytopenia and anaemia. Non-haematological adverse events reported in >15% of patients included diarrhoea (the most frequently reported event), hypertension, upper respiratory tract infection and pyrexia [44]. Serious AEs occurred in 6 patients (19%). All patients remained alive at data cut off, with no events of IgM flare, AF or major bleeding. Two patients discontinued ibrutinib: 1 patient discontinued due to early PD (MYD88 wild type) and 1 patient discontinued after 8 days of treatment due to an AE of gastrointestinal (amyloid light chain, AL) amyloidosis unrelated to ibrutinib[44, 45].

These preliminary results are consistent with the findings reported by Treon et al. 2015 in Study 1118E, despite the heavily pre-treated population in this study, who had received a median of four prior lines of therapy [45]. In addition, no new or unexpected AEs were observed, with a manageable safety profile consistent with previous studies of single-agent ibrutinib in WM, CLL and MCL[45].

5. Cost effectiveness

5.1. *Published cost-effectiveness studies*

Identification of studies

A Systematic Literature Review (SLR) was conducted to identify economic models and studies reporting economic outcomes and data related to the treatment of WM patients with any chemotherapeutic, biologic or investigational pharmaceutical agents. An initial literature search of economic evidence was conducted on 06 February 2015 and updated on 03 May 2016; the search strings and the methods used for the update were the same as for the initial search. The methods and results presented in this Section relate to the full SLR, covering both the initial and updated searches.

Search strategy

The databases searched included:

- MEDLINE (via PubMed) and MEDLINE (R) In-process (via PubMed);
- Embase, and Embase In-process;
- CENTRAL;
- Database of Abstracts of Reviews of Effects (DARE);
- National Health Service Economic Evaluation Database (NHS EED);
- National Health Services Health Technology assessment (HTA) database;
- EconLit.

The search algorithms used in these databases were generated using the PICOS framework (Population, Intervention, Comparators, Outcomes, Study design) in line with the research question[84]. All searches were run without limitations (e.g., no date or language limits). Non-relevant designs (i.e., comments or editorials) were removed from the search hits prior to review of the abstracts.

Additional searches were conducted via the Cochrane Library and the above databases for high-quality, recently conducted systematic reviews (published from 2011 to 2015) to serve as supplemental data sources.

Finally, bibliographies of relevant systematic review articles published since 2011 and the bibliographies of accepted studies were also reviewed to obtain any additional, relevant references.

In addition to the above searches within key databases, ‘grey’ literature (i.e., material that can be referenced but is not typically published in peer-reviewed, database-indexed medical journals) was also searched for relevant meeting abstracts or posters. Proceedings from the past three years (as available) for the follow key conferences were reviewed:

- ASCO 2013–2015 (via Embase)
- ASH 2013–2015 (via Embase)
- EHA 2013–2015 (via Embase)

- ISPOR 2013–2015 (international and European meetings): http://www.ispor.org/
- IWWM 2013 and 2015: http://www.wmworkshop.org/

Search strategies were developed in line with the NICE Methods Guide and are provided in Appendix 5.

Study selection

Records identified from the searches underwent two rounds of screening according to pre-specified inclusion/exclusion criteria as described in Appendix 5. In the first round, two independent investigators evaluated the title/abstracts of all unique records. In the second round, full-texts/publications of all records that met the inclusion criteria during the title/abstract screening were retrieved and reviewed by two independent investigators. None of the exclusion criteria and all of the protocol-specified inclusion criteria had to be met for a record to have passed this stage of screening. During both rounds of the screening process, discrepancies were resolved through consensus by a third investigator.

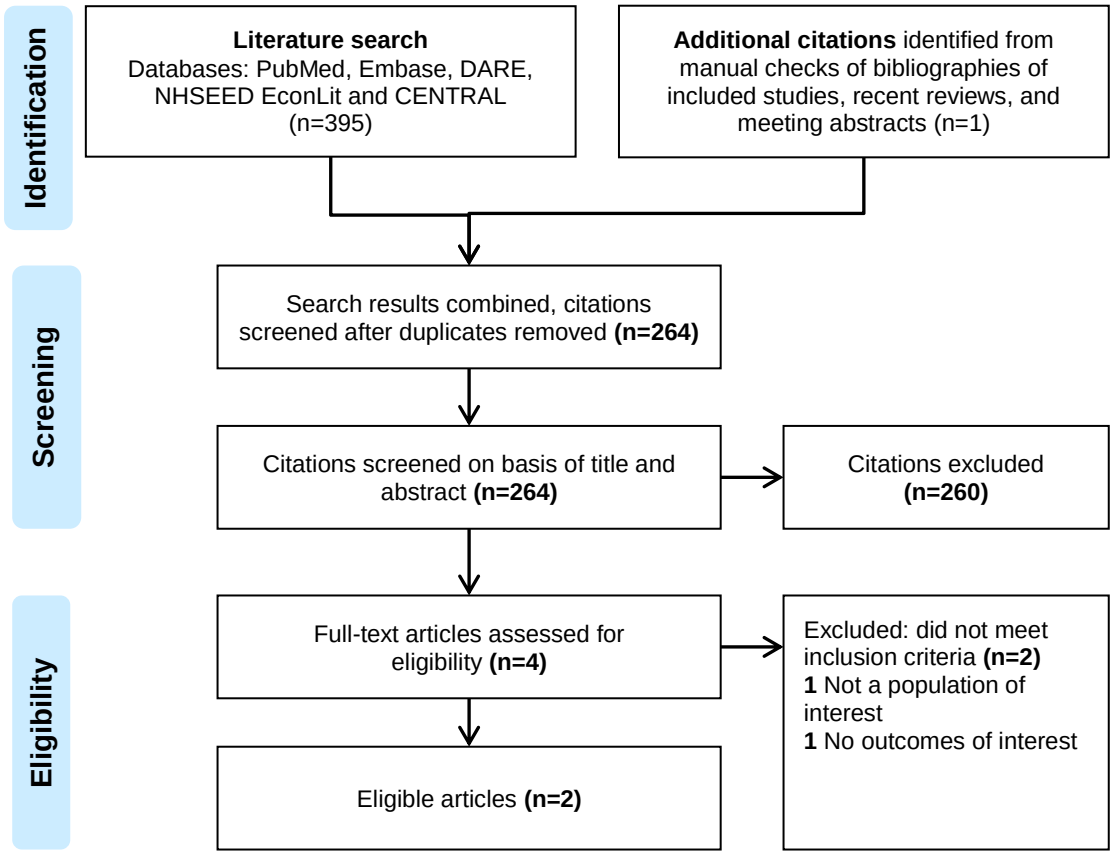
Relevant data elements were extracted by one investigator and validated by a second independent investigator. All discrepancies were resolved in discussion with a third investigator. A number of control measures were put in place to ensure the quality and consistency of data extraction. These include pilot testing of the extraction form on several included studies, resolution of potential ambiguities and differences in the interpretation of findings, and written instructions on outcomes measures to be extracted from the full papers. The results of this process are discussed in detail in the following section.

PRISMA flow diagram for the economic SLR

A total of 395 records were identified across the databases searched. After the removal of duplicate citations and the inclusion of one additional citation based on a hand search, the abstracts of 264 publications were screened according to the pre-specified eligibility criteria (Appendix 5). Of these, 260 citations were excluded. Following the full text review of the 4 remaining citations, 2 further citations were rejected following further application of the eligibility criteria. Therefore, the SLR identified a total of 2 studies. Of note, these studies were cost studies i.e. the SLR did not identify any cost-effectiveness (CE) studies that involved WM patients. Figure 18 below illustrates the process of eliminating references based on the protocol.

Given that no CE study was identified by the SLR, no detail can be provided on any CE study. Furthermore, no quality assessment could be provided.

Figure 18: PRISMA Flow Diagram of Economic Evidence



5.2. *De novo analysis*

Patient population

Ibrutinib as a single agent is indicated for the treatment of adult patients with WM who have received at least one prior therapy, or in first line (1L) for patients for whom chemo-immunotherapy is unsuitable[1]. The population modelled in this evaluation is in line with the population studied in the pivotal trial (Study 1118E), namely the relapsed or refractory (R/R) population described in the first part of the label, and upon which the European Medicines Agency (EMA) granted ibrutinib the broader WM label[23].

Study 1118E is the most robust data set currently available for ibrutinib in the WM setting. The baseline characteristics used in the model therefore reflect this population, to ensure alignment with the most rigorous source of clinical evidence of ibrutinib's efficacy in WM [23].

Model structure

Given that no cost-effectiveness study in WM was identified by the SLR, a *de novo* cost-effectiveness model was developed to support this submission.

The model structure was informed by a thorough review of i) various modelling approaches published in the literature and in HTA submissions[1] in an expanded disease area (including non-Hodgkin's lymphoma subtypes and multiple myeloma), ii) the disease and treatment pathways of WM, and iii) the available clinical data to inform modelling.

The modelling approaches identified through this review included the following:

- Discrete event simulation: as this approach is highly data intensive, it was deemed inappropriate, given the limited data available for clinical efficacy.
- Cohort survival partition: while this approach was commonly used and well accepted, it requires relatively complete long-term survival data, which were not available for this analysis given the very few progression and death events observed in Study 1118E (PFS and OS Kaplan-Meier (KM) curves remained remarkably flat)[23]. Consequently, the survival partition approach was ruled out.
- Markov state-transition: a Markov (or health state transition) model was the most commonly adopted approach and was widely accepted by multiple HTA bodies. This approach captures PFS explicitly in the model and allows incorporation of external data sources to inform post-progression outcomes. This approach was therefore deemed the most relevant modelling approach to capture the benefits, consequences, and costs associated with the treatment of WM patients while also bearing in mind the available evidence base.

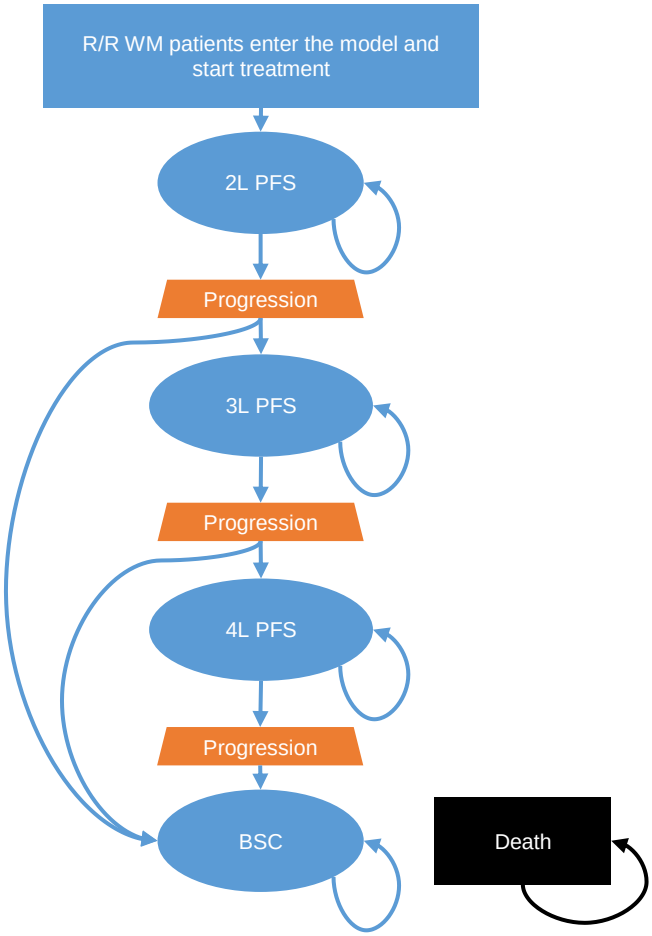
Figure 19 is a schematic of the model which follows patients through five health states (HS):

1. Second line (2L) treatment: patients enter the model here and initiate either ibrutinib or the comparator, PC. Patients can remain progression-free in this state, progress and initiate the next line of treatment (which can either be 3L active treatment or BSC), or die.
2. Third line (3L) treatment: a proportion of patients who progress following 2L treatment, enter this state and initiate 3L (active) treatment. Patients can remain progression-free in this state, progress and initiate the next line of treatment (which can either be 4L active treatment or BSC), or die.
3. Fourth line (4L) treatment: a proportion of patients who progress following 3L treatment, enter this state and initiate 4L (active) treatment. Patients can remain progression-free in this state, progress and initiate BSC, or die.
4. BSC: a proportion of patients will initiate BSC following progression from 2L, 3L, or 4L because they may not be eligible for further active treatment. Patients can remain progression-free in this state or die.
5. Death: patients can enter this absorbing state from any of the four other HS.

For ease of referencing, PFS is represented by time in the 2L HS; post-progression survival (PPS) is represented by the sum of time in 3L, 4L and BSC; OS is the time spent is PFS and PPS.

[1] These HTAs included bodies such as NICE, the National Centre for Pharmacoeconomics (NCPE) Ireland, and Scottish Medicines Consortium (SMC)

Figure 19: Model structure



R/R: relapsed or refractory; WM: Waldenström's macroglobulinaemia; 2L: second line; 3L: third line; 4L; fourth line; PFS: Progression-free survival; BSC: Best supportive care

Two lines of subsequent treatment (i.e. 3L and 4L) were included in the model to maintain face validity because clinical expert opinion and the chart review indicated that WM patients tend to receive multiple lines of treatment during their lifetimes [2, 3, 85]. Treatments received in these two HS are assumed to be active treatments for WM.

BSC refers to a non-interventional form of treatment with the intent of symptom management. This was assumed to consist of no active therapy and four annual haematologist visits.

Transition probabilities are used to distribute patients across HS. Costs and health effects (i.e., utility values) are then assigned in each HS. A four-week model cycle is used to capture the administration schedule of comparator treatment regimens. As patients progress cycle-by-cycle through the model, costs and utility values are summed per treatment arm for the duration of the time horizon, allowing for the calculation of total costs and total effectiveness per treatment arm.

A half-cycle correction was applied to both the ibrutinib and the PC comparator arms. The model assumes wastage associated with IV interventions.

Table 31 below provides the main features of the *de novo* cost-effectiveness analysis.

Table 31: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	30 years	Patients with WM can live for many years and may receive multiple lines of therapy. Therefore, this time horizon is considered sufficiently long to capture the long-term clinical and economic impact of ibrutinib in WM. Shorter and longer time horizons were tested in sensitivity analyses.
Were health effects measured in QALYs; if not, what was used?	Health effects were measured in both QALYs and LYs	In line with the NICE reference case.
Discount of 3.5% for utilities and costs	Health and cost outcomes were discounted by 3.5%	In line with NICE methods guide.
Perspective (NHS/PSS)	The model takes the perspective of the NHS and PSS	In line with the NICE reference case.
QALYs: quality-adjusted life years; LYs: life years; NHS: National Health Service; PSS: personal social services;		

Intervention technology and comparators

Intervention

Ibrutinib was applied in the economic model as per its SmPC and in accordance with its usage in Study 1118E: 420 mg/day (3 capsules) administered until disease progression or until no longer tolerated by the patient [1, 23].

Selection of comparators

The selection of comparators for inclusion in the economic model was based upon consideration of the following criteria, in accordance with the NICE Methods Guide (Section 5.1.6) [86]:

Relevance to UK clinical practice, based on NICE Final Scope and input from UK clinical experts [87]

As noted in Section 1, the NICE Final scope for ibrutinib in treating WM (April 2016)[87] recommended the following comparators for the R/R population:

- bendamustine + rituximab (BR)
- dexamethasone + rituximab + cyclophosphamide (DRC)
- fludarabine + rituximab +/- cyclophosphamide (FR/FCR)
- cladribine +/ rituximab
- rituximab
- chlorambucil

Clinical guidelines (see Section 3.3) and UK clinical experts (Appendix 4) confirm that there is no established standard of care for patients with R/R WM in the UK. Furthermore,

clinicians advised that rituximab in combination with fludarabine but *without* cyclophosphamide (i.e. FR) is not commonly used while chlorambucil *with* rituximab is a relevant combination in UK clinical practice.

Quality and rigour of data for establishing relative treatment effects

The following hierarchy of data was considered:

1. The most rigorous source of comparative efficacy is a head-to-head, RCT against the relevant comparator.

2. In the absence of RCT data, the NICE Methods Guide recommends establishing a network meta-analysis (NMA) or, if not all comparators can be included in one network, an ITC using common treatment arms [86]. Such methods are considered to generate unbiased estimates of the relative treatment effect, under the assumption of relative treatment effects being similar across heterogeneity of trial characteristics.

3. When indirect comparisons cannot be conducted due to lack of a common comparator, alternative statistical methods, such as matched-adjusted indirection comparison (MAIC) and pooled multivariate analysis, can be employed to estimate relative treatment efficacy between two treatments, adjusting for population differences between trials and therefore improving on naïve, unadjusted comparisons that can be introduce bias.

Comparators included in the economic model

Physician choice (PC) is the most relevant comparator for ibrutinib, as demonstrated by the lack of a standard of care in clinical guidelines [10, 12] and based upon UK clinical expert opinion (Appendix 4).

Numerous treatment options are used, depending on a patient's risk factors, age, and fitness levels; moreover, clinicians often enrol patients in clinical trials which clearly demonstrates the lack of effective and tolerable options in current practice. PC captures this variability of treatment options being used in UK clinical practice and addresses the fact that there is no gold standard. As such, PC is not only used as the comparator arm to ibrutinib (in 2L) but it is also used to represent the subsequent treatment option (with a slightly different composition) in 3L and 4L.

The composition of PC was defined for each line of therapy captured in the model (2L, 3L and 4L) bearing the following points in mind:

- The scope and distribution of treatments in the 2L setting was assumed to be very close to that in the 3L and 4L setting, based on clinician opinion, reflecting that treatment options are broadly similar across the lines but used differently in patients as the disease becomes more severe [88].
- UK clinicians acknowledged that the scope and the distribution of treatments used in 3L and 4L would be very similar [2, 60] and therefore, the same PC composition was assumed for 3L and 4L in the model.
- The scope and distribution of PC in 2L, 3L, and 4L impact the cost associated with therapy whilst patients are in the respective HS; the efficacy associated with PC in each HS is taken from the pan-European chart review and clinical opinion supports this proxy assumption.

In summary, PC is broadly aligned to the Final Scope; all the comparators listed in the Final Scope are encompassed within the PC comparator with the exception of FR which has been excluded and chlorambucil *with* rituximab which has been included, as per UK clinical opinion. The scope and distribution of treatments which represent PC in the model for each line of therapy is described in Table 32 below.

Table 32: Scope and distribution of treatments included in comparator arm (physician choice) – per line of therapy

Treatments	2L	3L/4L
FCR	11%	9%
DRC	31%	15%
BR	47%	43%
Cladribine + R	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.
Source: Clinical opinion [2, 60]

The "other treatments" component of PC was created as it was difficult for clinicians to provide exact estimates for the uptake of a few individual treatments and, overall, these treatments are rarely used in clinical practice[2, 60]. As such, these were grouped to ensure they are captured and the cost of each component was given equal weight within the group.

As mentioned above, the efficacy estimates associated with PC in each HS are taken from the pan-European chart review and clinical opinion supports this proxy assumption. With no RCT and no other relevant single-arm trial reporting relevant data, there are no head-to-head data and no way to carry out an ITC or an MAIC. Instead, the availability of anonymised patient level data (n = 454) from the pan-European chart review of WM patients allowed for a robust pooled multivariate analysis to establish the comparative efficacy of ibrutinib relative to current practice. The details of this analysis have been discussed in Section 4.11.

Treatment continuation rule

The dosing and continuation rules for ibrutinib have been implemented in accordance with the marketing authorisation. Comparators are implemented in the model as per their marketing authorisations.

The dosing regimen and continuation rules for ibrutinib and the relevant comparators are summarised in Table 33.

Table 33: Dosing regimen and treatment duration

Treatment	Dosing Regimen	Continuation rule and justification
Ibrutinib	420 mg/day (3 capsules) daily [1]	Treatment should continue until disease progression or no longer tolerated by the patient as per SmPC[1]

PC	FCR	Fludarabine: 25 mg/m^2 on days 2–4 every 28 days for six cycles Cyclophosphamide: 250 mg/m^2 on days 2–4 every 28 days for six cycles Rituximab: 375 mg/m^2 on day 1 every 28 days for six cycles	Treatment should continue until disease progression, or no longer tolerated by the patient or maximum treatment duration as per respective SmPC.
	DRC	Dexamethasone: 20 mg IV on day 1 every 21 days for six cycles Rituximab: 375 mg/m^2 IV on day 1 every 21 days for six cycles Cyclophosphamide:100mg/m^2 orally on days 1–5 every 21 days for six cycles	
	BR	Bendamustine: 90 mg/m^2 every 28 days for 6 cycles Rituximab: 375 mg/m^2 every 28 days for six cycles	
	Cladribine + R	Cladribine: 0,14 mg/kg every 28 days for 4 cycles Rituximab: 375 mg/m^2 every 28 days for 4 cycles	

Mg: milligram; m: meter; IV: intravenous; FRC: Fludarabine Rituximab; DRC: Dexamethasone Rituximab Cyclophosphamide; BR: Bendamustine Rituximab

5.3. *Clinical parameters and variables*

Incorporation of clinical data

Overview of clinical data used in the model

The economic model required a method to simulate the time patients spent in each model HS in order to track transition between HS; this required data to inform the probability of progression on each treatment line and the probability of death during PFS for each treatment line (2L, 3L and 4L) and BSC.

The clinical inputs which inform the transition probabilities for the various HS are from different sources and are summarised in Table 34 below.

Table 34: Overview of sources used to inform clinical inputs

Health state		Arm	% of patients who remain progression-free in HS	% of patients who progress from HS	% of patients who die within the HS
PFS	2L	Ibrutinib	Direct input Source: Parametric fitting to PFS KM data from Study 1118E (reference curve)	Derived Patients who progress from HS = 1 – percent patients who remain progression-free in HS – percent patients who die within the HS	Direct input Source: General population mortality as proxy Justification: the mortality rate from Study 1118E was based on limited data (3 deaths); therefore, the rate was compared to age-adjusted UK general population mortality for validation. As the data matched well, the general population mortality was used.
		Physician's choice (PC)	Derived The HR derived from the Cox regression model (see Section 4.11) was applied to the ibrutinib reference curve	Derived Patients who progress from HS = 1 – percent patients who remain progression-free in HS – percent patients who die within the HS	Direct input Source: pan-European chart review mortality rate
PPS	3L		Derived Patients who remain progression-free in HS = 1 – patients who progress from HS - percent patients who die within the HS	Direct input Source: pan-European chart review 4L treated cohort as proxy Justification: the Study 1118E cohort had median 3 lines of treatment and therefore once they progressed, they would be on fourth line; as such, the 4L treated cohort from the chart review was used as a proxy.	Direct input Source: the pan-European chart review PPS of 3L population as proxy Justification: the 3L treated population matches Study 1118E population median line of treatment. Parametric fitting found that exponential was the best fit, and indicated a constant mortality rate post-progression. Therefore, the same

	4L	Derived Patients who remain progression-free in HS = 1 – patients who progress from HS - percent patients who die within the HS	Direct input Source: pan-European chart review 4L treated cohort as proxy Justification: the chart review 5L cohort would have been the preferred data to use; however, it was not reliable due to the small sample size and therefore, the data from 4L was applied.	mortality rate is applied in all PPS states (i.e. 3L, 4L, and BSC).
	BSC	Not applicable	Not applicable	

BSC: best supportive care, 2L: 2nd line, 3L: 3rd line, 4L: 4th line, PC: physician choice
Sources: [2, 23, 60]

In summary:

- For the 2L HS (PFS), parametric fitting of Study 1118E trial data for ibrutinib was used as the reference curve, and comparative efficacy was based on the Cox regression analysis conducted with the patient-level data from the pan-European chart review cohort.
- For the 3L, 4L, and BSC HS (PPS), Study 1118E follow-up did not provide sufficient information, thus the chart review was used. Given that patients in Study 1118E had received a median of two prior therapies before trial enrolment meant that upon progression from ibrutinib, they would have had a median of three prior lines. Therefore, clinical data from the chart review for patients who experienced at least three lines of treatment were used as proxy. The progression rate and the post-progression mortality associated with the subsequent treatments (3L and 4L) were derived from the chart review cohort to estimate the duration of time patients spent in each HS. The same assumptions were applied for both the ibrutinib and the PC arms of the model.

The following sections describe the methods by which the model inputs were derived from available clinical data and assumptions that were made to overcome data limitations.

Progression-free survival health state (ibrutinib and PC)

The efficacy of ibrutinib and PC (i.e. efficacy within the 2L HS) was captured in terms of PFS (probability of progression or death) and probability of death and these parameters were informed by Study 1118E and the pan-European chart review [23, 85]. PFS and probability of death were used to derive the probability of progression:

Equation 1: Estimation of the probability of progression

$$Probability\ of\ progression = \frac{(\%PFS\ at\ cycle\ start - \%\ PFS\ at\ cycle\ end - \%\ died\ within\ the\ current\ cycle)}{\%PFS\ at\ cycle\ start - \%\ died\ within\ the\ current\ cycle}$$

These inputs are discussed in further detail below.

Probability of progression in 2L

Median PFS for ibrutinib had not yet been reached at median 24 months of follow-up (the latest data cut available), at which time 69.1% of patients remained alive and progression-free. As such, the long-term PFS of ibrutinib is projected directly from the KM data reported in Study 1118E [23] while the PFS of PC was estimated based on the HR derived from the Cox model and applied to the PFS of ibrutinib which was the reference curve (see Section 4.11).

The PFS of ibrutinib was extrapolated using a parametric function for long-term projection. Patient-level data were analysed and fitted with commonly used distributions, such as exponential, Weibull, log-normal, and log-logistic. To ensure the most appropriate fit was selected, the following steps were taken:

- Goodness of fit was tested using statistical criteria (Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]).
- The observed KM data curve was graphically compared to the predicted distributions to check for an appropriate match
- The long-term projections were assessed in terms of clinical plausibility.

Table 35 below lists the parameter fittings, the AIC, and the BIC while Figure 20 illustrates the various curves plotted against the KM data.

Statistical goodness of fit and visual inspection aid selection of the most appropriate curve fitting for the *observed* data. The AIC and BIC values are quite close and visual inspection does not allow for differentiation between the fittings eithers. In such situations where there are limited data (and it is difficult to distinguish a best fit of the observed data), it is crucial to assess the long-term plausibility of each fitting[89].

Visual inspection of the long-term extrapolations (i.e., beyond the period of observed KM data), suggests that the exponential and log-normal functions are likely an overestimation because at 10 years, over 20% of patients treated with ibrutinib estimate to remain progression-free and alive. The log-logistic and Weibull functions are estimating median PFS to be reached at similar times (approximately four years); however, log-logistic usually results in a long-term flat tail (as evidenced by Figure 20). Given the long-term flat tail of the log-logistic parametric function, more than 15% of patients treated with ibrutinib are projected to remain progression-free and alive after 10 years and more than 5% after 20 years.

Following discussion with UK clinical experts, whilst Janssen hope that ibrutinib is able to demonstrate such clinical efficacy in the long-term, exponential, log-normal, and log-logistic distributions were deemed to over-estimate the long-term efficacy in WM patients. Therefore, the Weibull distribution was considered more clinically plausible. Visual inspection of Figure 20 does not contradict that as the Weibull matches the observed KM data well and the trend at the tail-end of the KM data remains in line with the Weibull distribution.

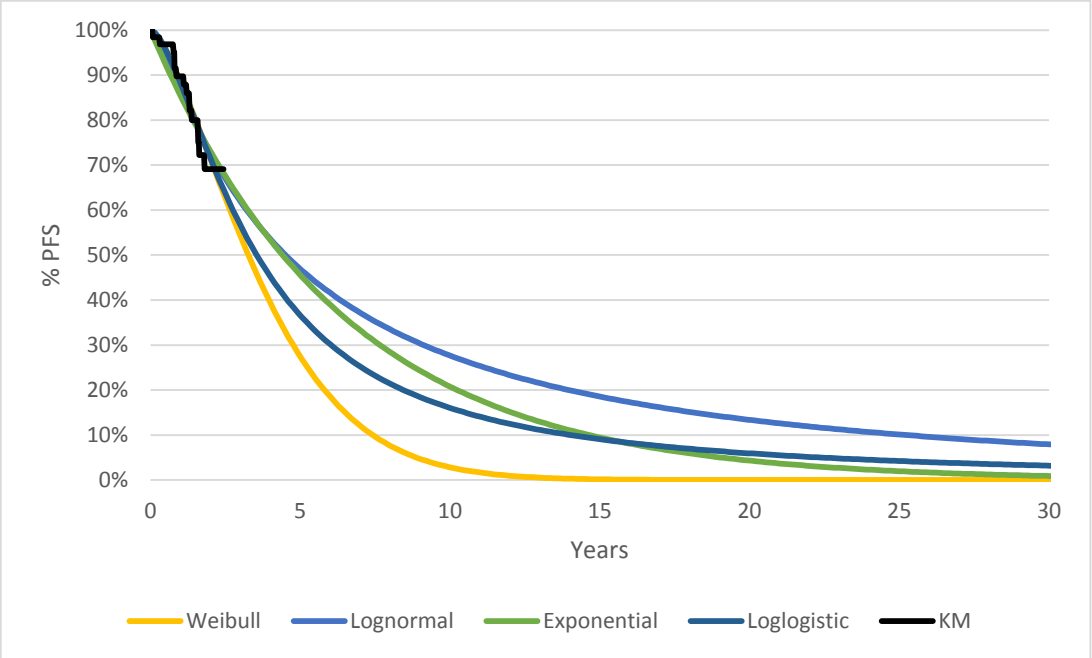
It is in consideration of all the above factors that the Weibull distribution was used in the base-case analysis and log-logistic was tested via a scenario analysis.

Table 35: PFS parametric fitting for ibrutinib Study 1118E data

Analysis	Intercept	Scale	AIC	BIC
Weibull	[redacted]	[redacted]	89.266	93.552
Log-normal	[redacted]	[redacted]	90.220	94.506
Log-logistic	[redacted]	[redacted]	89.138	93.424
Exponential	[redacted]	[redacted]	89.930	92.073

AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Figure 20: PFS Parametric fitting



PFS: Progression Free Survival; KM: Kaplan Meier

Probability of death in 2L

Only three deaths were reported in Study 1118E during the trial follow-up (24 months), with approximately 122 patient years of patient exposure. All three deaths occurred before disease progression. The mortality rate was estimated to be 2.5 per 100 patient-years and it was compared to the age-adjusted UK general population mortality for validation. As the data matched well, the general population mortality was used.

The following formula was used to convert annual probabilities of death to mortality rates per model cycle:

Equation 2: Conversion of annual to cycle mortality rates

$$\text{Cycle mortality rate} = 1 - e^{\frac{\ln(1-\text{annual probability})}{365.25/28}}$$

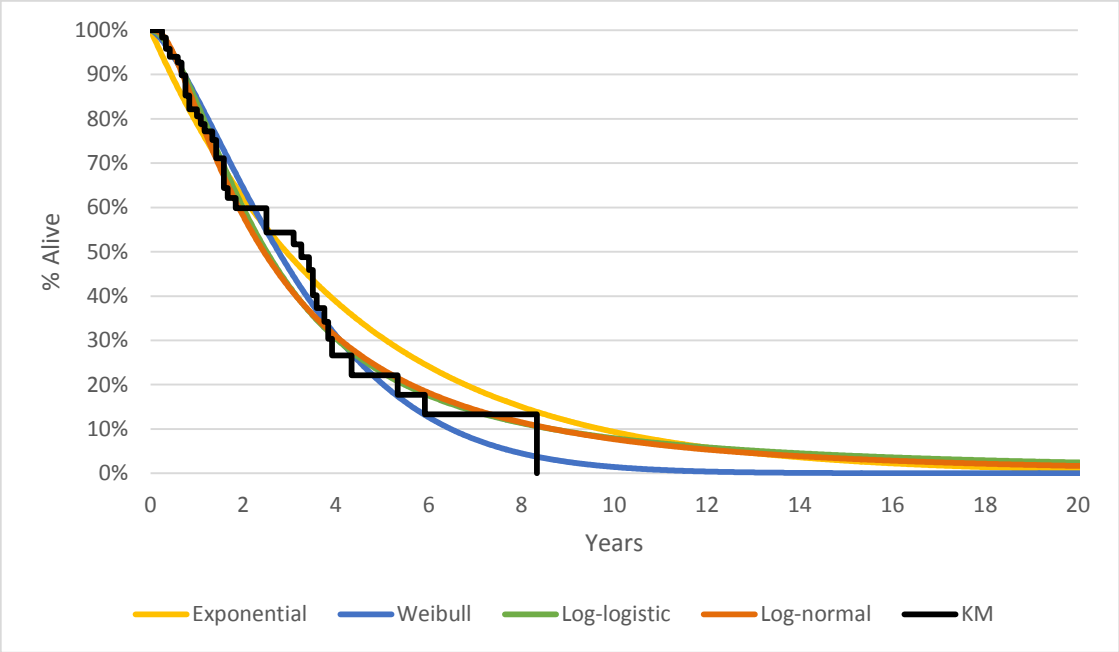
Probability of death associated with PC in the 2L HS was informed by the pan-European chart review. Table 36 below lists the parameter fittings, the AIC, and the BIC while Figure 21 illustrates the various curves plotted against the overall survival (i.e. time to death) KM data. Log-normal was selected for the model base case, as it was the best fit according to the AIC and BIC as well as visual inspection of both the fit to the observed KM data and the long-term clinical plausibility. Weibull was tested in sensitivity analyses because it offered the second best fit. Statistical goodness of fit was useful in this estimation of OS extrapolation, where it wasn't for PFS, as the

pan-European chart review contained a relatively large and mature dataset showing patient survival.

Table 36: Time to death parametric fitting for PC pan-European chart review data

Analysis	Intercept	Scale	AIC	BIC
Weibull	[redacted]	[redacted]	167.121	173.451
Log-normal	[redacted]	[redacted]	165.151	171.480
Log-logistic	[redacted]	[redacted]	167.382	173.712
Exponential	[redacted]	[redacted]	174.989	178.154

Figure 21: Time to death parametric fitting for PC



The following formula was used to calculate the probability of death per model cycle:

Equation 3: Probabilities of death from PC

$$Probability\ of\ death = \frac{(\%OS\ at\ cycle\ start - \%OS\ at\ cycle\ end)}{\%OS\ at\ cycle\ start}$$

Post-progression survival health state (subsequent treatment and BSC)

Following progression from 2L, patients enter the PPS HS (i.e. they enter 3L, then 4L, and then the BSC HS). There are three key clinical inputs required for modelling once patients progress from 2L (i.e. from ibrutinib or PC):

- The probability of receiving subsequent active treatment (vs. receiving BSC following progression from 2L and 3L)
- If receiving subsequent active treatment,
    - The probability of further progression (from 3L to 4L and then from 4L to BSC)
    - The probability of death in 3L, 4L and BSC.

Data for the probability of receiving subsequent active treatment (i.e. progressing from 2L to 3L and then from 3L to 4L) were available from the pan-European chart review (Table 37) [3]. However, UK clinical opinion did not support that *more* patients would receive subsequent treatment following progression on 3L versus progression on 2L; they believed it would be fewer patients and, as such, the data was slightly amended to reflect UK clinical practice (Table 37).

Table 37: Probability of receiving subsequent treatment

Parameter	Chart review	UK opinion
% receiving 3L treatment among patients progressed from 2L	[redacted]	86%
% receiving 4L treatment among patients progressed from 3L	[redacted]	70%

Source: Pan-European chart review study [3], UK KOL opinion (see Appendix 4)

For the proportion of patients assumed to receive subsequent treatment (3L or 4L), transition probabilities were estimated for progression whilst in those HS based on clinical evidence from the chart review [85]. Survival was determined by the probability of death, and was not influenced by the probability of progression.

PFS associated with 3L and 4L were informed by data from the chart review based on patients who had progressed from 3L treatment [85]. A parametric fitting was conducted for the OS of this cohort; an exponential function (see Table 38) was found to be the best fit, which indicates a constant hazard of death regardless of treatment. Therefore, a constant probability of death was assigned to 3L, 4L, and BSC (Table 39). Time to progression was analysed for the 4L and 5L cohorts from the original chart review [85]. Parametric fittings of the time to progression curve for the 4L found that an exponential model was the best fit, which indicates a constant probability of progression. The time-to-progression data for the 5L were shown to progress slower than the 4L data, which is counterintuitive and is likely due to the small sample size (n=26). Consequently, it was not appropriate to use the 5L data, and therefore, 4L data were used as proxy to inform the probability of progression for both 3L and 4L treatment (Table 39). The percentage of patients who remained progression-free in 3L and 4L was derived from the percentage of patients who progressed and the percentage of patients who died.

Table 38: Post-progression Survival – Chart Review 3L Parametric Fittings

Analysis	Intercept	Scale	AIC	BIC
Weibull	[redacted]	[redacted]	109.395	113.584
Log-normal	[redacted]	[redacted]	107.046	111.234
Log-logistic	[redacted]	[redacted]	108.204	112.392
Exponential	[redacted]	[redacted]	107.813	109.907
Generalised gamma	[redacted]	[redacted]	109.000	115.283
Gompertz	[redacted]		109.811	114.000
Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion				

Table 39: Probability of progression and death in 3L and 4L

Treatment	Probability of Progression (per 4 weeks)	Probability of Death (per 4 weeks)
3L	[redacted]	[redacted]
4L	[redacted]	[redacted]
BSC	[redacted]	[redacted]
Abbreviations: BSC = Best supportive care		

Evidence of probabilities changing over time

Clinical outcomes were based on time-to-event data, which takes into account changes over time in treatment effect, condition, or disease.

Assessment by clinical experts

Clinical experts were consulted to validate a number of assumptions, including extrapolation of the clinical parameters to ensure plausibility from the UK perspective.

Six clinicians were invited to participate in the completion of a clinical assumptions survey which would feed into a report of consolidated anonymised opinion; all six were available and able to participate. The clinicians were given two weeks to complete the survey followed by one-to-one calls to clarify their responses and / or to answer any questions or concerns the clinician had. Following the call, a report was generated which aggregated all of the responses to ensure anonymity of the clinicians. The final report was circulated for review and sign-off by the clinical experts.

The questionnaire sought opinion from the clinical experts on the following points:

- The potential position of ibrutinib within UK clinical practice
- Relevant comparators for assessment within this appraisal and the most robust clinical evidence to demonstrate comparative efficacy
- Survival assumptions including validation of extrapolated clinical data

- Assumptions on subsequent therapy used in patients who may eventually fail ibrutinib
- AEs in WM and their management within UK clinical practice
- Treatment dosing and administration
- Medical resource use

The consolidated report can be found in Appendix 4.

5.4. *Measurement and valuation of health effects*

HRQoL data from clinical trials

No HRQoL data were collected as part of Study 1118E [23]. No further health-related quality-of life data were identified by the SLR (see section X below).

Consequently, no mapping exercises were required.

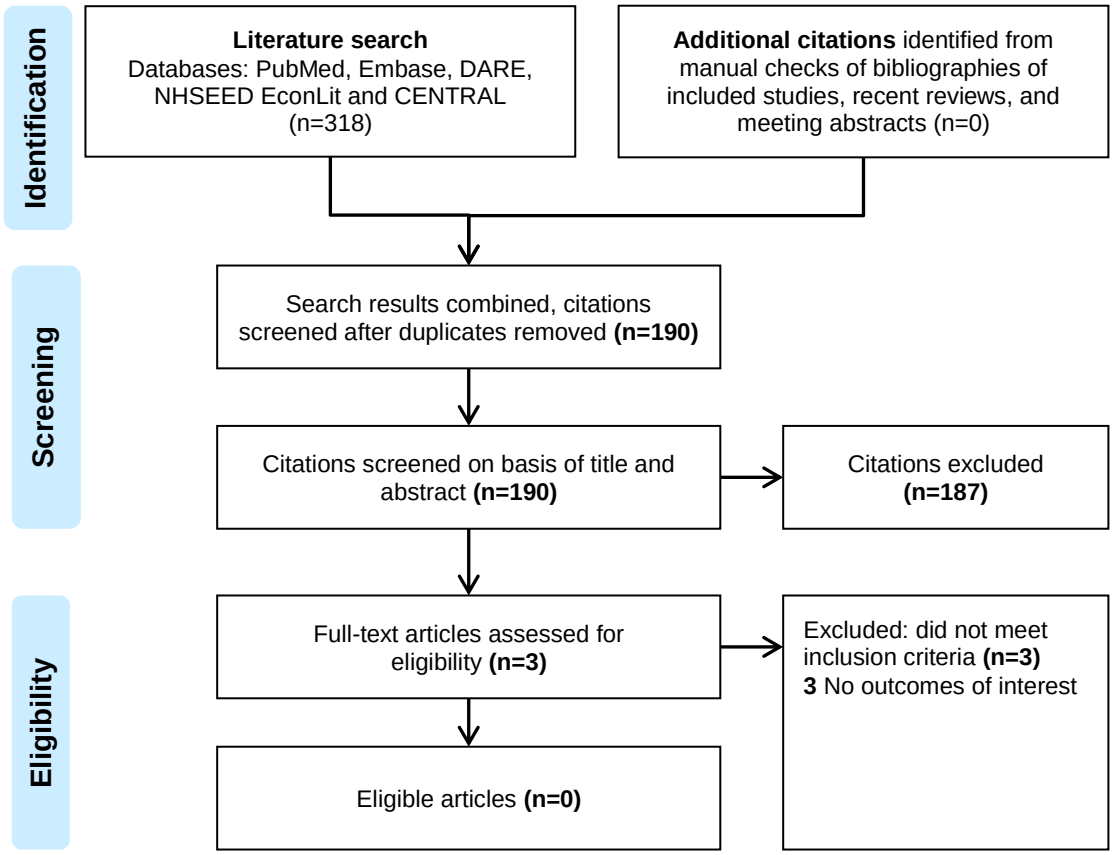
HRQoL data from published studies

The SLR conducted to identify published cost-effectiveness studies also aimed to identify HRQoL studies. The search dates, databases searched, and methodology for review and study selection were the same and as such, please refer to Section 5.1 for full details.

A total of 318 records were identified across the databases searched. After the removal of duplicate citations (no additional citation based on a hand search were identified), the abstracts of 190 publications were screened according to the pre-specified eligibility criteria (Appendix 6). Of these, 187 citations were excluded. Following the full text review of the 3 remaining citations, all 3 were rejected following further application of the eligibility criteria. Therefore, the SLR identified no studies reporting HRQoL data for patients with WM. Figure 22 below illustrates the process of eliminating references based on the protocol.

Furthermore, given that no HRQoL study was identified by the SLR, no detail can be provided on any study and no quality assessment could be provided.

Figure 22: PRISMA Flow Diagram of HRQoL



Adverse reactions and their impact of HRQoL

AE decrements were sourced from Beusterien et al. (2010) [90] and Tolley et al. (2013) [91] and are summarised in Table 40.

Table 40: Utility Decrement by AE

AE	Utility Decrement	Source
Anaemia	-0.088	Beusterien, 2010
Leukopenia	-0.185	Assumption
Neutropenia	-0.185	Tolley, 2013
Thrombocytopenia	-0.123	Tolley, 2013
Lymphocytopenia	-0.185	Assumption
Infection (non-pneumonia)	-0.195	Tolley, 2013
Neuropathy	-0.195	Assumption

AE	Utility Decrement	Source
Renal toxicity	-0.195	Assumption
Lung toxicity	-0.195	Assumption
Diarrhoea	-0.195	Assumption
Constipation	-0.195	Assumption
Abbreviations: AE = Adverse event		

Sources: [90, 91]

The AE decrement applied for PC was an average of the utility decrements weighted by the respective distribution of each treatment within PC (shown in Table 41 and Table 42).

Table 41: Disutilities for components of PC in relation to AEs (one off decrement)

Treatment	Utility decrement
FCR	-0.0065
Cladribine + rituximab	-0.0028
DRC	-0.0006
BR	-0.0041
Abbreviations: BR = Bendamustine + rituximab; DRC = Dexamethasone + rituximab + cyclophosphamide; FCR = Fludarabine + cyclophosphamide + rituximab	

Table 42: Disutilities for AEs (one off decrement)

	Mean	SE*
Ibrutinib	-0.0021	0.0002
PC	-0.0045	0.0004
Abbreviations: SE = standard error * based on 10% of mean value		

The AE decrements were applied over an assumed duration of 14 days and as a one-off decrement at treatment initiation in 2L. AEs were not considered for subsequent lines of therapy (3L and 4L) or for BSC, which is likely a conservative assumption as patients receiving PC at 2L would be more likely to proceed to the 3L and 4L health states than patients receiving ibrutinib at 2L.

HRQoL data used in cost-effectiveness analysis

As no utility data were collected in Study 1118E and no WM-specific data was identified in the literature, utility inputs in the model were informed by the RESONATE study of ibrutinib in R/R CLL, in which EuroQol– Five Dimensions (EQ-

5D) data were collected during the course of treatments [92]. This proxy was recommended by an EU advisory board when the lack of WM-specific data became clear [2]

Patients who remained progression-free in each health state were assigned a utility value of 0.799, based on the weighted average of "on treatment" utility over time from RESONATE [92]. This value was derived as the weighted average EQ-5D-5L score for patients who remained in the PFS health state from weeks 4 to 60 in the RESONATE CLL trial [92].

After progressing within the WM model and entering BSC HS, patients were assigned a utility value of 0.665. This value was calculated by applying a utility decrement of 12.8% to the baseline utility of 0.763 generated from the RESONATE EQ-5D-5L data for R/R CLL [92]. This percentage utility decrement was derived from Beusterien et al. (2010), a time trade-off QoL study carried out to ascertain CLL utilities in the UK [90].

Utility decrements associated with AEs (ranging from 0.123 to 0.195) were applied to patients as they experienced AEs in the model. The utility decrements associated with progression and adverse events were based on published literature, as analysis of RESONATE EQ-5D-5L data did not identify differences for these events [92].

A summary of the utility values applied in the model is provided in Table 43.

Table 43: 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		

Adjustment of health state utilities in model

Utility data were age adjusted within the model base case. In a study by Ara and Brazier (2010), age was found to have a negative association with EQ-5D utility [93] the coefficient was -0.0002587 for age and -0.0000332 for age^2. These coefficients were applied in the model.

No further health effects were found in the literature or clinical trials.

5.5. *Cost and healthcare resource use identification, measurement and valuation*

Resource identification, measurement and valuation studies

The SLR conducted to identify published cost-effectiveness studies also aimed to identify resource studies and inputs related to cost and healthcare resource use. The

search dates, databases searched, and methodology for review and study selection were the same and as such, please refer to Section 5.1 for full details.

Two studies reporting drug cost for various chemotherapies in Italy and the US were identified [94, 95]. Though these two studies were accepted per the SLR protocol, they were not considered of use to the model, as the model estimates the drug cost from current, UK-specific unit costs and treatment regimen. Furthermore, the publications were only available in abstract form and the reported costs were not described in sufficient detail to be useful to the model (e.g., no detail on resource use impact associated with the cost estimates).

Resource use in the management of WM

Given no studies were identified reporting this information, to understand UK standard practice for the management of WM, a questionnaire was designed to obtain the types and frequency of medical resource use (MRU) (including visits, procedures, and tests) for an average patient. This process has been described in Section 5.3 and the related report is available in Appendix 4. The summary of key findings is presented here.

Frequency of resource use required applied in the model was defined based on expert opinion and reflects a decrease of resource use over time. Table 44 describes the frequency of reported monitoring tests.

Table 44: Frequency of use of resources over time

	Frequency per year		
	In years 1-2	**In years 3-5**	**In years 6+**
Full blood count	5/year	4/year	3/year
Immunoglobulin	5/year	4/year	3/year
Chemistry	5/year	4/year	3/year
Ultrasound	Not included	Not included	Not included
Haematologist	5/year	4/year	3/year
Plasma viscosity / paraprotein	5/year	4/year	3/year

Patients receiving active treatment for WM are likely to experience AEs and symptoms related to progression that require unplanned medical attention and resource utilisation. In the model, unplanned medical resource use was based on the management of hyperviscosity which is managed with plasmapheresis. Incidence of hyperviscosity was stratified by HS based on the percentage of patients expected to have this condition in each HS; these percentages were based on clinical expert opinion (see Appendix 4) and are presented in Table 45.

Table 45: Unplanned Event Related Medical Resource Utilisation

Health state	% of patients experiencing unplanned events
2L	9%
3L	9%
4L	11%
BSC	11%
BSC: Best supportive care	

NHS reference costs currently cover a wide variety of conditions in oncology and are the most appropriate for costing purposes [96]. The clinical management of WM includes routine follow-up care such as visits to clinical specialists, tests and monitoring procedures.

As described above, UK clinical experts inform the exact type of visits, tests, and procedures and the frequency of care required depend on a patient's response to treatment (see Appendix 4). The specific types of resources and frequency of use for each response category and health state in the model are detailed in the sections which follow and the appropriate Healthcare Resource Groups (HRG) and PbR codes for each resource are provided.

The unit costs for the resource use included within the model are summarised in Table 46:

Table 46: Summary of variables

Items	Value	Reference
Full blood count	£ 3.01	NHS reference costs 2014/2015 DAPS 05 Haematology
Immunoglobulin	£ 5.49	NHS reference costs 2014/2015 DAPS 06 Immunology
Chemistry	£ 1.19	NHS reference costs 2014/2015 – DAPS 04 Biochemistry
Plasma viscosity	£150.38	NHS reference costs 2014/2015 WF01A Consultant Led, Non-admitted face to face follow-up Service code: 303
Haematologist	£ 5.49	NHS reference costs 2014/2015 DAPS 06 Immunology
Paraprotein	£ 1.19	NHS reference costs 2014/2015 – DAPS 04 Biochemistry
Hyperviscosity	£623.5	NHS reference cost 2014/2015. SA13A Single Plasma Exchange, Leucophoresis or Red Cell Exchange, 19 years and over
Adverse events except infections	£162	Weighted average of non-admitted clinical haematology visit codes: WF01A, WF01B, WF01C, WF01D, WF02A, WF02B, WF02C, WF02D.

Items	Value	Reference
Infections	£563	Infections or Other Complications of Procedures, without Interventions, with CC Score 0-4 (WH07F –WH07G).

Sources: [96]

Intervention and comparators' costs

Clinical opinion was further elicited to confirm correct dosages and dosing regimen for WM patients are included in the model. Dosing and continuation rules have been presented previously (Table 33). The associated costs are summarised in the following sections.

Drug acquisition and administration costs are presented in Table 47 Unit costs for drugs were retrieved from the British National Formulary (BNF) [43]. Where several pack sizes were available, the pack which was equal to the lowest cost per mg was used in the model calculations, as a conservative approach.

Table 47: Unit costs associated with the intervention and the comparator

Treatment	Unit size	Tablet / Vial Size	Administration route	Unit cost (£)	Administration cost (£)
Ibrutinib	140mg	1	Oral	51.10	0
PC					
Bendamustine	10.0mg/ml	10ml	IV	275.81	239.12
Chlorambucil	2.0 mg	25	Oral	40.51	0.00
Cyclophosphamide	500mg	1	IV	9.20	239.12
Dexamethasone	3.8mg	1	IV	1.99	239.12
Fludarabine	50mg	1	IV	147.07	239.12
Rituximab	10mg	50	IV	873.15	239.12
Cladribine	2.0 mg/ml	5 ml	IV	165.00	239.12

Mg: milligram; ml: millilitre
Source: drug costs from BNF; administration cost of IV based on NHS reference costs 2014-2015 SB12Z

Additional assumptions considered in relation to intervention and comparator cost inputs are as follow:

- The administration cost for IV therapies was estimated as a weighted mean of the different HRG related to chemotherapy injection in the NHS reference costs 2014-2015 (SB12Z to SB15Z) [96]; oral therapies are assumed to have no administration costs associated with them (weighted by number of cases).
- Vial sharing was assumed for IV drugs, and IV drug costs were estimated based on the actual dose infused and rather than on a per vial basis.

Wastage for IV drugs (i.e., no vial sharing) was explored in a sensitivity analysis. When wastage was considered, the dosing consumption per administration was rounded up to the closest number of vials.

- Body surface area (BSA) was required to estimate the cost associated with IV therapies within the PC comparator; the height (174.7cm) and weight (79.3kg) required to calculate BSA were taken from Study 1118E.
- According to the Study 1118E CSR, not all ibrutinib-treated patients received a full dose; the mean relative dose intensity was 93% [23]. Therefore, a relative dose intensity of 93% was included in the model for ibrutinib. No dose intensity data as available for the comparators arm; therefore, the same dose intensity percentage was assumed for the comparator arm.
- The treatment duration of ibrutinib was assumed to be the same as PFS, per the treat-to-progression indication. Patients were assumed to receive the PC treatment regimen until progression or maximum treatment duration, depending on which occurred first for each component of PC.

Health-state unit costs and resource use

It was assumed that medical resource use did not depend on treatment response. For the BSC health state, resource use consists of haematologist consultations; the frequency does not change over time. Costs per HS are summarised in Table 48.

Table 48: List of health states and associated costs in the economic model

Health states		Items	Value	Reference
PFS	2L	Technology	Ibrutinib: £4,599 per 30 days PC: £2,573/cycle	BNF
		Follow up costs (per year)	Year 1-2: £833.75 Year 3-5: £667 Year 6+: £500	NHS reference cost 2014/2015. DPAS 05
		Hyperviscosity	£224	NHS reference cost 2014/2015. SA13A Single Plasma Exchange, Leucophoresis or Red Cell Exchange, 19 years and over
		Total (per year)	Ibrutinib: Year 1-2: £52,915.43 Year 3-5: £52748.68 Year 6+: £52,581.68 PC: Year 1-2: £34,405.08 Year 3-5: £34,238.33 Year 6+: £34,071.33	Derived
PPS	3L	Technology	PC: £1,159/cycle	BNF

		Follow up costs	Year 1-2: £833.75 Year 3-5: £667 Year 6+: £500	NHS reference cost 2014/2015. DPAS 05
		Hyperviscosity	£ 224	NHS reference cost 2014/2015. SA13A Single Plasma Exchange, Leucophoresis or Red Cell Exchange, 19 years and over
		Total (per year)	PC: Year 1-2: 15,959.96 Year 3-5: £15,793.21 Year 6+:£15,626.21	Derived
	4L	Technology	PC: £1,159/cycle	BNF
		Follow up costs	Year 1-2: £833.75 Year 3-5: £667 Year 6+: £500	NHS reference cost 2014/2015. DPAS 05
		Hyperviscosity	£274	NHS reference cost 2014/2015. SA13A Single Plasma Exchange, Leucophoresis or Red Cell Exchange, 19 years and over
		Total (per year)	PC: Year 1-2: £15,961.62 Year 3-5: £15,794.87 Year 6+: £15,627.87	Derived
	BSC	Technology	Haematologist visits £601.52	NHS reference cost 201/2015
		Follow up costs	Year 1-2: £833.75 Year 3-5: £667 Year 6+: £500	NHS reference cost 201/2015
		Hyperviscosity	£274	NHS reference cost 201/2015
		Total (per year)	Year 1-2: £8,689.50 Year 3-5: £8,522.75 Year 6+: £8,355.74	Derived
BNF: British National Formulary; NHS: National Health System				

Sources: [43]

Adverse reaction unit costs and resource use

Common grade 3 and 4 AEs which occurred in ≥5% of patients in any of the treatments were considered in the model. Table 49 summarises these inputs. The respective AEs costs are summarised in Table 50.

A weighted average of the cost per AE (Table 49) multiplied by the treatment-specific rate (Table 50) resulted in the cost of AE associated with each treatment.

Table 49: Adverse event rates

Adverse event	Ibrutinib	PC				
		FCR	DRC	BR	Cladribine + R	Other treatment
Anaemia	0.02	0.02	NR	0.04	0.01	0.01
Leukopenia	NR	NR	NR	NR	0.10	0.10
Neutropenia	0.14	0.88	0.09	0.19	0.10	0.10
Thrombocytopenia	0.13	0.05	0.00	0.06	0.10	0.10
Lymphocytopenia	NR	NR	NR	NR	NR	NR
Constipation	NR	NR	NR	0.03	0.01	0.01
Neuropathy	NR	NR	NR	0.13	NR	NR
Lung Toxicity	NR	NR	NR	0.05	NR	NR
Diarrhoea	0.00	NR	NR	0.03	0.01	0.01
Infection (non-pneumonia)	0.06	NR	NR	0.06	0.10	0.10
Source	23	76, 97	98	assumed same as FR[77]	99	99

Table 50: Adverse events costs

Adverse event	NHS code used	Cost in the model (£)
Anaemia	Outpatient visit. Costed as weighted average of non-admitted clinical haematology visit codes: WF01A, WF01B, WF01C, WF01D, WF02A, WF02B, WF02C, WF02D	162
Leukopenia		162
Neutropenia		162
Thrombocytopenia		162
Lymphocytopenia		162
Constipation		162
Neuropathy		162
Lung Toxicity		162
Diarrhoea		162
Infection (non-pneumonia)	Infections or Other Complications of Procedures, without Interventions, with CC Score 0-4 (WH07F – WH07G). Costed as weighted average of: • Elective Inpatient • Non-elective inpatient (long and	563

Adverse event	NHS code used	Cost in the model (£)
	short stay) • Day case	

Miscellaneous unit costs and resource use

A one-off terminal care cost from Round et al. was applied within the model based on[100,101] which was inflated to reflect current prices (using the hospital and community health service (HCHS) inflation indices reported within the PSSRU [102]. This was estimated to be £7,287 per cancer related death in 2014 (inflated to £7,352). This terminal care cost was applied as a lump-sum one-off cost to patients transitioning into the death state.

5.6. *Summary of base-case de novo analysis inputs and assumptions*

Summary of base-case inputs

Table 51: Summary of variables applied in the economic model

Input	Base-case value	Source	Reference
Model settings			
Age	65	Study 1118E	Section 4.10
Body surface area	1.96 m^2		Section 5.5
Percent male	76%		Section 4.10
Dosing intensity	93%		Section 5.5
Time horizon	30	Assumption	Section 5.2
Discounting	3.50%	Assumption	Section 5.2
Clinical inputs			
PFS - HR ibrutinib vs PC	[redacted]	Indirect comparison	Section 4.11
PFS - Parametric distribution	Weibull	Study 1118E	Section 5.3
3L probability of progression	[redacted]	Chart review analysis	Section 5.3
3L probability of death	[redacted]		
4L probability of progression	[redacted]		
4Lprobability of death	[redacted]		
BSC probability of death	[redacted]		
Utility inputs			
Utility 2L PFS	0.799	RESONATE CLL study	Section 5.4
Utility 3L PFS	0.799		
Utility 4L PFS	0.799		
Utility BSC	0.665	RESONATE CLL study; Beusterien 2010	Section 5.4
Adverse event disutility – ibrutinib	-0.002	Beusterien 2010; Tolley 2013	Section 5.4
Adverse event disutility – PC	-0.004		Section 5.4
Medical resource use inputs			

Hyperviscosity - 2L PFS	9%	KOL opinion	Appendix 4
Hyperviscosity - 3L PFS	9%		
Hyperviscosity - 4L PFS	11%		
Hyperviscosity – BSC	11%		
Year 1-2 MRU Immunoglobulin, Chemistry, Plasma viscosity, Haematologist, Paraprotein	5/year		
Year 3-5 MRU Immunoglobulin, Chemistry, Plasma viscosity, Haematologist, Paraprotein	4/year		
Year 6+ MRU Immunoglobulin, Chemistry, Plasma viscosity, Haematologist, Paraprotein	3/year		
Annual MRU for BSC	4/year		
Cost inputs			
Bendamustine	£275.81	BNF	Section 5.5
Cyclophosphamide	£9.20		
Dexamethasone	£1.99		
Fludarabine	£147.07		
Chlorambucil	£40.51		
Cladribine	£165.00		
Rituximab	£873.15		
Administration cost - oral	£0	Assumption	
Administration cost – IV	£239.12	NHS reference costs 2014-2015	
Adverse events except infections	£162		
Infections	£563		
Terminal care	£7,352	Round et al, 2015[100,101]	

Summary on base-case assumptions

A list of all assumptions used in the *de novo* economic model and justification for each assumption is provided in Table 52 below.

Table 52: Assumptions used in the de novo economic model

	Assumption	Justification
Comparator	The PC comparator was assumed to be a mix of treatment options based on data from the pan-Europe CR	There is no standard of care for the treatment of WM in second- and subsequent lines.
Treatment	The treatment duration of ibrutinib was	As per SmPC of the respective

	Assumption	Justification
duration	assumed to be based on PFS, as per the treat-to-progression indication.	therapies.
	Patients were assumed to receive the PC treatment regimen until progression or maximum treatment duration, depending on which occurred first.	
Medical resource use	It was assumed that medical resource use (MRU) did not depend on treatment response.	Clinical experts suggested that while overall, medical resource use would not vary by response status (assuming none of the patients have complete response), patients with no response would be more regularly followed up than the others; however, data were limited so stratification was not considered.
	Patient MRU was assumed to be the same across all lines of therapy (2L, 3L and 4L), with a decrease in MRU over time e.g. a patient will incur a higher level of MRU in 2L Year 1 than in 2L Year 3, assuming they remained progression-free in 2L.	Clinical expert suggestion
	In the base case, five plasmapheresis treatments were assumed for each hyperviscosity case	Clinical expert suggestion
Treatment effect and transition probability	Hazard ratio of ibrutinib versus PC was assumed constant after the duration of the trial follow-up, over the entire time horizon	Assumption made based on data available to date
	Mortality rates for WM patients were assumed to be the same as the mortality of the general population	General population mortality was used because the mortality rate observed in Study 1118E was based on 3 deaths and found to be similar to general population mortality.
	The same post-progression efficacy was assumed for both ibrutinib and PC.	In the absence of further information, this was deemed a conservative assumption
	The probability of receiving the first subsequent treatment was assumed to be the same as that for patients who received 4L treatment after progression from 3L in the chart review. The probability of receiving a second subsequent treatment was assumed to be the same as receiving 5L treatment after progression from 4L in the chart review	Patients in Study 1118E had received a median of two prior therapies before trial enrolment.
	AEs that were not reported in some of	Conservative approach.

	Assumption	Justification
Adverse events	the studies were assumed to be 0% in the model for calculation purposes	
	AE decrements were applied over an assumed duration of 14 days and as a one-off decrement at treatment initiation.	Conservative approach.
Vial sharing	In the base case analysis, vial sharing was assumed for IV drugs only	

Sources: [3, 23]

5.7. *Model results*

Base-case results

Results of the base case analysis demonstrated unprecedented gains in LYs and QALYs comparing ibrutinib to PC. Ibrutinib was associated with an incremental increase of [redacted] LYs and [redacted] QALYs compared to PC. The base case ICER, at list price, was £78,647/QALY compared to the PC arm.

Table 53: Base-case results (at list price)

Technology (and comparators)	Total costs (£)	Total life years	Total QALYs	Incremental costs (£)	Incremental life years	Incremental QALYs	ICER versus baseline (£)
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	78,647
PC	[redacted]	[redacted]	[redacted]				
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years							

Table 54: Summary of disaggregated costs (at list price)

Parameter	Cost intervention (Ibrutinib)	Cost comparator (Physician's choice)	Increment
PFS			
2L - Drug cost	[redacted]	[redacted]	[redacted]
2L - Administration cost	[redacted]	[redacted]	[redacted]
2L - Planned FU	[redacted]	[redacted]	[redacted]
2L - Unplanned FU	[redacted]	[redacted]	[redacted]
2L - AE cost	[redacted]	[redacted]	[redacted]
PPS			
3rd line - Drug and admin cost	[redacted]	[redacted]	[redacted]
3rd line – FU	[redacted]	[redacted]	[redacted]

4th line - Drug and admin	[redacted]	[redacted]	2,466
4th line - FU	[redacted]	[redacted]	122
BSC	[redacted]	[redacted]	409

Clinical outcomes from the model

Neither the median PFS nor the median OS for ibrutinib were reached in Study 1118E [23]; therefore projected and actual PFS and OS at 24 months were compared. The projected and KM curves matched well. Results as presented in Table 55 of this exercise indicate that the model replicates the trial data accurately.

Table 55: Summary of model results compared with clinical data at 24 months

Outcome	Clinical trial result	Model result
Ibrutinib		
Progression free survival	69.1% at 24 months	71.8% at 24 months
Overall survival	95.2% at 24 months	94.6% at 24 months
Physician's choice		
Progression free survival	30% at 24 months for 3L 16% at 24 months for 4L	25.4% at 24 months
Overall survival	61% at 24 months for 3L 80% at 24 months for 4L	62.3% at 24 months

Provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying 1 for each comparator.

[redacted]

[redacted]

[redacted]

Disaggregated results of the base case incremental cost effectiveness analysis

Table 58, Table 59 and Table 60 summarise the QALY gains and total costs by health state, and the predicted resource use for ibrutinib vs. PC.

Ibrutinib was associated with substantially higher PFS QALYs of [redacted] and PPS QALYs of [redacted] compared with PC, which was associated with PFS and PPS QALYs of [redacted] and [redacted], respectively. Ibrutinib was also associated with higher costs vs. PC for PFS (incremental costs of [redacted]) and PPS (incremental costs of [redacted]). This was largely driven by the fact that patients survive on average [redacted] years longer than in PC, thus extending the time on treatment. Ibrutinib, however, was associated with slightly lower costs for other resource use, such as administration costs, adverse events and terminal care.

Incremental results comparing ibrutinib to PC yielded an incremental QALY benefit of [redacted] for PFS and [redacted] for PPS. The difference in total costs for PFS and PPS was [redacted] and [redacted], respectively.

Table 58: Summary of QALY gain by health state

	QALY intervention (Ibrutinib)	QALY comparator (Physician's choice)	Absolute increment	% absolute increment
Progression free survival (2L)	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression survival (3L, 4L, BSC)	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]
QALY, quality-adjusted life year; Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee				

Table 59: Summary of costs by health state

	Cost intervention (Ibrutinib)	Cost comparator (Physician's choice)	Absolute increment	% absolute increment
Progression free survival (2L)	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression survival (3L, 4L, BSC)	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee				

Table 60: Summary of predicted resource use by category of cost

	Cost intervention (Ibrutinib)	Cost comparator (Physician's choice)	Absolute increment	% absolute increment
PFS				
2L - Drug cost	[redacted]	[redacted]	[redacted]	[redacted]
2L - Administration cost	[redacted]	[redacted]	[redacted]	[redacted]

2L - Planned FU	[redacted]	[redacted]	[redacted]	[redacted]
2L - Unplanned FU	[redacted]	[redacted]	[redacted]	[redacted]
2L - AE cost	[redacted]	[redacted]	[redacted]	[redacted]
PPS				
3L - Drug and admin	[redacted]	[redacted]	[redacted]	[redacted]
3L – FU	[redacted]	[redacted]	[redacted]	[redacted]
4L - Drug and admin	[redacted]	[redacted]	[redacted]	[redacted]
4L – FU	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]
Terminal care	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

5.8. *Sensitivity analyses*

Probabilistic sensitivity analysis

The uncertainties around parameters were estimated in a PSA, including uncertainty around utility, PFS, OS, and costs. For each parametric function in the model, the model used distributions to correlate the function parameters. For each parameter, the same random number was used across all treatment arms when PSA variations were drawn to ensure consistency. Distributions used in the PSA along with justification are provided in Table 61.

Table 61: Model parameters varied in PSA with justification

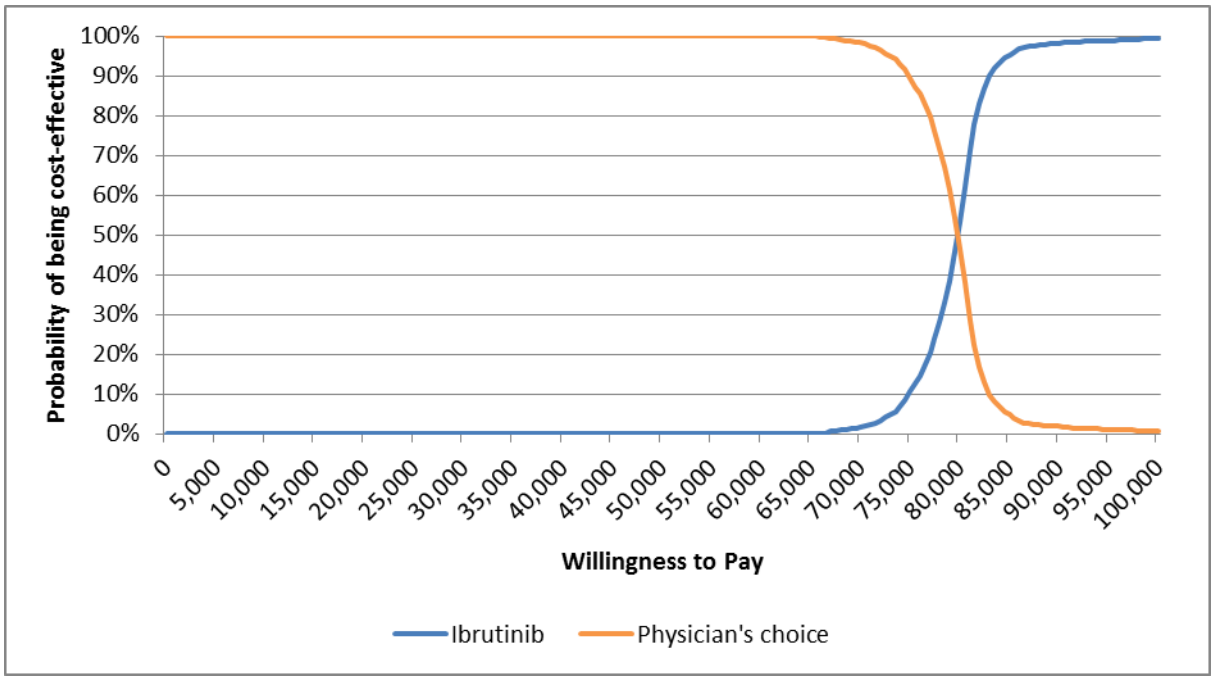
Parameter	PSA Distribution	Justification
PFS and OS in 2L	Normal Distribution (Cholesky decomposition)	PFS and OS of treatment are projected using parametric distributions fitted to KM trial results. The parametric fittings were conducted using the maximum-likelihood estimation which assumes the error to be normally distributed. Therefore normal distribution was chosen. Cholesky decomposition was used to maintain the correlation between parametric fitting parameters.
PFS, progression and death in subsequent lines	Beta distribution	A Beta distribution was chosen for the probabilities to ensure these were bound between 0 and 1.
Utility	Beta distribution	A Beta distribution was chosen for disutility to ensure the alternative values for PSA were between 0 and 1.
Follow-up costs	Gamma distribution	A Gamma distribution was chosen for costs to ensure the alternative values were positive
AE costs	Gamma distribution	A Gamma distribution was chosen for costs to

		ensure the alternative values were positive
MRU - % of patients	Beta distribution	A Beta distribution was chosen for % of patients using MRU to ensure the alternative values for PSA were between 0 and 1.
MRU cost	Gamma distribution	A Gamma distribution was chosen for costs to ensure the alternative values were positive
PFS: Progression Free Survival; OS: Overall Survival; MRU: Medical Resource Use; AE: Adverse Event; PSA: Probabilistic sensitivity analysis		

The PSA was run for 1,000 iterations. This analysis demonstrates the impact of parameter uncertainty within the economic model.

Figure 23 presents the ICER scatter plot for ibrutinib compared to PC, which shows the incremental costs and QALYs for each iteration. Figure 24 presents cost-effectiveness acceptability curves for each model comparator.

Figure 24: Cost-effectiveness acceptability curve for ibrutinib vs PC (at list price)



The following table compares the median results obtained in the PSA and those obtained in the base-case deterministic analysis (Table 62). Overall, both analyses provided similar results.

Table 62: Comparison of mean and median PSA outcomes (at list price)

	Mean PSA Outcomes			Median PSA Outcomes		
	Total costs (£)	Total life years	Total QALYs	Total costs (£)	Total life years	Total QALYs
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physician Choice	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	79,507			75,872		
PSA: Probabilistic Sensitivity Analysis; QALYs: Quality Adjusted Life Years						

Deterministic sensitivity analysis

All major model variables for which values were uncertain were tested in a one-way sensitivity analysis, in order to identify model drivers and examine key areas of uncertainty within the model. Where possible, confidence intervals or published ranges were used as alternative values. In the absence of confidence intervals or published ranges, upper and lower bounds tested in the one-way sensitivity analysis were calculated as -/+ 10% of the mean, base case value. The parameters were varied as shown in Appendix 7.

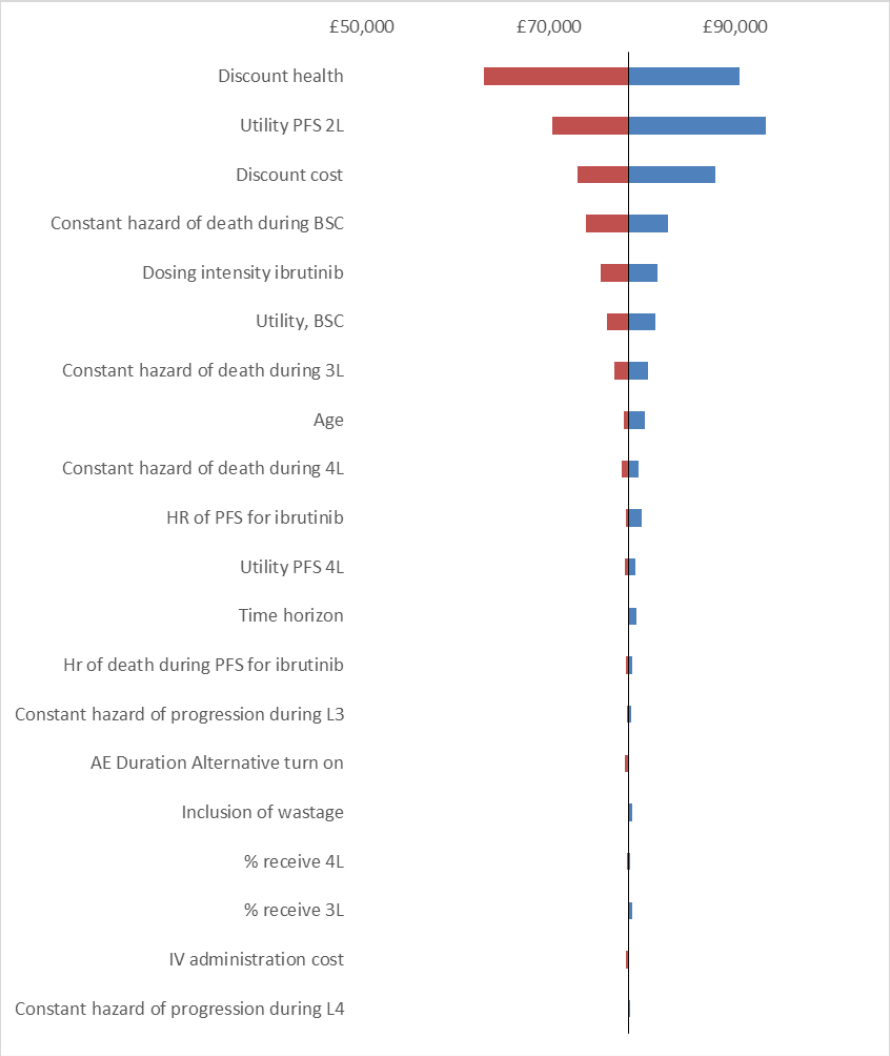
Results of the one-way sensitivity analysis for ibrutinib vs. PC, in which single parameters were varied one at a time to test impact on model results, are shown in tabular form in Table 63 and in graphical form in Figure 25 for the 20 most influential parameters.

Table 63: Sensitivity analysis results for ibrutinib vs PC (at list price)

Parameter	Base case value	Alternative value	ICER (£/QALY)
Base case			£78,647
Discount health	3.5%	0%	£63,114
		6%	£90,531
Utility PFS 2L	0.799	0.62	£70,456
		0.93	£93,372
Discount cost	3.5%	0%	£73,091
		6%	£87,952
Constant hazard of death during BSC	[redacted]	[redacted]	£74,006
		[redacted]	£82,780
Dosing intensity ibrutinib	[redacted]	[redacted]	£75,647
		[redacted]	£81,648
Utility, BSC	0.67	0.53	£76,237
		0.79	£81,489
HR of PFS for ibrutinib	[redacted]	[redacted]	£78,296
		[redacted]	£79,987
Constant hazard of death during 3L	[redacted]	[redacted]	£77,120
		[redacted]	£80,638
Utility PFS 3L	0.799	0.62	£78,724
		0.93	£78,572
Age	65	62	£78,078
		67	£80,385
Constant hazard of death during 4L	[redacted]	[redacted]	£77,846
		[redacted]	£79,667
Utility PFS 4L	0.799	0.62	£78,142
		0.93	£79,343
Time horizon	30 years	20	£78,647

Parameter	Base case value	Alternative value	ICER (£/QALY)
		30	£79,413
Inclusion of wastage	Yes	No	£78,647
		Yes	£79,034
HR of death during PFS for ibrutinib	[redacted]	[redacted]	£78,311
		[redacted]	£78,987
Constant hazard of progression during 3L	[redacted]	[redacted]	£77,120
		[redacted]	£80,638
Duration of AE disutility	14	180	£78,221
		14	£78,647
IV administration cost	239	239	£78,363
		389	£78,647
Constant hazard of progression during 4L	[redacted]	[redacted]	£78,543
		[redacted]	£78,721
% receive 4L	86%	86%	£78,467
		100%	£78,791

Figure 25: Tornado diagram of deterministic sensitivity analysis (at list price)



Scenario analysis

Scenario analyses were conducted for each comparator. The parameters varied for each comparator are shown in Table 64 below.

Table 64: Model parameters varied in scenario analysis

Variable	Base case	Parameter change	Rationale
Age adjustment for utilities	Yes	No	To assess the impact of not adjusting utilities by age

Distribution for PFS of ibrutinib	Weibull	Log-logistic	The Log logistic distribution had the best fitting with AIC BIC, although the Weibull distribution was deemed most appropriate for the base-case
HR PFS in 2L	[redacted]	[redacted]	Scenario 1: Imputed patient characteristics. No individual clinical measurement (risk category only)
HR PFS in 2L	[redacted]	[redacted]	Scenario 2: Sample with complete patient characteristics. No imputation. All Variable (individual clinical measurements & risk category)

The results of scenario analysis conducted are shown in Table 65 below.

Table 65: Scenario analysis results for ibrutinib vs PC (at list price)

Variable	Base case	Parameter change	ICER (£/QALY)
Base case			£78,647
Age adjustment for utilities	Yes	No	£75,986
Distribution for PFS of ibrutinib	Weibull	Log-logistic	£82,418
HR PFS in 2L	[redacted]	HR =[redacted] Scenario 1: Imputed pat. charac. No individual clinical measurement (risk category only)	£78,846
HR PFS in 2L	[redacted]	HR = [redacted] (Scenario 2: sample with complete pat. charac, No imputation. All Variable (individual clinical measurements & risk category)	£79,175

Summary of sensitivity analyses results

Throughout the extensive scenario analyses tested, the ICER remained stable with similar incremental costs and benefits gained.

Results of the one-way sensitivity analysis demonstrated that the model drivers were the discounting for health outcomes, the utility values in PFS of 2L and the discounting of costs. Results of scenario analyses indicated that model results were sensitive to the parametric distribution used for PFS projection. The model was also sensitive to age adjustment for utilities.

5.9. *Subgroup analysis*

There were no relevant sub-groups to assess.

5.10. *Validation*

The structure and programming of the Microsoft Excel model was validated by two modelling experts not involved in this study and a variety of stress tests were performed to ensure that the model results reflected the inputs entered. For example, both extreme values and equal values across treatment arms were input and actual results compared against expected results. In situations where actual results diverged from expected results, debugging was performed to investigate and remedy discrepancies. The model was also thoroughly examined by an external vendor (Amaris).

Statistical fittings for PFS were validated by comparing observed PFS KM data for ibrutinib to the curves derived from the predictions. The PFS extrapolated data matched well against the KM curves from the trial. Predicted PFS survival curve for ibrutinib and for the comparator (see Section 5.6), as well as major model assumptions, were validated by clinical experts practicing in the UK [2, 60]

5.11. *Interpretation and conclusions of economic evidence*

No other published cost-effectiveness analyses of ibrutinib were identified in the SLR and, therefore, results of the current analysis cannot be directly compared to and validated by an external source. There are also no other published cost-effectiveness analyses of other treatments of WM to compare to.

The current analysis provides estimates of the cost-effectiveness of ibrutinib the relevant patient group based on the best available data. In the base case, cost-effectiveness is assessed for treatment of all R/R WM patients. In the absence of data for first line use of ibrutinib in patients with WM, we ask the Committee to refer to Section 7 for consideration of a proposal to collect data around this and other uncertainties which may be raised.

To ensure results of this analysis are generalizable to clinical practice in England and Wales, clinical experts currently practicing in England and Wales were interviewed to confirm clinical assumptions and model inputs. Specifically, local experts provided input on:

- Relevant comparators, including composition of PC and subsequent lines of treatment
- The potential position of ibrutinib within UK clinical practice
- Survival assumptions including validation of extrapolated clinical data
- Assumptions on subsequent therapy used in patients who may eventually fail ibrutinib
- AEs in WM and their management within UK clinical practice
- Treatment dosing and administration
- Medical resource use

The economic analysis was based on a *de novo* economic decision model designed to best capture the unique aspects of the disease and treatment pathway in question, and to make the best use of clinical trial data in order to capture the benefits and costs associated with ibrutinib and its comparator treatments. The structure of the model is consistent with standard oncology modelling and previously published models in blood cancers, which have been well accepted by NICE [103, 104].

The analysis used the most recent interim data cut (24 months of follow-up) from Study 1118E, which represents the most mature data available, to inform inputs for ibrutinib.

Comparative data to inform the relative treatment effect of ibrutinib vs. PC were based on a robust chart review on over 400 WM patients across Europe (71 of who were from the UK). The analysis made the best use of the available data by conducting a pooled Cox-regression analysis comparing ibrutinib with PC and limits the bias that naïve comparison of clinical trial results would have introduced.

The economic analysis was limited in certain respects, largely due to the availability of data. However, extensive sensitivity analyses and scenario analyses were conducted to test the impact of uncertainty around data inputs. With 69.1% of ibrutinib patients still alive and progression-free at a median of 24 months in Study 1118E, PFS outcomes had to be extrapolated in the economic model and predicted outcomes cannot be well validated by trial data. To minimise uncertainty related to survival projections, alternative parametric fittings for survival were tested in the scenario analysis. Furthermore, Section 7 discusses extensively a proposal to address the uncertainties with real-world data collection which will confirm the cost-effective and positive impact ibrutinib will have on patients with WM and the NHS alike.

Ibrutinib has the potential to provide additional benefits to patients not captured in this analysis. Ibrutinib is an orally-administrated treatment, which reduces patient burden in comparison to standard infused treatments. The potential utility benefit of ibrutinib's oral administration was not captured in this economic analysis.

In summary, ibrutinib addresses a high unmet need, dramatically prolonging PFS where current treatment options are suboptimal. Ibrutinib's manageable tolerability profile allows patients to stay on treatment longer, delaying the use of other more toxic treatments. Median PFS and OS for patients treated with ibrutinib have not been reached in Study 1118E; these trials are ongoing and will continue to provide evidence of ibrutinib's treatment benefits.

6. Assessment of factors relevant to the NHS and other parties

A budget impact analysis (BIA) was performed by comparing the budget impact to the NHS in England and Wales in a world without ibrutinib to a world in which ibrutinib is recommended for use by NICE. A 5-year time horizon was used and the BIA was calculated for the WM population within ibrutinib's full license, which was estimated to be 150 patients in 2017 rising to 155 patients in 2021.

Market share data were estimated based on data collected from a clinician report. Drug acquisition and administration costs used were assumed to equal the treatment cost for a R/R WM patient throughout the BIA, and were the same as those applied in the CEA for such values (see Section 5).

The results of the BIA estimated the introduction of ibrutinib to be associated with a budget impact of £1,987,046 in 2017 and a cumulative budget impact of £12,631,638 over the 5 years following NICE recommendation.

6.1. *Overview of the budget impact analysis*

The budget impact of introducing ibrutinib for the treatment of WM to the NHS was estimated using a Microsoft Excel budget impact model. The BIA calculates the difference in total costs treating patients with R/R and frontline CI in two Scenarios:

- World without ibrutinib: ibrutinib is not recommended for WM
- World with ibrutinib: ibrutinib is recommended for WM

The model calculates drug acquisition and administration costs on a 5-year time horizon for WM patients from an NHS perspective.

Displaced therapies included in the BIA reflect treatment options routinely used in England to treat R/R WM patients who have failed one prior line of treatment or for whom chemoimmunotherapy is inappropriate ineligible. These treatments are consistent with clinician opinion.

A confidential commercial access arrangement is currently being agreed with NHSE; therefore, the budget impact of ibrutinib has been estimated separately using the list price and the price after the agreed final price of ibrutinib (see Appendix 9).

6.2. *Patient numbers*

Patient numbers were estimated using a simple methodology (see Table 66):

1. Overall population in England and Wales: the populations in England and Wales in 2014 were reported by the Office of National Statistics [105] in February 2016 (ONS) Constant growth rates, also from the ONS, were applied in order to derive the England and Wales populations from 2017 to 2021 [105]

2. The incidence of WM was obtained by an estimate provided by the BMJ in its overview of WM. This estimate was confirmed by a publication regarding the incidence and survival of WM in South East England [9].

3. WM is a very indolent disease, thus only symptomatic patients are eligible for treatment. The percent of WM patients who will require treatment was established using Ansell et al, 2010 [8].

4. An EU Advisory board held 19 March 2015 confirmed clinician opinion on the number of WM patients for whom chemoimmunotherapy is inappropriate [2].

5. The Pan-European chart-based observational study was used to audit the number of WM patients who received 1 prior line of therapy [3].

The estimated incidence of WM was assumed to remain constant in the 5 years of the BIA. This was considered a reasonable assumption as no evidence is available to suggest that the prevalence of WM in England will change in the short-term.

Ibrutinib is indicated for the treatment of WM patients who have received one prior line of therapy, or who have not received prior therapy but are CIT ineligible. The number of patients eligible for ibrutinib was therefore modelled for the entire label population present in

England and Wales. The population of patients estimated to be eligible to treatment with ibrutinib for WM is reported in Table 67.

Table 66: Population Inputs

Description of input	Input value	Source
England population in 2014	54,300,000	ONS[105]
Wales population in 2014	3,100,000	ONS[105]
Constant population growth rate England	0.79%	ONS[105]
Constant population growth rate Wales	0.45%	ONS[105]
Incidence of WM	0.0006%	Phekoo et al 2008[9]; BMJ:Overview of WM[106]
WM patients who require treatment (symptomatic)	75.00%	Ansell et al. 2010[8]
WM patients ineligible for CIT	5.00%	EU Advisory board held March 2015[2]
WM patients who received 1 prior line of therapy	57.00%	Pan-European chart-based observational study[3]

WM: Waldenström's macroglobulinaemia

Table 67: Projected population

	2017	2018	2019	2020	2021
Projected population (England and Wales)	58,739,142	59,192,498	59,649,388	60,109,839	60,573,879
Number of WM cases per year (incident cases)	323	326	328	331	333
WM patients who require treatment (symptomatic)	242	244	246	248	250
WM patients ineligible for CIT	12	12	12	12	12
WM patients who received 1 prior line of therapy	138	139	140	141	142
Total number of eligible patients	150	151	153	154	155

WM: Waldenström's macroglobulinaemia, CIT: chemoimmunotherapy ineligible

6.3. *Market shares*

Market shares were estimated for the world without and with ibrutinib based on clinician opinion. In order to account for the full eligible ibrutinib population in WM, the 'world without ibrutinib' comparator distribution is an average of the 2nd, 3rd and 4th line distributions from

the CEA, which was originally informed by clinician opinion (see Section 5.2). If ibrutinib is not funded, BR is expected to be used in most patients.

Market shares in the 'world without ibrutinib' were estimated for the year 1 of the BIA (2017) and assumed to remain constant in the following years, as no meaningful changes in the market are expected, except for the introduction of ibrutinib.

Ibrutinib's projected uptake (Janssen's forecast) per year was applied to determine the final number of patients expected to be treated with ibrutinib each year ('world with ibrutinib'). It was assumed that ibrutinib would gain market share from existing therapies equally in proportion to their current use as time progressed. Based upon Janssen's forecast ibrutinib is expected to gain a high proportion of the market (40%) after NICE recommendation in 2017. This share is expected to increase constantly and reach 60% in year 2020.

The market shares in the world without and with ibrutinib and the expected number of patients expected to be treated with ibrutinib based on market penetration are reported in Table 68.

Table 68: Predicted market shares

	2017	2018	2019	2020	2021
World without ibrutinib					
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FCR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DRC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine +R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
World with ibrutinib					
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FCR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DRC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine +R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients expected to receive ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

FCR: fludarabine + cyclophosphamide + rituximab, DRC: dexamethasone + rituximab + cyclophosphamide, BR: bendamustine + rituximab, Cladribine + R: cladribine + rituximab

6.4. *Cost inputs included in the BIA*

The drug acquisition and administration costs for ibrutinib and comparators in the BIA (Table 71) were taken from the CEA (see Section 5.5). For the purpose of simplicity, all patients in

the BIA were assumed to incur the per annum cost of a 2L patient in the CEA throughout the model.

Table 69: Annual drug acquisition and administration costs used in the BIA

	Drug acquisition costs per patient per annum	Administration costs per patient per annum
Ibrutinib (list price)	£55,887	£0
FCR	£16,464	£4,304
DRC	£10,068	£1,435
BR	£15,900	£1,435
Cladribine +R	£44,911	£5,978
Other treatments	£7,285	£6,058

FCR: fludarabine + cyclophosphamide + rituximab, DRC: dexamethasone + rituximab + cyclophosphamide, BR: bendamustine + rituximab, Cladribine + R: cladribine + rituximab

6.5. *Results of the BIA*

Base case analysis (at list price)

Table 70 presents the base case budget impact of introducing ibrutinib at list price. The net total budget impact ranged from £1,987,046 in 2017 increasing to £3,073,668 in 2021.

Table 70: Budget impact of introducing ibrutinib to NHS (at list price)

	World without ibrutinib	World with ibrutinib	Budget impact
2017	£3,428,036	£5,415,082	£1,987,046
2018	£3,454,494	£5,707,174	£2,252,680
2019	£3,481,158	£6,003,456	£2,522,298
2020	£3,508,030	£6,303,976	£2,795,945
2021	£3,535,112	£6,608,780	£3,073,668
Total	**£17,406,831**	**£30,038,469**	**£12,631,638**

Table 71: Total (drug acquisition + administration) costs in the world with ibrutinib (at list price)

	2017	2018	2019	2020	2021
Ibrutinib	£3,358,261	£3,807,203	£4,262,877	£4,725,362	£5,194,736
FCR	£176,251	£162,810	£149,152	£135,273	£121,171

DRC	£205,334	£189,676	£173,763	£157,594	£141,165
BR	£715,304	£660,756	£605,324	£548,997	£491,764
Cladribine +R	£893,553	£825,413	£756,167	£685,804	£614,309
Other treatments	£66,379	£61,318	£56,173	£50,946	£45,635
Total	£5,415,082	£5,707,174	£6,003,456	£6,303,976	£6,608,780

FCR: fludarabine + cyclophosphamide + rituximab, DRC: dexamethasone + rituximab + cyclophosphamide, BR: bendamustine + rituximab, Cladribine + R: cladribine + rituximab

6.6. *Discussion*

Given the unprecedented benefits in terms of, ORR, DOR, PFS, and OS, demonstrated in the clinical trial programme, the lack of funded therapeutic options for WM in England, a rapid market penetration for ibrutinib is expected.

The net budget impact of introducing ibrutinib as a treatment option of WM in NHSE is expected to range between £1,987,046 in 2017, to £3,073,668 in 2021, using the list price of ibrutinib. As an oral drug, ibrutinib's acquisition costs are partially offset by savings in administration costs. It is worth noting that only drug acquisition and administration costs were included in this BIA, where ibrutinib is expected to reduce costs in terms of monitoring required, treatment of AEs, resources associated with NHS staff and carers' time and productivity loss from a societal perspective.

7. Managed Entry Agreement

Ibrutinib is a first in class Bruton's tyrosine kinase (BTK) inhibitor in a disease area with extremely poor prognosis and significant unmet need. It represents a clear step-change in the treatment of WM which has orphan designation by the EMA. There are currently no licensed (besides ibrutinib) or recommended treatments for WM in the UK. Current treatment options include immunotherapy and combinations of immunotherapy with chemotherapy with no proven evidence of their efficacy and safety in WM. Data are scarce and the selection of a trial comparator challenging.

As described in the preceding sections, the ibrutinib efficacy data in WM and the long-term safety data across all licenced indications show a considerable positive impact of ibrutinib on patients with WM. Janssen recognise that while the data are promising, the phase 2 non-comparative nature of our pivotal trial (Study 1118E) may not meet the evidence base standards required for a recommendation from the Committee, and that there is a need for further data collection to substantiate the clinical data and to address a number of uncertainties.

Managed Entry Agreements (MEA) are schemes designed to address potential cost issues and unanswered research questions which can reduce uncertainty. MEAs have been used by decision makers to recommend technologies under two broad conditions: (1) that the price of the technology be reduced and/or (2) that further research be conducted. Both conditions have the aim of reducing risk and decision uncertainty. We are proposing a MEA for this indication and in combination with further research we believe we will substantially reduce the decision risk associated with recommending ibrutinib for WM.

It is in this light that Janssen would request a recommendation for inclusion in the CDF based on a MEA. We believe further real world data collection would address any uncertainties highlighted by the Committee following a review of this submission. It would also inform a future review of the guidance which would ultimately lead to a positive recommendation through baseline commissioning for ibrutinib in WM.

7.1. *Overview and purpose*

We envisage the Committee will expect the following questions to be addressed in their consideration of the appropriateness of a MEA [89]:

- Which intervention do we expect to be most cost-effective given proposed prices and current evidence? This is addressed in the cost effectiveness section and by the proposed MEA.
- How uncertain are we? Certainty will come from a combination of price, efficacy and safety. Price is addressed in the cost-effectiveness analyses and with the MEA. Efficacy and safety, whilst partially satisfied, would be more conclusively addressed by way of further research.
- How useful would it be to eliminate uncertainty? The cost-effectiveness analysis and MEA will address uncertainty around cost; the further research would enable us to address uncertainty around efficacy, safety and relative efficacy.

- Given current evidence and proposed prices, what is the strategy-specific risk to the NHS? If cost is addressed appropriately through the cost-effective analyses (including appropriate sensitivity analyses) and MEA, the strategy-specific risk to the NSH is minimal as there are no other evidenced-based options for effective treatment(s) for WM patients in the UK. The continued research arrangement would ensure that uncertainty around efficacy and safety (which the Committee may not feel is satisfied by Study 1118E) is addressed in a reasonable timeframe, while enabling access to patients as a part of the treatment options.
- How much would the NHS expect to gain by eliminating the risks associated with both uncertainty and the strategy? Janssen believe this is clear - patients would have access to a highly effective and safe treatment (of which there is currently none).

We would like to work with NICE to ensure that the additional data captured will be informative to the decision making of the Committee. Our proposal to be considered for the CDF is supported by leading UK WM experts who recognise the clinical value that ibrutinib offers and would like the opportunity to explore it as a treatment for patients in both the relapsed / refractory setting as well as in the treatment-naive setting where chemoimmunotherapy may not be appropriate. Generation of these real world data would not only be beneficial for the future re-appraisal of ibrutinib but additionally, the development and population of a WM which would allow ongoing data collection in a disease area where very little information is available and will also be very informative to the wider WM community i.e. beyond the UK.

In consideration of the opportunity costs and net benefit to all NHS patients for this recommendation over a period of time (to be agreed), cost-effectiveness analyses have been provided which include the current simply PAS agreed with the DH. Please note that discussions with NHS England in relation to the final price of ibrutinib continue; we are confident an agreement will be reached and allowing access to ibrutinib while real-world data are being collected would be an efficient use of NHS resources.

We propose to utilise a specialised UK registry for which WM is specifically researched and audited (covered in more detail in section 7.3 below). WM is rare disease which is predominantly treated by highly specialised clinicians. Dr Shirley D'Sa, consultant haematologist, with the support of University College London, has set up a registry for WM as part of the wider biobank study currently running. The WM registry is an 'add-on' to the biobank study which will facilitate and expansion of the endpoints captured and geography covered. The registry collects, inter alia, demographic data, characteristics of diagnosis and testing, treatments, symptoms of the disease and treatments given, covering a number of lines of treatment from newly diagnosed to up to 8 lines of therapy, survival status, comorbidities, and Cumulative Illness Rating Scale-Geriatric (CIRS-G).

We have been working with Dr D'Sa to assess the ease with which an amendment to the registry can enable prospective real-world data collection of efficacy, safety, quality of life (QoL), and medical resource use data (which could include adherence data) on all patients prescribed any treatment, including ibrutinib, as per UK clinical practice. This would enable an assessment of the relative effectiveness of ibrutinib in comparison to other therapeutic approaches which are currently used in clinical practice. Dr D'Sa has provided full support for this proposal of using the registry for an MEA.

We do not believe the Systemic Anti-Cancer Therapies (SACT) dataset would be the relevant means by which to collect this data. Currently, the SACT is understood to be deficient in collecting data on oral cancer treatments. In addition, WM is a rare condition treated by very few physicians and requires a specialism that most clinicians do not have. In addition, the WM Registry is already set up and patients enrolled and consented (as a part of the broader biobank study), meaning any amendments and research questions, can be quickly and efficient addressed.

In the remainder of this section we provide detail around the manner in which some of the uncertainty that may be raised by the Committee will be addressed using an MEA. We also include information on all additional sources of data which may become available over the course of the data collection period.

We believe this data collection will support a positive recommendation for ibrutinib, the first and only licensed product for WM. WM patients face a substantial clinical unmet need and challenges accessing this innovative medicine. A negative recommendation based on uncertainties that we believe can be addressed would leave patients with no alternative but to receive treatment with off-label ineffective therapies rather than licensed, effective, and well tolerated ibrutinib.

7.2. *Remit of data collection*

There are five key areas where further research would allow for confirmation of clinical and safety data as well as greater certainty in the analyses presented in this appraisal document. These areas are discussed in turn below with details on what would be gained by re-appraising ibrutinib in light of the research findings.

Efficacy and safety data

To date, the phase 2 single-arm 1118E trial is the only data available on the efficacy and safety of monotherapy ibrutinib in WM. This trial is focused on relapsed and refractory WM patients and with a sample size of 63 patients, demonstrates the promising positive impact of ibrutinib on PFS (69.1% alive and progression free at 24 months) and OS (95.2% alive at 24 months).

Median has not been met for either PFS or OS in Study 1118E which has a median follow-up of 24 months. We hypothesise that the longer term collection of PFS and OS outcomes data in the WM Registry as a part of the MEA, in newly initiated ibrutinib patients, will corroborate and expand the findings of Study 1118E in a real-world, UK-specific setting. We propose a minimum of two years of data collection, aligning with the median follow-up available for Study 1118E (24 months). This will allow for Study 1118E data to be corroborated, reducing the uncertainty surrounding these data and providing additional data around QoL, medical resource utilisation and safety. At the end of the two years, the data collection period can either be extended or, assuming a positive recommendation is gained at that point, it can continue and be reassessed when the technology appraisal guidance (TAG) becomes due for review, as part of the usual NICE process.

With respect to the safety data for ibrutinib in WM, Study 1118E is consistent with what is known for ibrutinib from treated patients with CLL and MCL, which includes data with long-term median follow-up of up to 30 months. Janssen stand by the high tolerability and strong safety profile of ibrutinib which has been captured not just via trial data across the WM, CLL

and MCL indications, but is also clear from anecdotal evidence from patients and clinicians alike. As patient safety is paramount, Janssen propose to also collect further safety data alongside efficacy data as this will ensure any concerns are addressed with real-world data.

Utility data

The quality of life (QoL) benefit of ibrutinib is a key area of uncertainty due to a number of factors:

- no quality of life data were collected as part of Study 1118E
- no published quality of life data for WM has been identified
- CLL utility data, as measured by the EQ-5D, is used as a proxy as a result of clinical opinion stating this is the best proxy in the face of no other data
- EQ-5D, while a gold standard in measuring quality of life, is not the most appropriate instrument to capture changes to patient functions such as fatigue, which is a major side effect of haematological malignancies, impacting heavily on QoL, and where ibrutinib has been demonstrated (with other instruments) to have a notable positive impact. In particular, the EQ-5D-5L measure contains no explicit measure of fatigue.

While available QoL data does indicate a positive impact resulting from ibrutinib, data specific to WM and an instrument more relevant for a lymphoma would capture the true impact of ibrutinib on patients' QoL. In addition to the benefit of ibrutinib on patient QoL, ibrutinib is anticipated to improve the QoL of carers looking after patients with WM. Ibrutinib as an oral treatment is unlike any other treatment option currently available for WM patients and as such, it does not require frequent hospital visits for infusion or monitoring.

This is likely to improve not only patient QoL but also carers' QoL as they will no longer be required to provide transport to hospital or help with household activities, for example. Most patients receiving chemotherapy are not fit enough to drive to hospital and may live in rural areas without local access or transport to a chemotherapy day unit, thereby requiring the use of a carer to attend chemotherapy administration sessions. Furthermore, the burden of WM on carers in terms of QoL is likely to increase as the disease progresses and patients relapse. In addition, there may well be a psychological benefit for patients and carers alike in seeing the patients experiencing improved QoL on ibrutinib and enjoying life as they would have had they not been diagnosed with WM.

Janssen would propose that data collection plans include the capture of QoL data in patients, and if possible, in carers as well. A disease-specific instrument, such as FACT-LYM, could more accurately capture the impressive benefit of ibrutinib though we recognise the NICE preference for the EQ-5D. As such, we would propose to work with NICE to ensure the most appropriate instrument(s) are used in the collection of QoL data and that appropriate mapping algorithms are available for translation and use within the economic evaluation.

Comparative efficacy

No RCT evidence is available to inform any of the comparators listed in the final scope within the published literature for WM. Extensive efforts have been made to source evidence to inform any of the comparators and the best source of evidence found was the pan-European

chart review which allowed for the pooling of patient-level data and a Cox-regression analysis as described in Section 4.11 to compare ibrutinib with Physician's Choice (PC) given no one clear standard of care is available in WM. The resulting comparison strongly suggests that ibrutinib's relative efficacy is substantial and significant (a PFS HR of [redacted] meaning patients are [redacted] less likely to progress on ibrutinib than any of the currently used treatment options).

These data provide strong initial evidence to demonstrate the relative efficacy of ibrutinib and Janssen would propose to include comparative data collection. Details of how the comparator data might be collected are presented in the following sub-section (7.3).

With respect to how the comparator data are analysed relative to ibrutinib, Janssen would work in collaboration with the Registry owners to ensure the most appropriate and rigorous statistical methodologies are applied to ensure the resulting comparative efficacy data are to a standard acceptable to NICE.

Resource use and compliance

Ibrutinib is an oral monotherapy treatment licensed specifically for WM and as such, it is unlike any other treatment option currently available for WM patients and does not require frequent hospital visits for infusion or monitoring. Janssen have made efforts to ensure we have appropriately captured the resource use within the NHS via clinical opinion. We believe real-world data collection will be an ideal opportunity to not only confirm the estimates but to understand more fully the impact on NHS resources of shifting patients away from infusion-based therapies requiring monitoring and management of adverse events to an oral monotherapy which can be taken at home with limited monitoring and a tolerable safety profile.

At the 2015 American Society Clinical Oncology (ASCO) meeting, analysis of the systemic anti-cancer therapy (SACT) in a US registry, found that, prior to FDA approval of ibrutinib, health resource utilisation (HRU) and costs were high among WM patients initiating SACT. By conducting the MEA, it is anticipated that by collecting data on all treatments, lines of therapy and data relevant to estimating the costs to the NHS of managing WM, our hypothesis of the value ibrutinib will have on HRU will be demonstrated. Furthermore, our economic analysis accounts for the dose intensity of ibrutinib, which was taken from Study 1118E as this directly impacts the efficacy outcomes. The data collection will allow for dose intensity, as well as continuation rates, to be confirmed in a real-world setting.

Treatment-naïve WM patients

The final scope of this appraisal includes both the relapsed and refractory patient population as well as the treatment-naïve population for whom chemoimmunotherapy is inappropriate. This is in line with the ibrutinib license which was granted for a population broader than Study 1118E (relapsed and refractory patients).

Janssen are in agreement with the regulatory assessment and resulting license and propose that ibrutinib should be made available for all WM patients within its licensed indication. Data collection in the treatment-naïve population would address any uncertainty on the extrapolation of results from the relapsed and refractory setting to the treatment-naïve setting. As such, we would ask that the Committee recommend ibrutinib for the broad WM

population and allow data collection to be conducted across the populations covered by the ibrutinib license. Indeed, the registry currently collects this data (i.e. data in treatment-naïve patients).

7.3. *Method of data collection*

In the event of a NICE recommendation for ibrutinib through the CDF, Janssen proposes to utilise The Rory Morrison Waldenström's Macroglobulinaemia UK Clinical Registry (the WM Registry), a longitudinal registry, over a minimum of two years to generate real-world data for ibrutinib as prescribed in UK clinical practice for the treatment of the relapsed and refractory population as well as the treatment-naïve population for whom CIT is inappropriate. The WM Registry currently represents data from the longest running WM-specific clinic in the UK based at University College London Hospital (UCLH) and aims to incorporate further data from additional WM clinics across Great Britain who share a specific commitment to the study of WM. The WM Registry incorporates 10 years' worth of retrospective data providing a strong historical control data set and aims to incorporate prospective data moving forward. To date, data from more than 270 WM patients have been incorporated into the registry. As highlighted above, there is no valid reason to use the SACT database for the collection of the data for the MEA when this registry is more sensitive and specific to WM and fit for purpose. Appendix 10 provides an overview of The Rory Morrison Waldenström's Macroglobulinaemia UK Clinical Registry data requirements.

The cohort followed comprises all WM patients including those you are asymptomatic and symptomatic. The registry study is led by Doctor Shirley D'Sa, University College London Hospitals NHS Foundation Trust (London) and the Mount Vernon Cancer Centre (Northwood). University College London is the sponsor and has ownership of the data.

The registry has a number of formal quality control and assurance steps in place to ensure the integrity of the data such as centre staff training and data quality checks. It is currently under the umbrella of the wider biobank study which has NHS Ethics approval and on agreeing to the MEA for ibrutinib, an amended form of consent and protocol can be submitted to address the MEA.

Funding for the registry is from UCL and from the pharmaceutical industry. Janssen will ensure sufficient funding is available to the WM Registry to collect the required quality assured data and analysis to successfully deliver the proposal in time for a NICE review of the guidance. Verbal agreement has been obtained from the WM Registry group that they support the use of the WM Registry for this purpose.

A top-line summary of data available retrospectively and the additional data which will be collected prospectively are listed here (this list is not exhaustive) while Appendix 10 provides a visual of the data collection interface as well as a proposed study protocol.

Data available retrospectively:

- Baseline characteristics: age, gender, risk group, Hb levels, IgM level, symptomatic vs asymptomatic, etc.
- Treatment: previous treatment(s), current treatment, median lines of treatment, start and end date of treatment, number of cycles if relevant, reasons for initiation, reason for discontinuation
- Efficacy data: Clinical response, PFS, OS

- Diagnostics: chemistry, haematology, bone morrow, scans, etc.

Data to be collected prospectively:

- Safety data: incidence of adverse events and serious adverse events, hospitalisations and their causes, malignancy and death, other serious adverse events including atrial fibrillation and bleeds
- Ibrutinib treatment details: date started / stopped / restarted, reason for discontinuation (as appropriate)
- Quality of Life and HRQoL data: CIRS-G, EORTC, Peripheral neuropathy self-assessment, Rasch overall disability score, WM complications, FACT-LYM, EQ-5D (as agreed)
- Lifestyle questionnaire (for example, drinking, smoking, employment status); Patient diary (recording hospital admissions, visits to outpatients and medications); Concomitant medications; Comorbidities; Laboratory parameters.

The Rory Morrison Waldenström's Macroglobulinaemia UK Clinical Registry provides the most sensitive and specific method by which real world data can be collected to satisfy a MEA.

7.4. *Additional sources of data*

Janssen would propose to rely on the data collected through the WM registry.

We would aim to also include any follow-up data that becomes available from the 118e trial during the course of the data collection period.

Furthermore, the iNNOVATE trial described in section 4.14 will report during the data collection period - the study was initiated in July 2014, and the estimated completion date is January 2019 with interim results expected in April 2017 at the earliest. We aim to include any relevant data from Arm C, the ibrutinib monotherapy arm, to further substantiate the evidence base. It should be noted that we have a post-marketing commitment to submit the iNNOVATE trial data to the regulatory body.

7.5. *Plausible cost-effectiveness and commercial access arrangements*

Janssen are currently under discussion with NHSE to agree a commercial access arrangement for ibrutinib, and will update the final price of the drug in this submission once the price has been agreed. As the CLL and MCL indications for ibrutinib are currently listed on the CDF, ibrutinib represents a CDF-transition drug and thus there is the added complexity around transitioning the drug off of the current CDF and into baseline commissioning.

7.6. *Concluding remarks*

Janssen believe that the collection of real-world data will help to confirm the key assumptions used in the health economic model and address the concerns which may be raised in relation to the clinical and safety evidence during the Committee's assessment of this appraisal. Importantly, data collection will capture QoL data specific to WM and if greater benefits with ibrutinib are observed in clinical practice (e.g. in reducing fatigue) compared with the proxy CLL utility data currently being used, this will only improve the estimate of

cost-effectiveness especially as we are confident the efficacy and safety data will be confirmed.

We welcome the Committee to seek further advice on the above proposal from research commissioners, expert consultees, and the wider research and clinical communities who are aware of the data limitations and the unmet need in WM to confirm that our proposal is feasible, relevant, and informative (both in relation to ibrutinib and to the wider WM community). Most importantly, we ask the Committee to enable access to ibrutinib for WM patients.

We strongly believe that the additional research is possible in the circumstance that ibrutinib is recommended for research via the CDF funding route. Furthermore, we would prefer to work in collaboration with NICE to ensure that the data collection and subsequent appraisal of ibrutinib ensures that overall, the potential value to the NHS of the recommendation for research represents good value in the context of limited research resources.

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9. Appendices

1	Search strategy for relevant clinical studies
2	Findings from clinical search
3	Ibrutinib safety data from CLL and MCL clinical trials
4	[redacted]
5	Search strategy for cost-effectiveness studies
6	Search strategy for measurement and valuation of health effects
7	[redacted]
8	List of variables included in probabilistic sensitivity analyses
9	[redacted]
10	[redacted]

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Single Technology Appraisal (STA)

Ibrutinib for treating Waldenström's macroglobulinaemia [ID884]

Dear company,

The Evidence Review Group, ScHARR-TAG, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 17th June 2016 by Janssen. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on **26th July 2016**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact [redacted]. Any procedural questions should be addressed to [redacted] Project Manager in the first instance.

Yours sincerely

Zoe Charles
Technology Advisor – Technology Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: General matters of clarification

A1. Executive summary, page 18 and Section 7.5, page 127. Please provide any further information regarding the proposed managed entry agreement price, if available.

A2. Section 7.2, pages 123-126. Please clarify how the use of the proposed WM UK registry will reduce uncertainty regarding the cost-effectiveness of ibrutinib in WM. Please give an indication of how the additional data collection will inform any future analysis of the model.

A3. Section 5.11, page 114. When will the final datacut of Study 1118E be undertaken?

A4. Section 5.4, page 92. Why are the utility values used in the model highlighted as being commercial in confidence?

Section B: Clarification on effectiveness data

Literature searching

B1. Section 4.1, page 36. The search for relevant systematic reviews was limited to 2011-2015, but this limitation was also described as being "the last 3 years." The search string reported in Appendix 1, Table 3, limits the search to 2012-15. Please clarify these inconsistencies.

Clarification on effectiveness data

B2. **Priority:** Section 1.3, pages 15-16 and Figure 1, and Section 4.11, pages 51-52 and Figure 12. Please clarify the relevance of this figure to the decision problem, which does not include ibrutinib for treatment naïve (TN) patients generally, only for those for whom chemo-immunotherapy is not appropriate (and who would only be eligible for rituximab and chlorambucil).

B3. **Priority:** Section 3.3, page 31. The text states "The goals of treatment, once started, are to reduce the tumour mass, provide symptomatic relief and reduce the risk of organ damage." Please clarify how tumour mass, symptomatic relief and risk of organ damage are measured in clinical practice and in Study 1118E.

B4. Section 3.3. Page 32. Please provide a list of comorbidities (including those associated with WM) which may (i) preclude treatment with ibrutinib, or (ii) impact upon treatment efficacy.

Identification and selection of relevant studies

B5. Appendix 1, Table 2. With respect to the exclusion criteria, please explain the exclusion of "Non-randomised, comparative clinical efficacy and safety studies reporting on only one treatment of interest", but the inclusion of single-arm, non-comparative studies. Please comment if this approach could exclude studies including a single treatment of interest and/or potentially hinder the opportunity to undertake an indirect comparison?

B6. **Priority:** Section 4.1, page 39, Figure 6 and Appendix 2, page 12. Please provide a table of the 130 studies excluded after full-paper screening, detailing, for each study, their populations, interventions, and the specific reasons for exclusion.

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B7. Appendix 2, page 13. The submission states regarding study selection that studies which were "only available in abstract format without accompanying full-text publications… were discarded from the review". However, the European Chart Review (Section 4.11) and iNNOVATE (Section 4.14) had both been published only as abstracts, but were included in the submission (although iNNOVATE is explicitly excluded from the review at this point). Please clarify and explain this inconsistency.

B8. Section 4.1, page 37. How many non-English studies were rejected?

B9. Section 4.1, page 38. Given the limited evidence available for ibrutinib in this indication, please clarify why three ibrutinib abstracts were rejected.

B10. Section 4.1, page 39, Figure 6. Please include boxes detailing the exclusion of 27 publications on the basis of having interventions and comparators outside of the NICE scope and the exclusion of studies published only in abstract form.

B11. Section 4.1, page 39, Figure 6. The final box for the treatment-naïve WM population has the figure of "3 studies" (consistent with Appendix 2, page 16, Table 16), but lists a total of 6 studies, including 2 cladribine studies and 1 DRC study, none of which are listed in Appendix 2, page 16, Table 16. Please clarify this inconsistency.

B12. **Priority:** Appendix 2, page 15, Table 15. Please provide in the table full details (references, study characteristics, populations, interventions, outcomes measured) for each of the studies excluded for having interventions and comparators outside of the final NICE scope.

Non-randomised and non-controlled evidence

B13. **Priority:** Section 4.10, page 41 (methods) and page 44 (results). Please conduct a quality assessment of the included study using an appropriate tool for this study design and report both the processes undertaken and the findings, as required by systematic review guidelines such as PRISMA.

B14. Executive summary, page 15, and Section 4.10, page 42 and Table 12. IgM is a surrogate outcome. Please provide evidence of the acceptability of overall response rate (ORR) as a surrogate outcome for WM.

B15. **Priority:** Section 4.10, page 42 and Table 12. Study 1118E has the primary outcome of ORR. The European Chart Review and the iNNOVATE study included progression-free survival (PFS) as the primary outcome. Why were these different between the studies?

B16. **Priority:** Section 4.10, page 42 and Table 12, Section 4.11, page 53 and Section 4.14, page 68, Table 28. Please provide full definitions of PFS for the following studies:

- Study 1118E
- The European Chart Review
- The iNNOVATE study

B17. Section 4.10 page 42 and Table 12. CR and PR have the same definition. Please correct.

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B18. Section 4.10, page 43. Please provide details of the statistical basis for the sample size, including whether the confidence interval used at the design stage was exact or asymptotic, and whether any account was taken of the population being effectively finite.

B19. Section 4.10, pages 47-48. Please comment on the less favourable outcomes observed for the $MYD88^{WT}CXCR4^{WT}$ mutations. Please also provide *p*-values of the interaction for each subgroup in Figures 7 and 8, and comment on any subgroups across which a potentially differential effect is identified.

B20. Section 4.11, page 53. The number of patients who receive second-line treatment is stated as 397 while it is 387 in Figure 13. Please clarify.

Section 4.11: Indirect comparison

B21. Appendix 1, Table 2. With respect to exclusion criteria for retrospective studies. Please explain how the European Chart Review was included here, given that this type of study design was explicitly excluded from the clinical review.

B22. Section 4.11, page 52. The submission states "Data in this section are predominantly drawn from the abstract presented at the 2015 American Society of Hematology (ASH) annual conference". However, Appendix 2 (page 13) also states that studies which were "only available in abstract format without accompanying full-text publications … were discarded from the review." Please explain and justify the inclusion of this retrospective study, which has been published only as an abstract.

B23. Section 4.11, pages 51-52. Please clarify why data from the European Chart Review are presented for comparison from 2000-2010, while some R/R studies are excluded from the indirect comparison for being "outdated (published in the 1990s)", even though the company submission also presents evidence that only minor differences in OS were found between 1980-1999 and 2000-2010, to demonstrate the absence of genuine therapeutic advances (Section 3.1, page 29).

B24. Section 4.11. Please provide more information regarding the European Chart Review. In particular, please comment on the following:

- Who funded this study?
- How were patients identified and selected for inclusion?
- What measures were taken to minimise bias in patient selection?
- Comment on how pre-specified balance across countries was achieved without introducing bias.
- Provide a breakdown of treatments received by line of therapy (for those patients included in the Cox model and for the overall cohort).

B25. Section 4.11, Table 21, page 57. There are differences in age, gender, IPSSWM risk and serum antibody levels between the matched chart review cohort and the Study 1118E population. Please comment on the likely direction of bias caused by this imbalance. Also, for IPSSWM high-risk in columns 3 (Study 1118E), should the figures be: "35 (22)"? In addition, please present the data in Table 21 for the Study 1118E patients included in the analysis (n=47) rather than the whole Study 1118E population (n=63).

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B26. Section 4.11, pages 59-61, Tables 22, 23 and 24. Please clarify the model used to estimate the HR provided in these tables. Are these adjusted estimates from the full multivariable Cox model, or univariate HR estimated on inclusion of each covariate individually in the model? It is stated that the HR for treatment "is a univariate HR based on the Cox-model, only including treatment and all other covariates are not significant". If these have not already been provided then please provide the results from the full adjusted multivariable Cox regression. Please also provide the observed Kaplan-Meier curve for the 2L PFS data from the European Chart Review data used in the Cox model (n=175).

B27. Section 4.11, page 58. Why was the multivariable Cox model assumed? Which other methods of comparison were tested? Please also provide justification regarding the assumption of proportional hazards underlying the use of the Cox model in this instance.

B28. Section 5.2, page 79. Given that patient-level data were available from both the European Chart Review and Study 1118E, please clarify why there was "no way to carry out" a matching-adjusted indirect comparison (MAIC). Please refer to the section titled "Additional analyses requested" below.

B29. Section 4.11, page 56, Table 20. Please comment on the likely impact of differences in the definitions of progression in Study 1118E and the European Chart Review?

B30. Section 4.11, pages 56-57. The method used to define the "matched chart review cohort" does not define a unique sample of individuals. Please perform sensitivity analyses using a repeated (different) random sample.

Safety

B31. **Priority:** Section 4.12, pages 61 and 65-66, and Section 2.5, page 25. Please describe the process by which the ibrutinib studies in CLL and MCL populations were identified and selected (search strategy and processes, inclusion and exclusion criteria applied), and provide full details of any ibrutinib studies that were excluded.

B32. **Priority:** Section 4.12, pages 61-63. Please provide the following tables of adverse events for Study 1118E:

- Overall frequencies (numbers of patients) of any AEs (only numbers for AEs of $\geq$ Grade 2 are currently provided).
- Serious AEs (numbers of patients and type)
- Severe AEs (numbers of patients and type)

B33. **Priority:** Appendix 3, Table 19. In order to facilitate comparison across trials, please provide equivalent tables for adverse events (including discontinuations due to adverse events) of Grade 2 or higher for RENOVATE; and separate tables for any AEs, and Grade 2 or higher AEs, and severe and serious AES, for the following trials: RENOVATE 2 and PCYC-1102/1103 (in CLL patients) and PCYC-1104 (in MCL patients).

B34. Section 4.12, page 61. The text which states "of the 19% of patients who stopped treatment, only 6% discontinued as a result of toxicity"; this seems to be in contradiction with Table 25. Also, page 66 states "Ibrutinib was well tolerated with a discontinuation rate of 9.5% following a median treatment duration of 19.1 months." Please clarify this apparent

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inconsistency. Please provide the number of patients who discontinued, the number of these who discontinued due to toxicity and what each toxicity consisted of.

B35. Section 4.12. Please provide AE data from the European Chart Review.

Section C: Clarification on cost-effectiveness data

Cost-effectiveness evidence

C1. Section 5.1, page 73. The text states pilot extraction form tested on several included studies. How is this possible given that only 2 studies were identified?

C2. Section 5.2, page 74. Please comment on the likely cost-effectiveness of ibrutinib in patients for whom chemo-immunotherapy is unsuitable.

C3. **Priority:** Section 5.2, page 79, Table 33. Please include dosing regimens and frequencies for other regimens used in the model which are mentioned in Table 32 but not in Table 33. In addition, other options e.g. SCT are mentioned as second-line options in Appendix 4 – why were these not included in the model? Please clarify how estimates of the proportionate use of each regimen were derived.

C4. Section 5.2, page 76, and Section 5.5, page 96. The text states on page 76 that wastage was assumed but page 96 states that wastage was considered in sensitivity analyses. Please clarify.

C5. Section 5.2, page 79, Table 32. Please comment on the validity of using the European Chart Review to derive estimates of relative treatment effect and separate expert opinion to derive the use of specific chemotherapy/rituximab regimens for costing.

C6. Section 5.3, page 81, Table 34. Please comment on the appropriateness of assuming a model structure beginning with second-line therapy given that 62% of patients in Study 118E had already received more than one prior therapy.

C7. Section 5.3, page 84. Please explain why only Weibull, log-normal, log logistic and exponential curves were fitted to the data from Study 1118E. Why were other parametric functions not considered?

C8. **Priority:** Section 5.3, page 85. Given the use of general population mortality hazards for patients on ibrutinib, is the model suggesting that all patients are temporarily cured of WM whilst they remain on treatment? Please comment on the strength of evidence available to support this assumption and the uncertainty surrounding it.

C9. **Priority:** Section 5.3, page 86, Figure 21. The ERG has concerns that the survival curve used to inform the 2L death rate for physician's choice reflects overall survival (pre- and post-progression deaths) rather than pre-progression mortality, thereby producing an inflated death rate. Please confirm that Figure 21 does not include censoring for progression. Please also refer to the section titled "Additional analyses requested" below.

C10. **Priority:** Section 5.3, page 81, Table 34. The ERG is unclear regarding which data were used to inform the time-to-event parameters in the model (and why). Please clarify and

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justify the data used to inform PFS and OS at 2L, 3L 4L and BSC in the European Chart Review and Study 1118E. To enhance transparency, please complete the following table, including details of evidence source, patient population used to derive parameters (including number of previous therapies received) and number of patients included in each analysis.

Line of therapy	Ibrutinib		Physician's choice	
	PFS	OS	PFS	OS
2L	RESPONSE	RESPONSE	RESPONSE	RESPONSE
3L	RESPONSE	RESPONSE	RESPONSE	RESPONSE
4L				
BSC	n/a		n/a	

C11. **Priority:** Section 5.3, page 85, Figure 20. Please provide an amended version of the Kaplan-Meier chart showing numbers of patients at risk over time.

C12. Section 5.3, page 87. The text states "A parametric fitting was conducted for OS of this cohort; an exponential function (see Table 38) was found to be the best fit." Please explain how goodness-of-fit was judged in this instance. Please also provide the Kaplan-Meier curves for PFS and OS for the time-to-event data used to inform the 3L and 4L PFS and OS estimates together with the accompanying parametric curve fits.

C13. **Priority:** Section 5.3, page 88, Table 38. With respect to the probabilities of progression and death for 3L and 4L, please clarify whether progression events have been censored for death and whether death events have been censored for progression (thereby dealing with competing risks).

C14. Section 5.4, page 91, Table 42. Are these data QALY losses per cycle? Also, the disutility of adverse events for physician's choice presented in Table 42 does not match the disutility used in the model (Worksheet "Utility" cell J20). Please clarify. Also, please explain why disutilities/QALY losses associated with AEs were not included for subsequent lines of therapy?

C15. **Priority:** Section 5.4, page 92. The previous relapsed/refractory mantle cell lymphoma model submitted to NICE assumed better HRQoL for patients receiving ibrutinib due to the avoidance of chemotherapy-related toxicity and fatigue. Please comment on the absence of this health effect from the WM model.

C16: **Priority:** Section 5.5, page 93, Table 44. Please provide further detail regarding how the resource use frequencies included in the table were elicited from experts.

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C17: **Priority:** Section 5.6, page 101, Table 52. The text states "The same post-progression efficacy was assumed for both ibrutinib and PC." The model however suggests that considerably more life years are gained after discontinuing ibrutinib compared with 2L physician's choice (4.18 life years versus 2.83 life years, undiscounted). Please comment on the validity of this model result.

C18: Section 7, page 121. The text refers to the WM patient population having "an extremely poor prognosis", yet the model suggests an undiscounted survival of 4.36 years for the comparator group. Please clarify.

C19: **Priority:** Section 7.2, page 123. Given the uncertainty surrounding long-term benefits of ibrutinib in terms of PFS and OS, please justify why the data collection in the registry will be only a minimum of 2 years.

Model

C20: Worksheet "Clinical Data" The parameters for the alternative distributions (e.g. log logistic for Ibrutinib PFS, cells P5:P6 and log normal for mortality risk, cells H5:H6) are not included as uncertain parameters in the probabilistic sensitivity analysis. Please comment.

C21: Worksheet "Markov RR (Ibr)", column AJ. Please clarify why a significant number of the logical consistency checks return a value of "FALSE"

C22: Worksheet "Clinical Inputs". Why are only log normal and Weibull PFS functions considered in the model?

C23: Worksheet "Parameter", cells D38:D39; D41:D42; D44. These are referred to as hazards (rates) but appear to be applied as probabilities. Please clarify.

C24: Worksheet "Clinical Data", column K. The following formula is applied to generate the HR-adjusted hazard rate: hazard/HR. Please confirm that this calculation is correct [redacted]

Section D: Additional analyses requested

Please conduct re-analyses of the health economic model which include:

D1. **Priority:** Re-fitting the PFS and mortality data for second-line physician's choice taking into account competing risks (i.e. censor post-progression death events in the OS curve). Please apply these curves in the model and present the new curve fits in the clarification response.

D2: **Priority:** Providing the hazard ratio from the full multivariable Cox model and applying this to the model taking account of Point D1 described above.

D3: **Priority:** Undertaking a matching adjusted treatment comparison using Study 1118E and the European Chart Review for second-line treatment and applying this in the health economic model as a scenario analysis, taking account of Point D1 described above.

Single Technology Appraisal (STA)
Ibrutinib for treating Waldenström's macroglobulinaemia [ID884]

The following notation is used: information submitted under '[redacted]' is highlighted in turquoise, and all information submitted under '[redacted]' in yellow.

[redacted]

[redacted] There is an accompanying Excel file to this document that contains requested additional data/analyses. Each worksheet is labelled with the question number the data pertain to. Please consider this Excel file as [redacted] (please refer to "cover" tab in this Excel file for further detail on which data are [redacted] vs [redacted]).

Section A: General matters of clarification

A1. Executive summary, page 18 and Section 7.5, page 127. Please provide any further information regarding the proposed managed entry agreement price, if available.

As explained in the original submission (p22), discussions remain ongoing between NHS England and Janssen as to the final managed entry agreement price of ibrutinib, given ibrutinib is a CDF-transition drug across various indications. No further information is available at this time.

A2. Section 7.2, pages 123-126. Please clarify how the use of the proposed WM UK registry will reduce uncertainty regarding the cost-effectiveness of ibrutinib in WM. Please give an indication of how the additional data collection will inform any future analysis of the model.

The estimation of the cost-effectiveness of ibrutinib is currently reliant on clinical and safety data from 63 WM patients on ibrutinib in the relapsed and refractory (R/R) setting (data from 47 patients were used in the model - see section on "creation of a "matched" chart review cohort" on p56-57 of the original submission for details as to why) and on health-related quality of life (HRQoL) data taken from chronic lymphocytic leukaemia (CLL) patients (a proxy recommended by clinical experts due to lack of HRQoL data in WM).

The WM UK registry will reduce uncertainty regarding the cost-effectiveness of ibrutinib in WM by facilitating additional data collection with the aim to inform future analysis. This data collection will provide further data *certainty* in the following ways:

- clinical data (efficacy and safety) will be collected from a larger sample size of patients and therefore further certainty can be given to the positive trends observed thus far from the Study 1118E;
- HRQoL data will be collected and therefore proxy CLL utility data will be replaced with data related directly to WM;
- all data (clinical and HRQoL) will be collected within the treatment-naïve (TN) setting and the R/R setting, in line with the ibrutinib licence for WM and therefore assumptions of ibrutinib's effective in all lines of treatment will be confirmed.

It is important to note that due to the nature of the WM disease, it is not likely that data *maturity* will be reached within the relatively short timeframe of a MEA, assuming the timeframe is two years (i.e., median PFS and median OS may not be met). In summary, additional data collection will provide further data certainty to demonstrate that ibrutinib is a well-tolerated and efficacious treatment.

A3. Section 5.11, page 114. When will the final datacut of Study 1118E be undertaken?

Study 1118E is anticipated to be completed in October 2018 at which point a final report will be prepared. As this is an Investigator Initiated Study (IIS) led by Professor Treon, the timelines of the final report are subject to change.

A4. Section 5.4, page 92. Why are the utility values used in the model highlighted as being commercial in confidence?

Appendix H of the original submission states that "Data associated with utility values from RESONATE [the phase 3 ibrutinib trial in CLL] are unpublished and from the CSR. There are currently no plans to publish these data; Janssen request that they remain confidential." The marking as commercial in confidence for the utility values is in line with the approach followed for the ibrutinib submission for the treatment of CLL [ID749], in which the utility values derived from RESONATE are also marked as CIC.

After further discussions within Janssen, it has been decided that these utility values are no longer deemed confidential data and thus highlighting can be removed.

Section B: Clarification on effectiveness data

Literature searching

B1. Section 4.1, page 36. The search for relevant systematic reviews was limited to 2011-2015, but this limitation was also described as being "the last 3 years." The search string reported in Appendix 1, Table 3, limits the search to 2012-15. Please clarify these inconsistencies.

The SLR was conducted in two parts: an initial SLR and then an update to ensure the most recent data were captured for this submission. The initial SLR restricted the search of published systematic literature reviews to the last 3 years from the search date (February 2015), representing studies published between 2012 and Feb 2015 (i.e., 2012, 2013 and 2014 with the two months in 2015); the update covered the period from February 2015 to May 2016. Therefore, the full search for relevant SLRs covered the period from January 2012 – May 2016; reference to 2011 can be removed as it is a typographical error.

Clarification on effectiveness data

B2. **Priority:** Section 1.3, pages 15-16 and Figure 1, and Section 4.11, pages 51-52 and Figure 12. Please clarify the relevance of this figure to the decision problem, which does not include ibrutinib for treatment naïve (TN) patients generally, only for those for whom chemo-immunotherapy is not appropriate (and who would only be eligible for rituximab and chlorambucil).

The relevance of this figure, with the caveat that it is a naïve comparison, is two-fold. Firstly, the figure illustrates the reasoning behind why EMA approved the broad licence for ibrutinib in WM despite the trial being focused on the R/R setting: PFS on ibrutinib in the R/R setting surpasses even what has been observed with available options in the TN setting to date. Secondly, the figure has been provided to the Committee in order to support Janssen's request that ibrutinib be recommended for the MEA in the full licensed indication despite data being available in the R/R setting only. Given the clinical view (generally, across oncology) that treatment options perform better the earlier they are prescribed within the treatment pathway, it is not clinically implausible that ibrutinib will perform even better when given in the treatment-naive setting. The MEA will provide an opportunity to collect data to support this view from an evidence-based perspective while also allowing patient access in an area of high unmet need in both the TN and R/R settings.

B3. **Priority:** Section 3.3, page 31. The text states "The goals of treatment, once started, are to reduce the tumour mass, provide symptomatic relief and reduce the risk of organ damage." Please clarify how tumour mass, symptomatic relief and risk of organ damage are measured in clinical practice and in Study 1118E.

Clarity on how these are measured by setting is as follow:

- Clinical practice:
  - Tumour mass is measured via bone marrow biopsy and aspirate, CT scan of chest, abdomen and pelvis for extramedullary disease (if present) and as IgM levels via blood test
  - Symptomatic relief – peripheral neuropathy is measured by symptomatic scoring and hyperviscosity, cryoglobulinaemia, cold agglutinaemia and anaemia is measured by blood test
  - Risk of organ damage – lymphadenopathy, hepatomegaly, splenomegaly and organomegaly are measured by physical examination and chemistry

- Please find below in Table 1 the calendar for Study 1118E that explains how these endpoints were measured in this study:

Table 1: 1118E Study Calendar

	Screening ≤ 30days from study entry	**Treatment Phase**		**Off Treatment Assessment** Within 4 weeks of completion of entire treatment plan(about 3 years total) or removal from study ± 2 weeks	**Follow-Up Phase** Post Treatment; Every 12 weeks ± 2 weeks for 2 years or until next therapy
		Cycles 1, 2 (4 weeks ±2 days) Cycles 3, 6, 9, etc. until 40 four	Week cycles completed (12 weeks± 1 week)		
Physical exams, vital signs, weight	X	X	X	X	X
ECOG performance status	X				
CT of the chest & abdomen / pelvis	X		X	X	
Bone marrow biopsy and aspiration	X		X	X	
Quantitative serum IgM, IgG, IgA	X	X	X	X	X
Serum immune-electrophoresis	X	X	X	X	X
Complete Blood Count plus differential	X	X	X	X	X
Coagulation profile: PT, PTT, PT-INR	X				
Chemistry/Comprehensive Metabolic Panel including: Electrolytes, Renal (BUN Creatinine) and Hepatic function testing [SLT (SGPT), AST (SGOT), Alk phos, total Bilirubin]	X	X	X	X	X
Pregnancy Test	X				
Magnesium	X	X			
Beta-2 microglobulin test	X				
Review patient diary		X	X		
Adverse event monitoring		X	X	X	X

B4. Section 3.3. Page 32. Please provide a list of comorbidities (including those associated with WM) which may (i) preclude treatment with ibrutinib, or (ii) impact upon treatment efficacy.

(i) A list of comorbidities which may preclude treatment with ibrutinib

a. Patients with severe cardiovascular disease were excluded from ibrutinib clinical studies

b. Atrial fibrillation and atrial flutter have been reported in patients treated with ibrutinib, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor all patients clinically for atrial fibrillation.
c. Ibrutinib is metabolised in the liver. It is not recommended to administer ibrutinib to patients with severe hepatic impairment (Child-Pugh class C). For patients with mild liver impairment (Child-Pugh class A) and moderate liver impairment (Child-Pugh class B) dose modifications are recommended.
d. A list of concomitant medications which are inhibitors of CYP3A4, prohibit the prescription of ibrutinib at full dose, and are specified in the SmPC.
e. Administration of ibrutinib to patients with severe renal impairment (< 30 mL/min creatinine clearance) is only recommended if the benefit outweighs the risk. Patients should be monitored closely for signs of toxicity.
f. There have been reports of haemorrhagic events in patients treated with ibrutinib, both with and without thrombocytopenia. Patients were excluded from participation in Study 1118 if they required warfarin or other vitamin K antagonists. Supplements such as fish oil and vitamin E preparations should be avoided. Use of ibrutinib in patients requiring other anticoagulants or medicinal products that inhibit platelet function may increase the risk of bleeding, and particular care should be taken if anticoagulant therapy is used. Patients with congenital bleeding diathesis have not been studied.

(ii) A list of comorbidities which may impact upon treatment efficacy
a. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction is specified within the protocol for Study 1118, although not specifically mentioned in the SmPC.
b. A list of concomitant medications which are inducers of CYP3A4, may lead to reduced efficacy of ibrutinib, and are specified in the SmPC.

Identification and selection of relevant studies

B5. Appendix 1, Table 2. With respect to the exclusion criteria, please explain the exclusion of “Non-randomised, comparative clinical efficacy and safety studies reporting on only one treatment of interest”, but the inclusion of single-arm, non-comparative studies. Please comment if this approach could exclude studies including a single treatment of interest and/or potentially hinder the opportunity to undertake an indirect comparison?

We confirm that this approach was appropriate. During the SLR process, these excluded studies were still tracked as it was apparent how limited the published data pool in WM is; it was noted that they did not provide sufficient data or a large enough sample size to inform an indirect comparison. The only exception to the rule was the inclusion of Study 1118E, the iNNOVATE study, and the pan-European Chart Review because Janssen had access to the study protocols, clinical study reports, and the patient level data related to these studies and thereby, was able to utilise unpublished data and conduct the indirect comparison. Note that no relevant data which could be used for an indirect comparison or pooled analysis has been reported for iNNOVATE and no such patient level data is available to Janssen for analysis as yet.

B6. **Priority:** Section 4.1, page 39, Figure 6 and Appendix 2, page 12. Please provide a table of the 130 studies excluded after full-paper screening, detailing, for each study, their populations, interventions, and the specific reasons for exclusion.

Please refer to tab "B6" in the MS Excel file submitted together with the clarification answers. Of note, for the 94 studies identified by the initial SLR, only the specific reason for exclusion could be provided within the timelines specified for the clarification questions.

B7. Appendix 2, page 13. The submission states regarding study selection that studies which were "only available in abstract format without accompanying full-text publications… were discarded from the review". However, the European Chart Review (Section 4.11) and iNNOVATE (Section 4.14) had both been published only as abstracts, but were included in the submission (although iNNOVATE is explicitly excluded from the review at this point). Please clarify and explain this inconsistency.

Please see our response to Question B5 - we confirm that this approach was appropriate. The only exception to the rule was the inclusion of Study 1118E, the iNNOVATE study, and the European Chart Review because we had access to the study protocols, clinical study reports, and the patient level data related to these studies and thereby, were able to utilise unpublished data and conduct the indirect comparison. No data that could be used for modelling purposes has been reported yet for iNNOVATE and therefore there was no information that could be used towards an analysis, indirect or otherwise, at this time. As such, we simply provided an overview of iNNOVATE because the relevant arm of this trial, Arm C, will report at a future date which aligns with the minimum two year data collection period we have proposed for the MEA.

B8. Section 4.1, page 37. How many non-English studies were rejected?

As shown in Figure 6 (p69) of the original submission, only one study was excluded on the grounds that it was not published in the English language, at the full text review stage: Lech-Maranda et al. 2015.

B9. Section 4.1, page 38. Given the limited evidence available for ibrutinib in this indication, please clarify why three ibrutinib abstracts were rejected.

The three ibrutinib abstracts were the following:

1. Treon, 2015 published in Haematologica: reports ORR, estimated PFS and AEs; it is the same data cut as the full peer-reviewed NEJM publication of Study 1118E
2. Treon, 2014 presented at IWW: reports ORR, estimated PFS and AEs; it is an earlier data cut of Study 1118E
3. Dimopoulos, 2015: does not report data that could be used for modelling purposes; it is Arm C (single agent ibrutinib) of the iNNOVATE trial based on a data cut with median 7 months follow-up

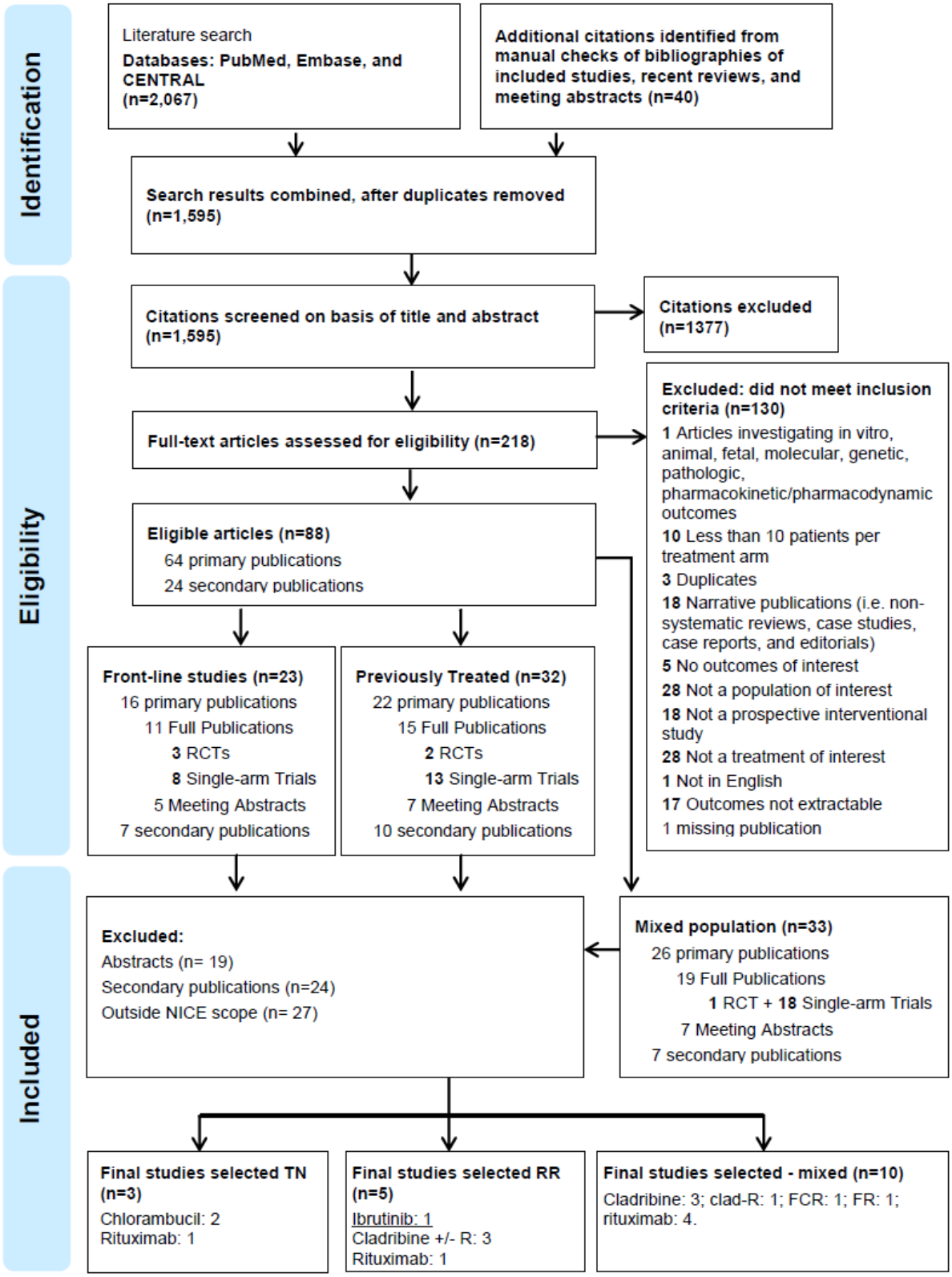
The first two ibrutinib abstracts were excluded from the SLR on the grounds that a peer-reviewed publication with the most up-to-date data of the same study was available and has been used as the foundational clinical and safety evidence presented in the submission. The third ibrutinib abstract was excluded because as explained in our response to Question B7, no data associated with outcomes of interest (i.e., no odds rations, hazard ratios, or Kaplan-Meier data) were reported in the abstract nor do we have this patient level as the study has yet to report. Although these three ibrutinib abstracts were excluded, we can confirm that no relevant evidence regarding ibrutinib in WM was omitted through their exclusion.

B10. Section 4.1, page 39, Figure 6. Please include boxes detailing the exclusion of 27 publications on the basis of having interventions and comparators outside of the NICE scope and the exclusion of studies published only in abstract form.

Figure 6 presented in the submission showed the PRIMSA flow diagram of clinical efficacy and safety studies. Figure 6 has been updated below with a box showing the exclusion of i) publications having interventions and comparators outside of the NICE scope and ii) studies published only in abstract form. Of note, the 19 abstracts have been excluded as no relevant outcomes data could be extracted (e.g., Kaplan-Meier data) to conduct a comparison, indirect or otherwise.

For further clarification, the box also captures the secondary publications which have not been retained by the SLR as they did not bring additional evidence relevant to the decision problem. This information seems not to have been shown in the submitted diagram as a result of an error when designing the two boxes presenting the detail of the selected front line (n=23) and previously treated (n=32) studies (the secondary publications however did appear in the box presenting the detail of the mixed population (n=33) studies).

Figure 1. Updated Figure 6. PRISMA Flow Diagram of Clinical Efficacy and Safety Studies



B11. Section 4.1, page 39, Figure 6. The final box for the treatment-naïve WM population has the figure of "3 studies" (consistent with Appendix 2, page 16, Table 16), but lists a total of 6 studies, including 2 cladribine studies and 1 DRC study, none of which are listed in Appendix 2, page 16, Table 16. Please clarify this inconsistency.

The correct number of studies selected by the clinical SLR for the treatment-naïve WM population should be 3 (2 with chlorambucil and 1 with rituximab), as described in Appendix 2, page 16, Table 16. Please refer to the updated Figure 6 above in our response to Question B10.

B12. **Priority:** Appendix 2, page 15, Table 15. Please provide in the table full details (references, study characteristics, populations, interventions, outcomes measured) for each of the studies excluded for having interventions and comparators outside of the final NICE scope.

Please refer to tab "B12" in the MS Excel file submitted together with the clarification answers.

Non-randomised and non-controlled evidence

B13. **Priority:** Section 4.10, page 41 (methods) and page 44 (results). Please conduct a quality assessment of the included study using an appropriate tool for this study design and report both the processes undertaken and the findings, as required by systematic review guidelines such as PRISMA.

A quality assessment of Study 1118E has been conducted using the Cochrane's Study Quality Guide for non-RCT studies[1]. The risk of bias was overall determined to be low, since methods were well detailed, and outcomes were complete and well reported. Personnel and participants were not blinded, neither was outcome assessment and therefore, these factors may have introduced a low risk of bias given the study is non-comparative. Evaluation is reported in Table 2 below:

Table 2: Quality assessment of Study 1118E (Treon et al 2015)

Study	Treon et al., 2015
Was the intervention independent of other changes?	Low risk
Was the shape of the intervention effect pre-specified?	Low risk
Was the intervention unlikely to affect data collection?	Low risk
Blinding of participants and personnel	Unclear
Blinding of outcome assessment	Unclear

B14. Executive summary, page 15, and Section 4.10, page 42 and Table 12. IgM is a surrogate outcome. Please provide evidence of the acceptability of overall response rate (ORR) as a surrogate outcome for WM.

In phase 2 single arm studies, it is commonplace for the primary end-point to be overall response rate (ORR). Where the treatment goal is to control the disease, measuring response rate gives an early indication of treatment effect and impact. With respect to how this relates to WM specifically Gertz et al.[2] and Treon et al.[3] have demonstrated that durable

[1] http://cccrg.cochrane.org/sites/cccrg.cochrane.org/files/uploads/StudyQualityGuide_May%202

[2] Gertz MA et al. Clinical value of minor responses after 4 doses of rituximab in Waldenström macroglobulinaemia: a followup of the Eastern Cooperative Oncology Group E3A98 trial. Brit. J. Haematol. 2009; 147(5):677-80

clinical benefit has been shown in minor responders, while deeper categorical responses such as VGPR or CR are associated with longer PFS.

B15. **Priority:** Section 4.10, page 42 and Table 12. Study 1118E has the primary outcome of ORR. The European Chart Review and the iNNOVATE study included progression-free survival (PFS) as the primary outcome. Why were these different between the studies?

Our understanding is that the choice of the primary outcome is determined by i) the research question and ii) the nature of study conducted to answer this question. The primary outcome for Study 1118E was overall response rate (ORR), which is, as stated in answer to Question B14, a standard primary outcome for a phase 2 non-randomised clinical trial in the broad oncology/haematology disease area.

Similarly, progression-free survival (PFS) is a standard primary outcome for phase 3 randomised controlled trials (RCTs) and PFS was selected as the primary outcome for the iNNOVATE RCT.

As per the abstract (Buske 2015) and EHA poster (Buske 2016) presenting the Pan-European Chart review (CR), several endpoints were explored in this study, including i) patient demographics, disease characteristics, and reasons for initiating treatment ii) initial and subsequent lines of treatment, iii) progression-free survival (PFS) and overall survival (OS) and iv) malignancies before and after being diagnosed with WM. As such, PFS was one of the endpoints considered in the CR.

B16. **Priority:** Section 4.10, page 42 and Table 12, Section 4.11, page 53 and Section 4.14, page 68, Table 28. Please provide full definitions of PFS for the following studies:
– Study 1118E
– The European Chart Review
– The iNNOVATE study

The definitions for PFS for the ibrutinib studies are provided in Table 3 below:

Table 3: Definitions for PFS across ibrutinib studies

Study 1118	Chart review	iNNOVATE study
Progression-free survival was defined as the time between the initiation of therapy and the date of disease progression, death, or last follow-up.	PFS is defined as duration in months from the start date of a given line of treatment for WM to the following occurrence of disease progression/relapse (month/year) or start of the next line of treatment (month/year) or death within the current treatment period, whichever occurs first. Subjects who initiated the current line of treatment and who did not have an event were censored at the last available date during the current therapy	PFS, as assessed by IRC, is defined as the duration from the date of randomisation to the date of disease progression or death, whichever is first reported, assessed according to the modified VIth IWWM (NCCN 2014) criteria.

[3] Treon SP et al. Attainment of complete/very good partial response following rituximab-based therapy is an important determinant to progression-free survival, and is impacted by polymorphisms in FCGR3A in Waldenstrom macroglobulinaemia. Brit. J. Haematol. 2011; 154(2): 223-8.

B17. Section 4.10 page 42 and Table 12. CR and PR have the same definition. Please correct.

Definition of the primary endpoint in general and of CR and PR in particular is clarified in Table 4 below.

Table 4: Definition of primary outcomes in Study 1118E

- ORR including:
  - Minor Response (≥25% reduction in serum IgM levels; Required 2 consecutive measurements of IgM)
  - PR (≥ 50% reduction in serum IgM levels; Required 2 consecutive measurements of IgM)
  - VGPR rate (≥ 90% reduction in serum IgM levels or IgM levels within normal range; Required 2 consecutive measurements of IgM)
  - CR (Resolution of all symptoms, normalization of serum IgM levels, required 2 consecutive measurements of IgM and negative serum immunofixation. Resolution of any adenopathy or splenomegaly by central radiology)
- Major Response Rate (PR or better)

Of note, upon revisiting this section Janssen identified a typographical error in the title for Table 13 on p43 which should be "Modified IWWM response criteria for IRRC assessment of response and progression", instead of "Modified IWWM response criteria for investigator assessment of response and progression"

B18. Section 4.10, page 43. Please provide details of the statistical basis for the sample size, including whether the confidence interval used at the design stage was exact or asymptotic, and whether any account was taken of the population being effectively finite.

Assuming the response rate for ibrutinib was 50% in the study population, approximately 60 evaluable subjects would be required to have at least 80% power to declare the ORR was 32% or higher at the 1-sided significance level of 0.025. Analysis of efficacy and safety was performed using the All-Treated Population and was based upon the clinical cut- off date of 28 February 2014.

The 95% confidence intervals (CIs) for the ORR and major response rate were calculated using exact binomial distribution. Exact (Clopper-Pearson) 95% CIs were presented. The null hypothesis was tested at the overall significance level of 0.025 (1-sided) and rejected if the lower bound of the CI exceeded 32%.

B19. Section 4.10, pages 47-48. Please comment on the less favourable outcomes observed for the MYD88WTCXCR4WT mutations. Please also provide p-values of the interaction for each subgroup in Figures 7 and 8, and comment on any subgroups across which a potentially differential effect is identified.

Responses to ibrutinib are influenced by MYD88 and CXCR4 mutation status and is lowest for the $MYD88^{WTCX}CR4^{WT}$ cohort, as demonstrated in Study 1118E.

Activating mutations have been identified in these genes. In tumour cells, $MYD88^{L265P}$ triggers activation of nuclear factor κB (NF-κB) through two divergent pathways involving Bruton's tyrosine kinase (BTK) and the interleukin-1 receptor–associated kinases (IRAK1 and IRAK4). Ibrutinib is an inhibitor of BTK that triggers apoptosis of Waldenström's macroglobulinaemia (WM) cells with $MYD88^{L265P}$.

Three genomic groups are identified in WM, two with $MYD88^{L265P}$ mutation and one without, i.e. $MYD88^{L265P}CXCR4^{WT}$, $MYD88^{L265P}CXCR4^{WHIM}$ and $MYD88^{WT}CXCR4^{WT}$.

Patients who are wild type (WT) for MYD88 demonstrate a reduced response to ibrutinib due to the rationale explained above (these are numerically the smallest group).

P-values of the interaction for each subgroup in Figures 7 and 8 of the submission, for ORR and MRR respectively, are presented in Table 6 below:

Table 5: Study 1118E Subgroup P-values

Subgroup	ORR	MRR
	Fisher's Exact P-value	
Age	[redacted]	[redacted]
ECOG at baseline	[redacted]	[redacted]
WM IPS	[redacted]	[redacted]
B2-microglobulin	[redacted]	[redacted]
Haemoglobin level	[redacted]	[redacted]
IgM	[redacted]	[redacted]
Bone marrow disease involvement	[redacted]	[redacted]
Disease status	[redacted]	[redacted]
Number of previous treatment regimens	[redacted]	[redacted]
MYD88 / CXCR4 mutation	[redacted]	[redacted]

Statistical significance has been observed for three subgroups (Haemoglobin level, Bone marrow disease involvement and MYD88 / CXCR4 mutation); differences in the remaining seven subgroups were not statistically significant.

B20. Section 4.11, page 53. The number of patients who receive second-line treatment is stated as 397 while it is 387 in Figure 13. Please clarify.

The correct number of patients who receive second-line treatment is 397.

Indirect comparison

B21. Appendix 1, Table 2. With respect to exclusion criteria for retrospective studies. Please explain how the European Chart Review was included here, given that this type of study design was explicitly excluded from the clinical review.

We confirm that retrospective studies were a study design that was part of the exclusion criteria. Once the full SLR was completed and the full extent of the limited data in WM was clear, we investigated the availability of retrospective studies in WM. The European Chart Review study is an initiative in collaboration with Janssen and as a result, we had access to the patient level data. As such, this study was included since it provided a longitudinal understanding of the treatment pathway and of the effectiveness of current treatment options in WM. When the patient level data are combined with the Study 1118E data, it also allowed comparative efficacy to be estimated relative to ibrutinib.

B22. Section 4.11, page 52. The submission states "Data in this section are predominantly drawn from the abstract presented at the 2015 American Society of Hematology (ASH) annual conference". However, Appendix 2 (page 13) also states that studies which were

“only available in abstract format without accompanying full-text publications … were discarded from the review.” Please explain and justify the inclusion of this retrospective study, which has been published only as an abstract.

We confirm that the approach taken in the SLR was appropriate. As mentioned previously, the only exceptions to the SLR rules were the inclusion of Study 1118E, the iNNOVATE study, and the European Chart Review because we had access to the study protocols, clinical study reports, and the patient level data related to these studies. Therefore, we were able to utilise unpublished data and conduct the indirect comparison.

B23. Section 4.11, pages 51-52. Please clarify why data from the European Chart Review are presented for comparison from 2000-2010, while some R/R studies are excluded from the indirect comparison for being “outdated (published in the 1990s)”, even though the company submission also presents evidence that only minor differences in OS were found between 1980-1999 and 2000-2010, to demonstrate the absence of genuine therapeutic advances (Section 3.1, page 29).

The European Chart Review study was conducted in collaboration with the European Consortium for Waldenström’s Macroglobulinemia (ECWM) and this was the agreed and established study protocol i.e. physicians completed a retrospective electronic record for patients who met inclusion criteria which included a diagnosis and initiation of therapy which occurred between January 2000 and January 2014.

B24. Section 4.11. Please provide more information regarding the European Chart Review. In particular, please comment on the following:

a) Who funded this study?

The European Chart Review was commissioned and funded by Pharmacylics (PCYC).

b) How were patients identified and selected for inclusion?

First, representative countries from the EU and individual centres from each country were selected by the agency executing the project on behalf of PCYC (Genactis) in collaboration with the European Consortium for Waldenström's Macroglobulinemia (ECWM). After the selection of each centre, the agency in collaboration with ECWM called upon the physician to ascertain if they were interested to explore identification, diagnosis and treatment of WM patients with a goal of collecting sufficient data to create a satisfactory retrospective dataset for this rare condition.

In order for the information collected to reflect clinical practice, the physicians were asked to complete retrospective anonymised electronic patient records (EPR) for their patients fitting the inclusion criteria. The project was conducted over the internet from December 11th, 2014 to the end of January 2015.

In addition the following questions were asked of the physicians:

- “Are you happy to participate in the survey on this basis?
- In which country do you practice the majority of the time?
- Which of the following describes your primary medical specialty (Haematology, Onco-haematology/Haemato-oncology, oncology, other, please specify).
- Do you confirm you treat adult patients (age ≥ 18) with WM?
- How many WM patients fitting the above outlined criteria do you estimate you will be able to record (participating centres will need to have at least 4 patients)?”

If all the above conditions were met, then the physician qualified for the study. The maximum sample size was set depending on the answers above, as well as based on the sample composition to ensure adequate geographical spread. Close monitoring was carried out to ensure that participating centres adhered to their commitment.

c) What measures were taken to minimise bias in patient selection?

Representative countries from EU and individual centres from each country were selected in collaboration with ECWM. The physicians from each centre were asked to complete retrospective anonymised EPR for their patients fitting the predetermined inclusion criteria. In addition, each physician from participating centres was required to have at least four eligible patients. Each centre was set a maximum number of patients based on the sample composition to ensure adequate geographical spread.

Thus by imposing the same set of conditions for each of the selected centres from the ECWM representative countries and recording the same set of information across all patients, bias in patient selection was reduced. This spread in countries and centres reduced any potential bias arising from selection from a limited number of centres or from countries not generalisable to the UK setting.

d) Comment on how pre-specified balance across countries was achieved without introducing bias.

Conducting a retrospective study without introducing bias is very difficult. It was judged that no pre-specified balance would introduce a greatest risk of bias and therefore pre-specified balance was carried out to minimise this.

The selected patient population was biased to some extent since it only included the ECWM member country/sites and included only patients from these countries and sites that met the inclusion criteria. However the sample that was selected from this biased population was performed in a systematic manner and hence minimised bias to this sample.

e) Provide a breakdown of treatments received by line of therapy (for those patients included in the Cox model and for the overall cohort).

For a breakdown of treatments received by line of therapy, please refer to tab “B24” in the MS Excel file submitted together with the clarification answers.

B25. Section 4.11, Table 21, page 57:

a) There are differences in age, gender, IPSSWM risk and serum antibody levels between the matched chart review cohort and the Study 1118E population. Please comment on the likely direction of bias caused by this imbalance.

A matched cohort was created by randomly selecting a subset of the overall pan-European chart review cohort (n = 454) that had received similar prior lines of therapy as Study 1118E (i.e., 1 to 4 prior lines of therapy). Adjustment for the differences between trial and chart review population in key prognostic factors (characteristics presented in Table 6 below which is an update of Table 21 from the original submission) was performed through the multivariable Cox regression analyses. Key prognostic factors known to impact disease progression in patients with WM were identified from a previous publication (Morel, 2009[4]) and clinical feedback.

With regard to the specified parameters, the patients are younger in Study 1118E with proportionately more men. The IPSSWM risk is incomplete for the Chart Review with the risk

[4] Morel P, Duhamel A, Gobbi P, Dimopoulos MA, Dhodapkar MV, McCoy J, Crowley J, Ocio EM, Garcia-Sanz R, Treon SP, Leblond V, Kyle RA, Barlogie B, Merlini G. International prognostic scoring system for Waldenstrom macroglobulinemia. Blood. 2009 Apr 30;113(18):4163-70.

score unknown for around a third of patients. Patients in Study 1118E did however demonstrate a high proportion with intermediate and high risk disease, with higher serum antibody levels (IgM) as well.

Thus certain observed differences across the studies will bias results against ibrutinib (e.g., serum antibody levels) while others will result in bias in favour of ibrutinib (e.g., age) and we therefore cannot infer the overall direction of potential bias. However, this is an example of the uncertainty which could be addressed through the WM registry if ibrutinib were recommended for the MEA.

b) Also, for IPSSWM high-risk in columns 3 (Study 1118E), should the figures be: "35 (22)"?

Yes, for IPSSWM high-risk in columns 3 (Study 1118E) the figure should be "35 (22)" according to Treon 2015. Of note, Janssen also noticed the data for IgA and IgG were reversed in the submission Table 21. The label is corrected in the updated submission Table 21 (Table 6 below).

c) In addition, please present the data in Table 21 for the Study 1118E patients included in the analysis (n=47) rather than the whole Study 1118E population (n=63).

Please see updated submission Table 21 below.

Table 6: Updated submission Table 21: Patient baseline characteristics: overall chart review matched, vs. Study 1118E vs. UK chart review cohorts

Characteristic	Overall chart review matched	Study 1118E	Study 1118E (Patients with at most four prior treatments)	UK chart review
	(n=175)	(n=63)[23]	(n=47)[23]	(n=72)
Age at initiation of 1L treatment				
Years, median	[redacted]	63	[redacted]	[redacted]
Years, range	[redacted]	44-86	[redacted]	[redacted]
Percent ≥65 (n)	[redacted]	NR	[redacted]	[redacted]
Percent Male (n)	[redacted]	76 (48)	[redacted]	[redacted]
Median number of previous treatment regimen (range)	[redacted]	2	[redacted]	[redacted]
	[redacted]	(1-9)	[redacted]	[redacted]
IPSSWM risk at initiation of frontline treatment*, % (n)	-	-	-	-
Low	[redacted]	22 (14)	[redacted]	[redacted]
Intermediate	[redacted]	43 (27)	[redacted]	[redacted]
High	[redacted]	35 (22)	[redacted]	[redacted]
Serum antibody levels	-	-	-	-
IgM	-	-	-	-
Median (range) — mg/dl	[redacted]	3,520	[redacted]	[redacted]
	[redacted]	(724-8,390)	[redacted]	[redacted]
Percent >4000 mg/dl (n)	[redacted]	41 (26)	[redacted]	[redacted]
Median IgA (range) — mg/dl	[redacted]	26	[redacted]	[redacted]
		(0-125)	[redacted]	
Median IgG (range) — mg/dl	[redacted]	381	[redacted]	[redacted]

		(49-2,770)	[redacted]	
Median β2-microglobulin, range *	[redacted]	1.3-14.2	[redacted]	[redacted]
Median β2-microglobulin, mg/L *	[redacted]	3.9	[redacted]	[redacted]
Any cytopenia*, % (n)	[redacted]	NR	[redacted]	[redacted]
Percent Haemoglobin ≤11 g/dL (n)	[redacted]	59(37)	[redacted]	[redacted]
Percent Platelets ≤100 × 109/L (n)	[redacted]	11 (7)	[redacted]	[redacted]
NR: not reported				
*Missing data are not included in calculations.				

B26. Section 4.11, pages 59-61, Tables 22, 23 and 24. Please clarify the model used to estimate the HR provided in these tables. Are these adjusted estimates from the full multivariable Cox model, or univariate HR estimated on inclusion of each covariate individually in the model? It is stated that the HR for treatment "is a univariate HR based on the Cox-model, only including treatment and all other covariates are not significant". If these have not already been provided then please provide the results from the full adjusted multivariable Cox regression. Please also provide the observed Kaplan-Meier curve for the 2L PFS data from the European Chart Review data used in the Cox model (n=175).

Section 4.11, page 60, of the original submission misrepresented the Cox regression model. The HRs provided in these tables are estimates from the full multivariable Cox regression model, and not from a univariate Cox regression model.

B27. Section 4.11, page 58. a) Why was the multivariable Cox model assumed? b) Which other methods of comparison were tested? c) Please also provide justification regarding the assumption of proportional hazards underlying the use of the Cox model in this instance.

a) Please refer to answer to question B28 below. Given that patient-level data were available from both the European Chart Review and Study 1118E, the pooled multivariate analysis was conducted as this was considered the most appropriate and robust method to estimate comparative efficacy given data available.

b) No other methods of comparison were tested.

c) Proportional hazard assumption was tested between the PFS of ibrutinib in Study 1118E and PFS of the matched chart review cohort. All statistical tests showed that proportionality assumption should not be rejected, including:
   - visual examination of the log of negative log of estimated survivor functions (please see Figure 2 below) and Epanechnikov Kernel-smoothed hazard function (please see Figure 3 below), using an interaction term of treatment with log of time,
   - and the Kolmogorov-Smirnov test.

The proportionality assumption determined that the multivariate Cox model was an appropriate statistical method to derive treatment effect between ibrutinib and the physician's choice.

Figure 2. Log of negative log of estimated survivor functions

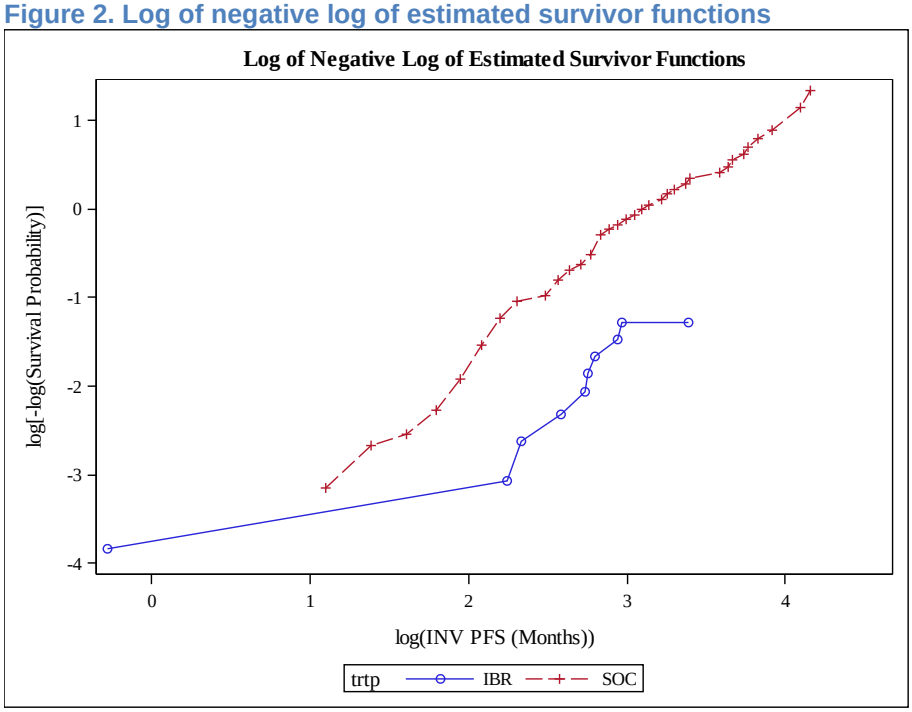
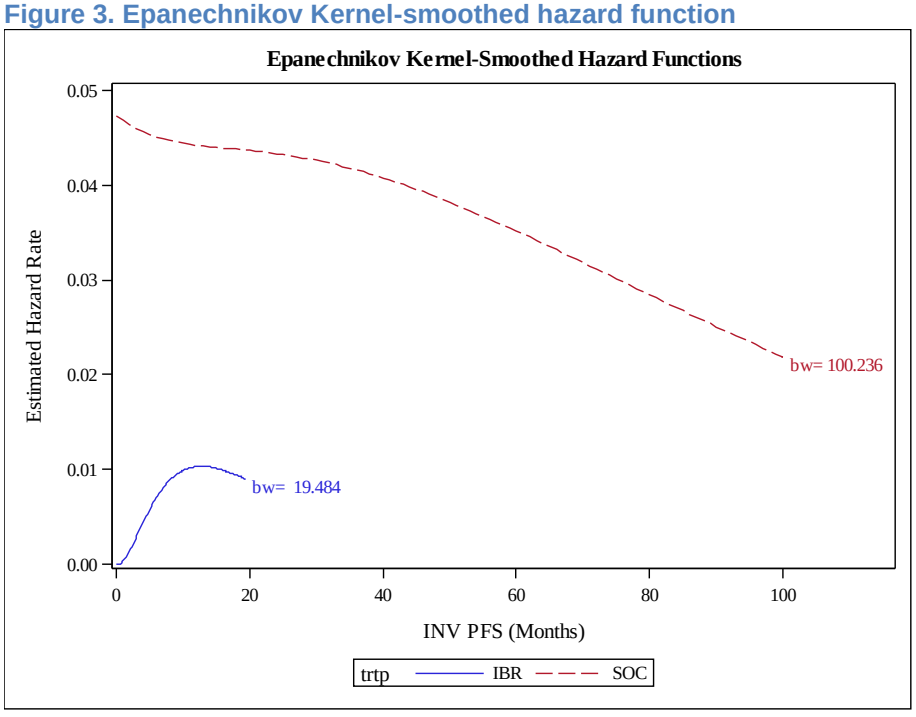


Figure 3. Epanechnikov Kernel-smoothed hazard function



B28. Section 5.2, page 79. Given that patient-level data were available from both the European Chart Review and Study 1118E, please clarify why there was “no way to carry out” a matching-adjusted indirect comparison (MAIC). Please refer to the section titled “Additional analyses requested” below.

As described in Section 5.2, page 78, Janssen considered a hierarchy of evidence with RCTs being of the most robust quality, followed by ITC assuming a network of evidence is possible, and finally alternative statistical methods such as an MAIC or pooled multivariate analysis where no common comparators are available. MAICs are particularly useful where one study has results in aggregated form (normally, these are published data for

comparators of interest and are, for example, KM data for PFS or OS) and another study has patient-level data available (normally, these are the manufacturer's own studies on the intervention of interest). In this situation, the patient-level intervention data can be matched to the aggregate comparator data and an indirect comparison can be conducted. Pooled multivariate analyses are possible where patient-level data are available for both the intervention and the comparator and therefore, a more robust 'matching' and/or sampling process can be applied.

Given that patient-level data were available from both the European Chart Review and Study 1118E, the pooled multivariate analysis was conducted. The statement that there was "no way to carry out an ITC or an MAIC" was applicable relative to all the other studies identified by the SLR.

B29. Section 4.11, page 56, Table 20. Please comment on the likely impact of differences in the definitions of progression in Study 1118E and the European Chart Review?

The definitions used within Study 1118E and the chart review are as below. We do not anticipate a significant impact from the differences in the definitions as changing IgM levels or progression of clinical features is captured in both studies.

- Definition from Study 1118E: When >25% increase in serum IgM level occurs from the lowest attained response value or progression of clinically significant disease related symptom(s) based on the consensus panel criteria of IgM response. Death from any cause or initiation of a new anti-neoplastic therapy will also be considered a progression event.

- Definition from Chart Review: 25% increase in serum IgM from lowest nadir, progression or re-appearance of clinical features, progression or re-appearance of hematopoietic insufficiency.

B30. Section 4.11, pages 56-57. The method used to define the "matched chart review cohort" does not define a unique sample of individuals. Please perform sensitivity analyses using a repeated (different) random sample.

A multivariate Cox regression analysis with repeated alternative sample was conducted as a sensitivity analysis. As shown in Table 7 below, the point estimate HR of ibrutinib's treatment effect changed slightly and remained within the 95% CI of the original Cox model presented in the submission document Table 22. This analysis supports that the probabilistic sensitivity analysis using 95% CI properly captured the variation in the HR of PFS.

Table 7. Original Cox Model analysis and Cox Model with alternative sampling

Covariates	Original Cox Model				Cox Model with Alternative Sampling			
	HR	95% CI		P value	HR	95% CI		P value
Ibrutinib treatment (versus SOC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta macroglobulin ≤3mg/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemoglobin ≤11 g/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IgM <40 g/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platelet ≤100x10^9/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPSSWM: low risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPSSWM: intermediate risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Safety

B31. **Priority:** Section 4.12, pages 61 and 65-66, and Section 2.5, page 25. Please describe the process by which the ibrutinib studies in CLL and MCL populations were identified and selected (search strategy and processes, inclusion and exclusion criteria applied), and provide full details of any ibrutinib studies that were excluded.

For detail of the CLL and mantle cell lymphoma (MCL) studies selection process, please refer to the manufacturer submissions for the two ongoing ibrutinib NICE submissions, respectively for CLL [ID749] and MCL [ID753].

B32. **Priority:** Section 4.12, pages 61-63. Please provide the following tables of adverse events for Study 1118E:

For questions a) to c), the safety data requested relate to data from the 19/12/2014 clinical cut-off (CCO) of Study 1118E, which were presented in the Treon 2015 publication. These data were reported in pages 61-63 of the submission (please see Figure 15 and Table 26 of the original submission).

a) Overall frequencies (numbers of patients) of any AEs (only numbers for AEs of > Grade 2 are currently provided).

Janssen is unable to present AE overall frequencies (number of patients) from the 19/12/2014 dataset within the timelines set to answer the ERG clarification questions.

However, data on treatment-emergent adverse events are available from Study 1118E clinical study report (CSR). Janssen acknowledge that the CSR was based on an earlier CCO date (28/02/2014). These data.(from the CSR) are presented in tab “B32” (Table A) in the MS Excel file submitted together with the clarification answers.

b) Serious AEs (numbers of patients and type)

No “serious” AE flag was set up for the AE data collected as part of the 19/12/2014 CCO; therefore no serious AE data are available for this CCO.

Serious AE are however available from the CSR for Study 1118E and Janssen have therefore presented these data in tab B32 (Table B) of the MS Excel file submitted together with the clarification answers.

c) Severe AEs (numbers of patients and type)

The protocol for Study 1118E clarifies that “severe” is used to describe “Grade 3” AEs - Janssen therefore asks the ERG to refer back to the rates presented in Table 26 (p64-65) of the original submission.

B33. **Priority:** Appendix 3, Table 19. In order to facilitate comparison across trials, please provide equivalent tables for adverse events (including discontinuations due to adverse events) of Grade 2 or higher for RENOVATE and separate tables for any AEs, and Grade 2 or higher AEs, and severe and serious AES, for the following trials: RENOVATE 2 and PCYC-1102/1103 (in CLL patients) and PCYC-1104 (in MCL patients).

Janssen would first like to correct the name of the two ibrutinib CLL trials, RESONATE and RESONATE-2, which have been misspelled in the ERG question above.

Due to discrepancies between available data sources and adverse event reporting, Janssen are unable to fulfil the ERG's exact request. Instead, the only ways to possibly compare AE data across the requested CLL and MCL trials was to report any grade AE occurring in ≥10% of subjects, grade 3 and 4 AEs occurring in ≥2% of subjects, serious AEs occurring in ≥2% of subjects, grade 5 AEs, and discontinuations. The only AE data available for PCYC1103 (the PCYC1102 extension trial) were not reported at a level suitable for answering this question and were therefore omitted.

The trial publication was used wherever possible, but when not available the trial's accompanying CSR was used to report the required AE data. Please refer to Table 8 below and Tab B33 for further information.

In order to facilitate comparison across trials, please refer to safety data presented in tab "B33" in the MS Excel file submitted together with the clarification answers.

Table 8: Overview of Requested AE Data

Trial Name	Requested data	Available data	Tab 33 Reference
RESONATE	Grade 2+ Discontinuations	[Grade 3+Grade 4] ≥2%+Grade 5 Discontinuations	Tables B and C Table E
RSONATE 2	Any AE Grade 2+ Severe and serious AEs	Any AE ≥10% [Grade 3+Grade 4] ≥2%+Grade 5 Serious AEs ≥2%	Table A Tables B and C Table D
PCYC1102	Any AE Grade 2+ Severe and serious AEs	Any AE ≥10% [Grade 3+Grade 4] ≥2%+Grade 5 Serious AEs ≥2%	Table A Tables B and C Table D
PCYC1103	Any AE Grade 2+ Severe and serious AEs	NA	NA
PCYC1104	Any AE Grade 2+ Severe and serious AEs	Any AE ≥10% [Grade 3+Grade 4] ≥2%+Grade 5 Serious AEs ≥2%	Table A Tables B and C Table D

AE: Adverse Event

B34. Section 4.12, page 61. The text which states "of the 19% of patients who stopped treatment, only 6% discontinued as a result of toxicity"; this seems to be in contradiction with Table 25. Also, page 66 states "Ibrutinib was well tolerated with a discontinuation rate of 9.5% following a median treatment duration of 19.1 months." Please clarify this apparent inconsistency. Please provide the number of patients who discontinued, the number of these who discontinued due to toxicity and what each toxicity consisted of.

On page 61 there is a typographical error; it should instead state that six patients discontinued treatment (9.5%). The statement on page 66 is correct.

With respect to number of patients who discontinued, number of those who discontinued due to toxicity and what each toxicity consisted of, please find below the summary.

- Number of patients who stopped treatment: n = 12 (please note that there is a typo in the original submission which stated that 21 patients had stopped treatment in Table 25 but this should be 12).
- Number of patients who stopped treatment due to toxicity: n = 6.
- Toxicity and the number of patients who experienced each:
    - Patient 1: myelodysplastic syndrome

- Patient 2: thrombocytopenia
- Patient 3 : post-procedural haematoma
- Patient 4: pleural effusion
- Patient 5: B-cell lymphoma
- Patient 6: atrial fibrillation.

B35. Section 4.12. Please provide AE data from the European Chart Review.

No adverse events (AE) were collected as part of this study.

Section C: Clarification on cost-effectiveness data

Cost-effectiveness evidence

C1. Section 5.1, page 73. The text states pilot extraction form tested on several included studies. How is this possible given that only 2 studies were identified?

This statement is incomplete and refers to the approach that was followed across the SLRs conducted by Janssen for ibrutinib in its various indications for which a NICE submission is ongoing (CLL, MCL and WM).

C2. Section 5.2, page 74. Please comment on the likely cost-effectiveness of ibrutinib in patients for whom chemo-immunotherapy is unsuitable.

Given the general clinical view in oncology that treatment options perform better the earlier they are prescribed within the treatment pathway, it is not clinically implausible that ibrutinib will perform even better when given in the treatment-naive setting relative to the results observed in the R/R setting. We refer the ERG and Committee to our response to Question B2 as this is a point that was considered by the EMA in the licensing of ibrutinib in WM. The MEA will provide the opportunity to collect data to support the assertion that ibrutinib will be equally effective, if not more effective, in the treatment-naive setting relative to the R/R setting. These data would also allow for an understanding of where clinicians believe ibrutinib is best used in the treatment pathway. Janssen believe that inclusion of the additional data from the UK WM Registry will support that ibrutinib is a cost-effective treatment option in WM.

C3. **Priority:** Section 5.2, page 79, Table 33.

a) Please include dosing regimens and frequencies for other regimens used in the model which are mentioned in Table 32 but not in Table 33.

Regimens used in the model (Table 32 of the original submission) but for which dosing regimens and frequencies are not explicitly provided in Table 33 of the original submission are regimens covered by the umbrella term "other treatment" in Table 32 and include: cladribine, chlorambucil, chlorambucil+ rituximab and rituximab.

For treatment with cladribine and rituximab (either in monotherapy or in combination), the same dosing regimens and frequencies were used as those presented in Table 33, i.e. 0.14 mg/kg every 28 days for 4 cycles for cladribine and 375 mg/m^2 every 28 days for 6 cycles for rituximab.

The only outstanding treatment that is not mentioned in Table 33 is chlorambucil. In the model, the dosing regimen and frequency was assumed to be 0.2 mg/kg/day for 8 weeks, based on chlorambucil SPC.

b) In addition, other options e.g. SCT are mentioned as second-line options in Appendix 4 – why were these not included in the model?

Janssen acknowledges that some treatment options, e.g. SCT, were mentioned by KOLs in Appendix 4, but were not modelled.

The primary reason for disregarding a treatment option in the economic evaluation was when the treatment was outside the NICE Final scope (e.g., bortezomib-based regimens). In addition, these options are often very rarely used in clinical practice as explained in Response 1 of Appendix 4 (p23), e.g. bortezomib being delisted from the CDF, R-CHOP which was no longer recommended in the BCSH WM guidelines, or in the case of RCVP, was largely interchangeable with another treatment included in the model (here) R-CVP (of note, DRC is more expensive than R-CVP (£1,505/cycle vs. £1,437/cycle respectively),reflecting a conservative modelling approach). With regards to SCT specifically,

in addition to not being mentioned by the NICE Final scope, it was deemed that its use was also scarce, with extreme variation in the country, and that, as stated on page 24 of Appendix 4 (Response 1), "SCT would be used in a very small proportion of patients that would be eligible for ibrutinib based on its license in WM."

c) Please clarify how estimates of the proportionate use of each regimen were derived.

The estimates were based on the responses collected through the KOL questionnaire and presented in Appendix 4. The average was taken from the responses received.

C4. Section 5.2, page 76, and Section 5.5, page 96. The text states on page 76 that wastage was assumed but page 96 states that wastage was considered in sensitivity analyses. Please clarify.

Wastage was applied in the base-case analysis. No wastage (i.e., vial-sharing) was explored as part of the deterministic sensitivity analysis, where inclusion of wastage was assumed for the lower value and the base case while no wastage was assumed for the upper value.

Further to this, we noticed a typographical error in Table 63 on p111: for parameter "inclusion of wastage", the "No" and "Yes" in column “Alternative value”. The alternative value should be inverted with "Yes" at the top matching a result ICER of £78,647 (in line with assumption used in base-case) and "No" at the bottom, matching the resulting ICER of £79,034. The assumptions around inclusion (base-case and lower values) and exclusion (upper values) of wastage have been correctly applied in the model.

Therefore the text on p95-96 should read as follows:
"Wastage (i.e., no vial sharing) was assumed for IV drugs in the base-case analysis and no wastage (i.e., vial sharing) was tested through the deterministic sensitivity analysis. When wastage was considered, the dosing consumption per administration was rounded up to the closest number of vials. When no wastage was assumed, IV drug costs were estimated based on the actual dose infused rather than on a per vial basis."

C5. Section 5.2, page 79, Table 32. Please comment on the validity of using the European Chart Review to derive estimates of relative treatment effect and separate expert opinion to derive the use of specific chemotherapy/rituximab regimens for costing.

Clinical experts were asked to comment of the plausibility of the efficacy data from the European Chart Review, on the plausibility of the relative treatment effect compared to ibrutinib, and on the treatment regimens in terms of their relevance to UK clinical practice. Clinical opinion confirmed the efficacy data were plausible, that the treatment effect was plausible, and that the treatment regimens may be slightly different in the UK but the impact of this could be limited to the cost as opposed to the efficacy. Therefore, as we did not have UK-specific trial data for clinical efficacy, clinicians confirmed it was appropriate to use the data from the Chart Review for the UK and to adjust the costing to better reflect the cost-impact to the NHS.

C6. Section 5.3, page 81, Table 34. Please comment on the appropriateness of assuming a model structure beginning with second-line therapy given that 62% of patients in Study 1118E had already received more than one prior therapy.

Janssen believe this is an appropriate approach because given our licence is broad; should clinicians have access to ibrutinib, it is likely that ibrutinib will be used early in the treatment pathway due to its strong efficacy and tolerable safety profile. As such, we aimed to reflect likely clinical practice. Furthermore, in order to estimate the relative efficacy of ibrutinib using the European Chart Review data, patients in Study 1118E who had 5+ lines of treatment were removed from the comparison dataset which shifted the median prior lines of therapy

patients were exposed to. Janssen believe that any uncertainty on the appropriateness of this modelling approach would be addressed via the MEA as the UK WM Registry should be able to demonstrate how ibrutinib is used in clinical practice and the associated efficacy, safety, and HRQoL data.

C7. Section 5.3, page 84. Please explain why only Weibull, log-normal, log logistic and exponential curves were fitted to the data from Study 1118E. Why were other parametric functions not considered?

In addition to Weibull, log-normal, log logistic and exponential, the Gompertz and generalised Gamma were also tested for long-term projection. The generalised gamma did not converge. Gompertz was shown to have worse a AIC and BIC than the Weibull, log-logistic and exponential functions. These were excluded from the report, but please see below for the parameterisation:

Table 8. Parameterisation for distributions used for PFS extrapolation

Analysis	Weibull	Log-normal	Log-logistic	Exponential	Generalised gamma	Gompertz
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	89.266	90.22	89.138	89.93	91.255	90.063
BIC	93.552	94.506	93.424	92.073	97.684	94.35

C8. **Priority:** Section 5.3, page 85. Given the use of general population mortality hazards for patients on ibrutinib, is the model suggesting that all patients are temporarily cured of WM whilst they remain on treatment? Please comment on the strength of evidence available to support this assumption and the uncertainty surrounding it.

With respect to the mortality data whilst on ibrutinib, observed data were limited as only three deaths occurred in Study 1118E during the median 24 month follow-up period. As such, Janssen had three options in terms of data to be applied in the model:

1) the age-adjusted UK general population mortality
2) the mortality data used for the comparator arm from the European Chart Review (i.e., assume that there is no difference in mortality with ibrutinib relative to PC, the comparator which is essentially R-chemo)
3) an estimate that lies between options 1 and 2.

Janssen did not pursue Option 3 as there are no data at present to estimate this option; therefore Option 3 was ruled out.

Janssen believes it is unlikely that mortality observed in the ibrutinib arm can be assumed the same as physician's choice and therefore Option 2 was ruled out.

The mortality rate from Study 1118E was compared to the age-adjusted UK general population mortality for validation since the observed data were limited to three events. Given the data were well matched, Option 1 was used.

We recognise that the trial data are limited and therefore an assumption had to be made on how best to capture this outcome. We believe that, should ibrutinib be recommended for the MEA during a minimum 2 year data collection period (aligning with the median follow-up period of Study 1118E), the data observed in the trial will be confirmed by the real world setting given the strong efficacy and safety data observed thus far with ibrutinib. This will confirm and/or replace the assumptions currently being used in the model.

C9. **Priority:** Section 5.3, page 86, Figure 21. The ERG has concerns that the survival curve used to inform the 2L death rate for physician's choice reflects overall survival (pre- and post-progression deaths) rather than pre-progression mortality, thereby producing an inflated death rate. Please confirm that Figure 21 does not include censoring for progression. Please also refer to the section titled "Additional analyses requested" below.

The time to death for physician's choice presented in Section 5.3, Figure 21 represents the pre-progression death only, and does not take into account post-progression survival. Patients who progressed are censored.

Please note that in the original submission, Section 5.3 'Progression-free survival health state (ibrutinib and PC)' stated that "the efficacy of ibrutinib and PC (i.e. efficacy within the 2L HS) was captured in terms of PFS (probability of progression or death) and probability of death and these parameters were informed by Study 1118E and the pan-European chart review". The term "probability of death" was inaccurate throughout Section 5.3 and should have instead stated more clearly "probability of death during PFS".

C10. **Priority:** Section 5.3, page 81, Table 34. The ERG is unclear regarding which data were used to inform the time-to-event parameters in the model (and why). Please clarify and justify the data used to inform PFS and OS at 2L, 3L 4L and BSC in the European Chart Review and Study 1118E. To enhance transparency, please complete the following table, including details of evidence source, patient population used to derive parameters (including number of previous therapies received) and number of patients included in each analysis.

OS was not modelled directly from OS data from a single source. Instead, OS was calculated as "OS = 1 – overall mortality" where overall mortality was estimated as the summation of death from the PFS phase (2L) and the post-progression phases (3L, 4L and BSC). The death rates in each disease phase are estimated based on the phase-specific probability of death. Thus, we revised the header for Table 9 below (in *italics and underlined*) accordingly.

Detailed information for each data piece are presented in bullet points following the table.

Table 9: Data sources and rationale for data were used to inform the time-to-event parameters in the model

Line of therapy	Ibrutinib		Physician's choice	
	PFS	***Probability of death***	**PFS**	***Probability of death***
2L	PFS for ibrutinib from Study 1118E *	Probability of death during PFS: Assume the same as general population mortality	Ibrutinib reference curve + HR from multivariate cox regression model	Probability of death during PFS: Death during the PFS of mixed chart review cohort

3L	PFS was not directly modelled Time to progression during PFS of 4L treatment of the original chart review	Probability of death during post-progression: PPS of patients who progressed from 3L treatment of the original chart review	PFS was not directly modelled Time to progression during PFS of 4L treatment of the original chart review	Probability of death during post-progression: PPS of patients who progressed from 3Lline treatment of the original chart review
4L	PFS was not directly modelled Time to progression during PFS of 4L treatment of the original chart review		PFS was not directly modelled Time to progression during PFS of 4L treatment of the original chart review	
BSC	n/a		n/a	
PFS: progression-free survival; PPS: post-progression survival *The PFS represents the PFS of a population with distributions of lines of treatments as captured in Study 1118E (median receiving 3L treatment).				

Detailed information of each data source:

- PFS for ibrutinib
  - Model implication: To inform the PFS of ibrutinib and the reference curve for PFS of 2L physician's choice
  - KM data: please refer to data presented in tab "C10" (PFS ibrutinib 2L) in the MS Excel file submitted together with the clarification answers
  - Parametric fitting: Submission figure 20 and table 35
  - Data source: Study 1118E population (n=63)
  - Number of previous therapies received: median 2

- Death during the PFS of mixed chart review cohort (progression censored)
  - Model implication: To inform the death during PFS for 2L physician's choice
  - KM data: please refer to data presented in tab "C10" (TTP PC 2L) in the MS Excel file submitted together with the clarification answers
  - Parametric fitting: Submission figure 21 and table 36
  - Data source: matched chart review cohort (n=175)
  - Number of previous therapies received: median 2

- PPS of patients who progressed from 3L line treatment of the original chart review
  - Model implication: To inform the probability of death during 3L, 4L and BSC. Constant mortality rate was assumed for post-progression health states.
  - KM data: please refer to data presented in tab "C10" (PPS 3L) in the MS Excel file submitted together with the clarification answers
  - Parametric fitting: Submission table 38 and 39
  - Data source: original chart review cohort (n=454 at baseline, n=60 at progression of 3L treatment)
  - Number of previous therapies received: 3

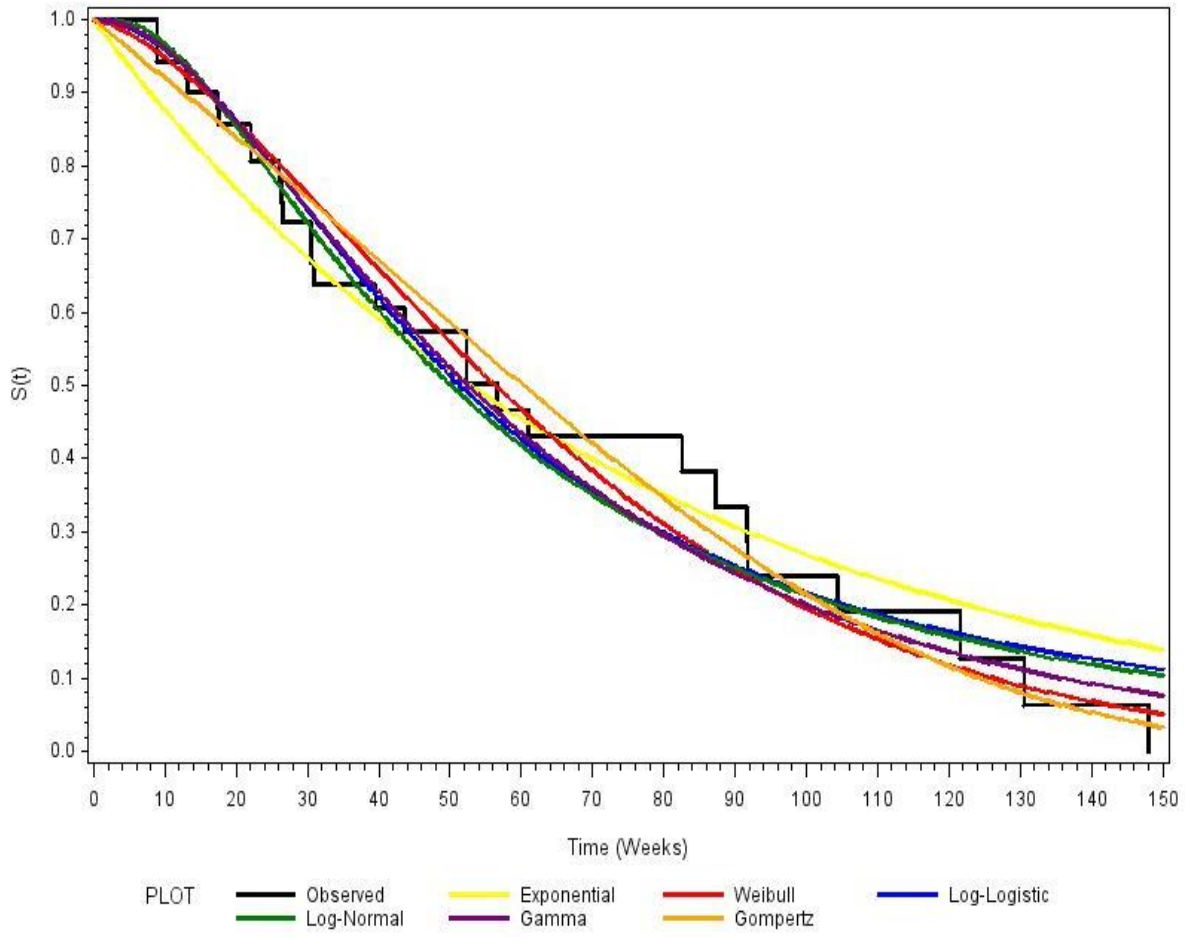
- Time to progression during PFS of 4L treatment of the original chart review
  - Model implication: To inform the probability of progression during 3L and 4L. Constant mortality rate was assumed.
  - KM data: please refer to data presented in tab "C10" (TTP 4L) in the MS Excel file submitted together with the clarification answers
  - Parametric fitting: (see Table 10 and Figure 3 below)

- Data source: original chart review cohort (n=454 at baseline, n=52 at start of 4L treatment)
- Number of previous therapies received: 3

Table 10: Time to progression during PFS of 4L treatment of the original chart review - parametric fitting

Analysis	Intercept	SE	Scale	SE	Shape	SE	AIC	BIC
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	97.579	101.801
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	97.552	101.774
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	99.439	103.661
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	102.632	104.743

Figure 4: Observed and predicted distributions



C11. **Priority:** Section 5.3, page 85, Figure 20. Please provide an amended version of the Kaplan-Meier chart showing numbers of patients at risk over time.
For an amended version of the Kaplan-Meier chart showing numbers of patients at risk over time, please refer to the 4 tabs for "C10" in the MS Excel file submitted together with the clarification answers.

C12. Section 5.3, page 87. The text states "A parametric fitting was conducted for OS of this cohort; an exponential function (see Table 38) was found to be the best fit." Please explain

how goodness-of-fit was judged in this instance. Please also provide the Kaplan-Meier curves for PFS and OS for the time-to-event data used to inform the 3L and 4L PFS and OS estimates together with the accompanying parametric curve fits.

A parametric fitting was conducted for the survival of patients who progressed from 3L treatment from the chart review. An exponential function was found to be the best fit according to the BIC goodness-of-fit statistics and is was found to be the second best fit (following log-normal) according to AIC. To accommodate the Markov model structure, exponential was chosen for model base case. Exponential indicates a constant hazard of death regardless of treatment. Therefore, a constant probability of death was assigned to 3L, 4L, and BSC. The probability of progression was explained in response to question C10 above.

There was no direct PFS estimation for 3L and 4L in the model. The probability of progression and the probability of death in 3L and 4L were separately informed in the model. Probability of progression was explicitly modelled based on parametric fitting to the time to progression of 4L treatment (death censored) in the chart review. Please see response to C10 for detailed information on the KM and the parametric fittings.

For further information, please refer to the four tabs for “C10” and in tab “C11” in the MS Excel file submitted together with the clarification answers.

C13. **Priority:** Section 5.3, page 88, Table 38. With respect to the probabilities of progression and death for 3L and 4L, please clarify whether progression events have been censored for death and whether death events have been censored for progression (thereby dealing with competing risks).

For the derivation of probability of progression of 4L in the chart review, death events occurring during the PFS of 4L treatment were censored. The survival of patients who progressed from 3L treatment was estimated as the post-progression survival of the 3L treated patients from the chart review. A constant hazard of death was assumed for all three post-progression health states (3L, 4L and BSC). Thus, competing risk was avoided in the model.

C14. Section 5.4, page 91, Table 42.

a) Are these data QALY losses per cycle?

The decrements described in Table 42 represent the QALY losses associated with AEs for ibrutinib and PC. The sources of the utility decrements are presented in Table 40. The duration of AEs was assumed to be 14 days, and the QALY decrements presented in Table 42 are based on the frequency of occurrence of each AE (Table 49). These calculations are presented in the AE worksheet (cells AE32 to AE37) of the original cost-effectiveness model. The decrements were applied as a one-off decrement at treatment initiation.

b) Also, the disutility of adverse events for physician’s choice presented in Table 42 does not match the disutility used in the model (Worksheet “Utility” cell J20). Please clarify.

The correct value for decrement of QALYs associated with AEs in the PC arm is -0.0031, i.e. the value in the model is correct but there is a typographical error in Table 42 of the submission.

c) Also, please explain why disutilities/QALY losses associated with AEs were not included for subsequent lines of therapy?

Disutility of AEs was only considered for the primary model comparators (i.e. in 2L) and not for the subsequent treatments. This is a simplification of the real world for the purpose of the economic model. Given that the AE cost is relatively small and the disutility of AE is only

applied to a 14 day period, considering AE for subsequent treatment will have minimal impact to the result. Furthermore, the same treatment pathway was assumed for the post-progression phase of both treatment arms.

C15. **Priority:** Section 5.4, page 92. [redacted] relapsed/refractory mantle cell lymphoma [redacted]

The assumption of improved HRQoL for patients receiving ibrutinib due to the avoidance of chemotherapy in the ibrutinib R/R MCL submission was based on strong and consistent anecdotal evidence and clinician opinion. UK trial centres were involved in all three R/R MCL trials for ibrutinib (with 54 UK patients enrolled across the three trials), a compassionate use programme was in operation between August 2014 to March 2015, with a total of 154 patients benefitting across England. In addition, ibrutinib has been available on the Cancer Drugs fund from January 2015 to the present, with very high uptake. These factors mean that there is considerable experience amongst patients and treating clinicians in the R/R MCL disease, giving confidence to the assumption that there is a considerable HRQoL benefit for ibrutinib over chemotherapy.

In the MCL submission, better HRQoL for patients receiving ibrutinib due to the avoidance of chemotherapy-related toxicity and fatigue was assumed. In the base-case analysis, an R-chemo decrement of 0.2 was used based on KOL opinion. A scenario analysis was conducted on this input using the estimate from Schenkel et al. 2014[5]. The Schenkel et al. study reported a mean utility of 0.61 using the EQ-5D VAS for 23 patients receiving treatment with antineoplastics for R/R MCL.

In contrast, the R/R WM trial was carried out only in US trial centres and there has been no compassionate use programme or CDF funding for ibrutinib in WM. While there is currently limited evidence specifically within WM upon which to base this assumption, there is no reason to believe that the same HRQoL benefit for ibrutinib due to the avoidance of chemotherapy-related toxicity and fatigue will not be seen in WM.

Table 11 and Table 12 below show the impact on the base-case ICER (at list price) if this assumption from the R/R MCL ibrutinib modelling is applied to the WM model: the impact on the WM updated base-case ICER (£78,647) is minimal.

Table 11: Decrement based on KOL opinion

Technologies	Total costs (GBP)	Total QALYs	Incremental costs (GBP)	Incremental QALYs	ICER incremental (QALYs) (GBP)
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	78,071
Physician's choice	[redacted]	[redacted]			

Table 12: Decrement based on Schenkel et al., 2014

Technologies	Total costs (GBP)	[redacted]	Incremental costs (GBP)	Incremental QALYs	ICER incremental (QALYs) (GBP)

[5] Schenkel B, Naim AB, Roland B, et al. Patient-Reported Experiences with Treatment of Chronic Lymphocytic Leukemia (CLL) and Mantle Cell Lymphoma (MCL): Results of a Quantitative Survey. Blood 2014;124:5442-5442.

Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	76,831
Physician's choice	[redacted]	[redacted]			

C16: **Priority**: Section 5.5, page 93, Table 44. Please provide further detail regarding how the resource use frequencies included in the table were elicited from experts.

As explained in Appendix 4 of the original submission, "A questionnaire was developed by Janssen that aimed to collect information on treatment practices and medical resource utilisation (MRU) based on the NHS experience of five key opinion leaders (KOLs) who practice in England in treating adult WM patients who have received at least one prior therapy. This appendix summarises the answers that the KOLs provided both in writing and verbally in a follow-up call in May 2016. Responses have been aggregated to reflect current clinical practice in five centres across England."

The MRU frequencies presented in Table 44 on page 93 are therefore aligned with the data presented in Table 26 in Appendix 4 (page 29).

C17: **Priority:** Section 5.6, page 101, Table 52. The text states “The same post-progression efficacy was assumed for both ibrutinib and PC.” The model however suggests that considerably more life years are gained after discontinuing ibrutinib compared with 2L physician’s choice (4.18 life years versus 2.83 life years, undiscounted). Please comment on the validity of this model result.

In the model it was assumed that the post-progression efficacy for any patients who progressed from ibrutinib or 2L physician’s choice was the same regardless of the previous treatment history. The mean post-progression survival results were dependent on the proportion of patients who progressed. Because ibrutinib was shown to have a lower death rate during PFS than the 2L physician’s choice, more patients remained alive and were thus eligible to progress in the ibrutinib arm than in the 2L physician’s choice arm. The percentage of patients who progressed and the percentage of patients dead during PFS can be calculated as the summation of column I and column H in the model engine tab. In the base case analysis, 95.4% of ibrutinib treated patients progressed and 4.6% of ibrutinib treated patients died during PFS, whereas 63.6% of physician’s choice treated patients progressed and 36.4% physician’s choice treated patients died during PFS. The difference in the percentage of patient progressed results in higher mean PPS for the ibrutinib arm, even though the post-progression efficacy of ibrutinib and physician’s choice were modelled to be the same.

C18: Section 7, page 121. The text refers to the WM patient population having “an extremely poor prognosis”, yet the model suggests an undiscounted survival of 4.36 years for the comparator group. Please clarify.

WM can be an indolent disease and prognosis in this statement refers not only to the likely course of the disease but also the quality of life a patient will experience during their time with the disease. Current treatment options are not effective; this unmet need not only means that prognosis in the traditional sense of the word is poor but the negative emotional impact of having limited (and no licensed) treatment options until recently confounds the prognosis further in terms of the HRQoL.

C19: **Priority:** Section 7.2, page 123. Given the uncertainty surrounding long-term benefits of ibrutinib in terms of PFS and OS, please justify why the data collection in the registry will be only a minimum of 2 years.

As per the email dated 19/07/2016 from Henry Edwards (NICE), "They [the ERG] acknowledge that the rationale that they were seeking is contained within the submission document as you suggested. Therefore they note that there is no need to answer that question".

Consequently Janssen has not provided an answer to this question.

Model

C20: Worksheet "Clinical Data" The parameters for the alternative distributions (e.g. log logistic for Ibrutinib PFS, cells P5:P6 and log normal for mortality risk, cells H5:H6) are not included as uncertain parameters in the probabilistic sensitivity analysis. Please comment.

As per an email from Henry Edwards (NICE) dated 27/07/2016, the ERG further clarified that the aim of this question was to understand "why the model does not include the functionality to fully assess all candidate survivor functions, both probabilistically and deterministically".

Janssen would like to refer back to the rationale provided for question C22 below: while we have explored several survivor functions, only the most robust functions were retained for the submission. An analysis using the log-logistic distribution for PFS was presented as a scenario analysis.

Should the ERG feel that additional analyses (both deterministic and probabilistic) using the outstanding survivor functions would be informative, Janssen would be happy to include this functionality in an updated version of the model.

C21: Worksheet "Markov RR (Ibr)", column AJ. Please clarify why a significant number of the logical consistency checks return a value of "FALSE"

This is a rounding issue with Excel. The logic which is tested in column AJ will all appear as "TRUE" when the equation is reset to "=IF(AND(AH5+AB5+U5+N5+G5<1+0.1^10,AH5+AB5+U5+N5+G5>1-0.1^10),TRUE,FALSE)" from "=IF(AH5+AB5+U5+N5+G5=1,TRUE,FALSE)".

C22: Worksheet "Clinical Inputs". Why are only log normal and Weibull PFS functions considered in the model?

To extrapolate Study 1118E KM PFS data beyond trial follow-up, a Weibull distribution was selected for the base-case analysis and the impact of using a log-logistic (not log-normal, as suggested by the ERG in question C22) distribution was explored in a scenario analysis, as explained on p84 of the original submission.

Janssen did not include the log-normal and exponential distributions in the model because, based on goodness of fit statistics, visual inspection, and long-term clinical plausibility, Weibull and log-logistic were deemed the overall more appropriate parametric fittings to explore (exponential has the third lowest AIC following Weibull and log-logistic; log-normal has a long tail which is deemed clinical implausible in the long term).

We would be happy to provide this additional functionality within the model, adding the options of modelling with exponential and lognormal functions.

C23: Worksheet "Parameter", cells D38:D39; D41:D42; D44. These are referred to as hazards (rates) but appear to be applied as probabilities. Please clarify.

Constant hazard of [redacted] and [redacted] for each 4 week-cycle was assumed for progression and death during post-progression, respectively. These inputs were used as transition probabilities for each model cycle.

These input values were estimated based on an exponential fitting of time to event data. The hazard of progression was estimated by fitting the original chart review time to progression data of patients in 4L treatment. The hazard of death during post-progression was estimated from fitting the original chart review PPS data of patients who progressed from 3rd line treatment (details presented in response to [C10]).. The exponential fitting parameters are presented in Table 13 below:

Table 13: Exponential fitting parameters

	Progression	Death
Exponential time unit	4.3348 (0.1857)	5.4809 (0.2085)
Exponential intercept	Week	Week
Constant hazard per 4 week cycle	[redacted]	[redacted]

C24: Worksheet “Clinical Data”, column K. The following formula is applied to generate the HR-adjusted hazard rate: hazard/HR. Please confirm that this calculation is correct ([redacted]

In the submitted WM model, the HR is applied on a model cycle basis. [redacted] as the approach used in the WM model does not use continuous integration.

In the current approach, the hazard function is derived using changes in predicted survival probabilities for ibrutinib arm, such as HazardRate(t)ibrutinib(=[S(t) ibrutinib -S(t+1) ibrutinib]/S(t) ibrutinib. For the comparator arm, the hazard function is derived as HazardRatecomparator as HazardRateibrutinib/HR. The survival for comparator arm is then estimated by S(t+1)comparator=S(t)comparator*(1-HazardRate(t)comparator). When the difference in t(1) – t(2) tend towards zero, the two different approaches will produce identical results.

[redacted]

[redacted] by updating the calculation in the worksheet “Clinical Data”, column L for PFS of current care. Implementing the revision has a very minor impact on the base-case ICER, decreasing the ICER from £78,647 in the submission to £78,610/QALY gained (at list price) as shown in Table 14.

Table 14: Updated ICER using MCL HR formula

Technology (and comparators)	Total costs (£)	Total life years	Total QALYs	Incremental costs (£)	Incremental life years	Incremental QALYs	ICER versus baseline (£)
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	78,610
PC	[redacted]	[redacted]	[redacted]				
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years							

Section D: Additional analyses requested
Please conduct re-analyses of the health economic model which include:

D1. **Priority:** Re-fitting the PFS and mortality data for second-line physician's choice taking into account competing risks (i.e. censor post-progression death events in the OS curve). Please apply these curves in the model and present the new curve fits in the clarification response.

Please see response to question C9. Patients who progressed were censored in the KM curve of time to death during PFS for PC (please refer to Figure 21 on p86 of the original submission). Thus, post-progression deaths were excluded from the submitted analysis and no additional analyses are provided.

D2: **Priority:** Providing the hazard ratio from the full multivariable Cox model and applying this to the model taking account of Point D1 described above.

As stated in the response to question B26, the hazard ratios used in the model were based on the full multivariable Cox model. Therefore no additional analyses are provided.

D3: **Priority**: Undertaking a matching adjusted treatment comparison using Study 1118E and the European Chart Review for second-line treatment and applying this in the health economic model as a scenario analysis, taking account of Point D1 described above.

As stated in the response to question B28, the Cox analyses are deemed more appropriate and more robust given the data available relative to an MAIC. Therefore no additional analyses are provided.

Single Technology Appraisal (STA)
Ibrutinib for treating Waldenström's macroglobulinaemia [ID884]

Email request from NICE dated 01/08/16

Dear Anne,

The Evidence Review Group, ScHARR-TAG, and the technical team at NICE have looked at the response to the points for clarification received on 26 July 2016 from Janssen. In general they felt that most points for clarification were responded to well. However, the ERG would like to seek further clarification on one point that will aid their review of your submission.

Request:
Regarding question C9 (the second-line survival curve from the European Chart Review, shown in Figure 21 of the company submission), Janssen's response states that there were inaccuracies in the submission and that the curve shown in Figure 21 is actually pre-progression survival rather than overall survival. As a consequence of these errors, the ERG did not request the overall survival curve from this cohort during clarification as they believed they already had this information.

The ERG would therefore like to request the overall survival Kaplan-Meier curve (or underlying time-to-event data) for the population used to produce the pre-progression mortality curve shown in Figure 21 of the company submission.

Given that the clarification response deadline has passed, NICE understands that this is an additional request that Janssen may not be able to respond to it. Please can you confirm by the end of the day whether you are able to respond to this additional request.

If you are able to provide a response to the ERG additional clarification request, the deadline for your response is **9:00am, Friday 5th August 2016**.

Your response and any supporting documents should be uploaded to NICE Docs via this link:
https://appraisals.nice.org.uk/request/14812

Please can you submit two versions of your written response; one with academic/ commercial-in-confidence information clearly marked and one with this informatio removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Henry Edwards, Technical Lead (henry.edwards@nice.org.uk). Any procedural questions should be addressed to Liv Gualda, Project Manager (Liv.Gualda@nice.org.uk).

Yours sincerely

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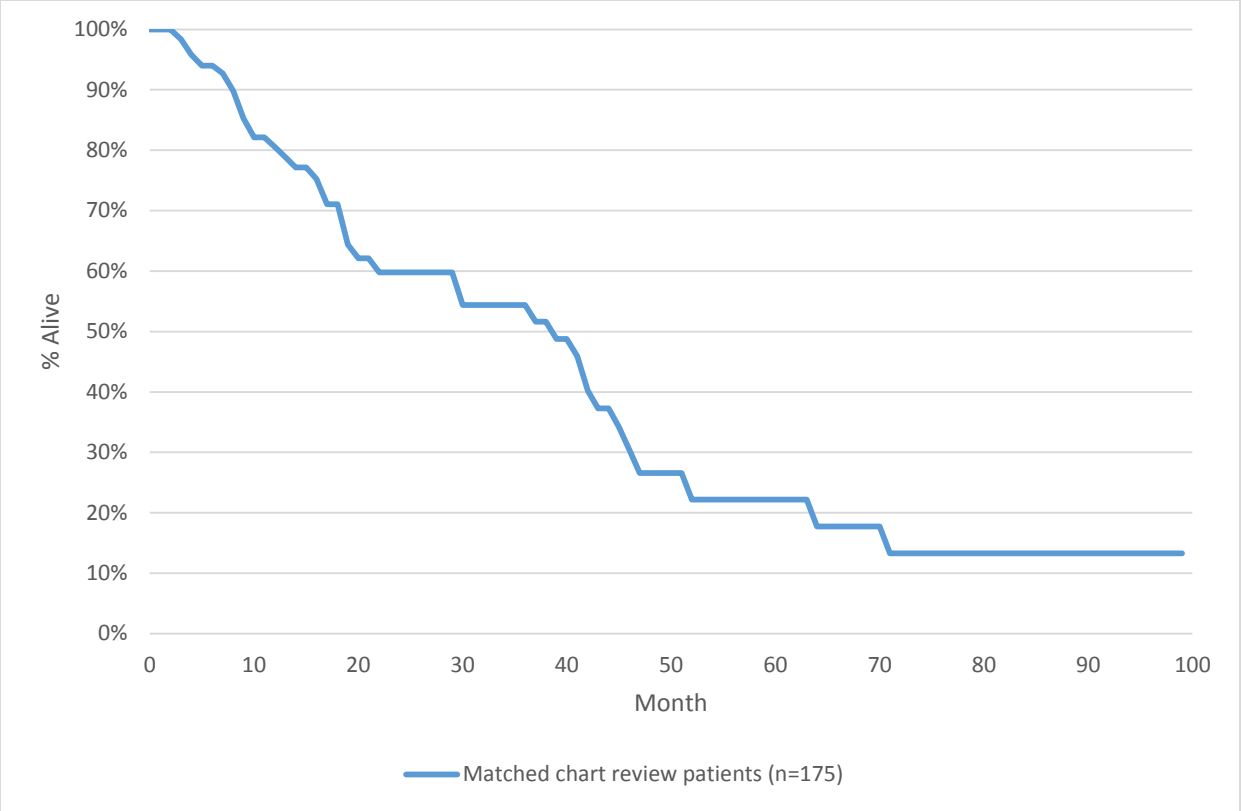
Janssen response to NICE dated 04/08/16

With respect to the follow-up query from the ERG relating to question C9 from the Clarification Questions, please find below Figure 1 which illustrates the overall survival (OS) Kaplan-Meier (KM) data for the matched chart review cohort (n=175) which is the population used to produce the pre-progression mortality curve shown in Figure 21 of the company submission.

Figure 1: OS KM curve for the population used to produce the pre-progression mortality curve shown in Figure 21 of the company submission



NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Ibrutinib for treating Waldenström's macroglobulinaemia [ID884]

1. About you and your organisation

Your name:

Name of your organisation: Lymphoma Association

Your position in the organisation: Chief Executive

Brief description of the organisation:

The Lymphoma Association is a national charity, established in 1986, which provides high quality information, advice and support to people affected by lymphoma (lymphatic cancer). We also provide education, training and support to healthcare practitioners who care for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the only UK charity which specialises in providing support and information on lymphomas.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

WM usually develops over many months or years. Patients may have no symptoms at all to start with. Some people with WM are diagnosed by chance, during a routine blood test or an investigation for another condition.

Most people with WM (and other types of lymphoplasmacytic lymphoma (LPL)) have abnormal B cells and plasma cells in their bone marrow. The bone marrow is then not able to make as many normal blood cells as usual. This can cause:

- anaemia (shortage of red blood cells), leading to tiredness, weakness and breathlessness
- neutropenia (shortage of neutrophils, a type of white blood cell), leading to an increased risk of infections
- thrombocytopenia (shortage of platelets), leading to a tendency to bruise and bleed easily.

Many people have symptoms related to hyperviscosity because of high levels of abnormal immunoglobulins in their blood, which can lead to eye complications and the need for further treatment.

People with WthM can also experience fevers, night sweats and weight loss, which are also symptoms of many types of lymphoma.

Enlarged (swollen) lymph nodes are less common in people with WM than with other types of lymphoma. However, around 1 in 5 people with WM have swollen lymph nodes or a swollen spleen. A swollen spleen can cause discomfort or pain in your abdomen.

WM can be difficult to live with and treat with compared with some other lymphomas. It can present in many different ways, with a constant threat of relapse in different forms after partial responses. This puts a huge burden on patients, carers and the NHS.

Treatment side effects are substantial and often permanent such as peripheral neuropathy, tinnitus and digestive tract dysfunction.

Patients are concerned with potential transformations, many treatment induced, eg, Richters (usually to diffuse large B-cell lymphoma), melanomas, Bing-Neel syndrome and amyloidosis and the need to use stem cell sparing therapies avoiding purine analogues such as cladribine and fludarabine in case of later stem cell transplant.

WM and the treatments currently used can compromise the immune system of patients and in turn lead to unplanned hospital visits and changes in lifestyle (such as limiting travel or appearance in public places). Long term effects of treatment and disease cause general deterioration in the immune system, leading to adventitious infections and organ failure.

Even reasonably effective treatment may leave constant fatigue – something reported by most patients.

Although generally classed as an indolent non-Hodgkin lymphoma, for a substantial minority it is far from indolent, with 38% higher grade patients at diagnosis (EBMT data 2015), particularly in increasing numbers of younger working patients with poor genetic prognostics.

Since the removal of Bortezomib from the Cancer Drugs Fund in 2015, there are limited treatment options for relapsed/refractory patients, with clinicians depending on 'trickle down'/off-label uses from related B-cell diseases such as chronic lymphocytic leukaemia, on a trial and error basis, which is less than satisfactory.

In preparing this submission we have taken account of the views and experience of patients as expressed in surveys carried out by Waldenstrom's Macroglobulinaemia UK (WMUK) in 2014 and 2016 (which we have supported and disseminated through our own patient networks), and from patient surveys on ibrutinib carried out by Lymphoma Canada (again which we have supported through our own networks) .

The patient views and experiences demonstrate unmet treatment need and the depth of feeling towards the lack of effective, long lasting treatments, together with hidden costs to both patients, carers NHS, and society.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Patients and carers in this small, but well-connected, community of patients are anxious and concerned about the likely treadmill of treatment, relapse and retreatment that will or does dominate their lives, leading to inevitable reduction in their immune systems and consequent infections. They are keenly aware of the lack of any specific treatment or standard of care for WM, despite the existence of BSH guidelines.

Patients want to be in a good remission for as long as possible, so quality and duration of remission following treatment, whether this is the initial treatment or treatment at relapse are important. They also want any symptoms or signs of their WM to resolve. However, as WM is an incurable condition, quality of life is also very important, so patients want a treatment that is as well tolerated as possible with the least detrimental effect on their quality of life.

In the 2016 WMUK survey, out of 231 responses, the following priorities were highlighted about treatments and treatment outcomes:

- 84% of patients rated "bringing about a remission" as 10 on a scale of importance going from 1 to 10 (with 10 being very importance) with 94% giving a rating of either 8, 9 or 10).
- 73% of patients rated "controlling the disease's symptoms" as 10 on a scale of importance going from 1 to 10 (with 10 being very importance) with 93% giving a rating of either 8, 9 or 10).
- 82% of patients rated "allowing me to live longer" as 10 on a scale of importance going from 1 to 10 (with 10 being very importance) with 91% giving a rating of either 8, 9 or 10).
- 71% of patients rated "improving quality of life" as 10 on a scale of importance going from 1 to 10 (with 10 being very importance) with 88% giving a rating of either 8, 9 or 10).
- 78% of patients rated "bringing about a remission" as 10 on a scale of importance going from 1 to 10 (with 10 being very importance) with 93% giving a rating of either 8, 9 or 10).
- 77% of patients rated "reducing strain on carer" as 10 on a scale of importance going from 1 to 10 (with 10 being very importance) with 81% giving a rating of either 8, 9 or 10).

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

In the 2016 WMUK survey, just over 200 patients reported experience of on or more of the following treatment regimes (the percentage of patients having experienced each regime is included in brackets):

- FCR (fludabrine, rituximab, cyclophosphamide) (25% of patients)
- Chlorambucil (19%)
- Bortezomib + rituximab (8%)
- DRC (dexamethasone, rituximab, cyclophosphamide) (20%)
- BR (bendamustine, rituximab) (24%)
- BDR (bortezomib, desamethasone, followed by rituximab) (3%)
- R-CHOP (17%)
- R-ESHAP(or other conditioning regime for autologous stem cell transplant) (5%)
- Autologous stem cell transplant (7%)
- Allogeneic stem cell transplant (1%)
- Rituximab maintenance (15%)

47% of the patients who responded had been on a watch and wait regime prior to treatment.

Available 'off label' treatments have substantial drawbacks in terms of depth/ length of remission and side effects. Many induce slow responses during which symptoms persist - up to 9 months' duration is common.

Patients find current treatments far less acceptable than clinicians. For example, FCR, which is commonly used and may be regarded as 'tolerable' by many clinicians, appears to be unacceptable with 20% of

patients reporting it as intolerable due to its effects, or not completing the target number of cycles - both for psychological and physical effects. The severe mood-altering properties of corticosteroids which accompany most chemotherapies are understated. Concern for neutropenia often dominates the time between cycles, and may need GCSF support administered by GPs or community nurses.
Choice of treatment seems random, almost postcode prescribed, particularly in smaller centres where clinician's choice or hospital policy determines treatment. Patients were offered a treatment choice in only 18% of cases, according to the 2016 WMUK survey.

Unplanned admissions or GP visits directly related to treatment was reported in 54% of cases in the 2016 WMUK survey. More tolerable treatments would presumably reduce the need for and number hospital admission or GP visits, which in turn would have a significant impact on NHS resources and efficiency savings, let alone delivering improved patient experience.

Options such as autologous stem cell transplants are not offered in some areas of England, but are common in London. In Europe 546 WM patients were transplanted over the last 10 years. (EBMT Data).

Multiple treatments and relapses mean clinicians may run up against lifetime chemotherapy limits for liver and kidney functions.

96% of WMUK's surveyed patients agreed that there was a need for more treatment options for WM.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Ibrutinib would be expected to improve WM patients' quality of life and experience of care. Many people with WM will be aware of the treatment being available in the US and being available in the UK via the CDF for other lymphoma subtypes (including CLL). They will also be aware of its reputation as a breakthrough or innovative treatment in its field. Given that it is administered orally (which is convenient and preferable to most patients as set against traditional chemotherapy regimes), and has limited and manageable side-effects and a well-tolerated toxicity profile, it is seen as a step-change in the management of WM.

Most patients with experience of ibrutinib state that the side effects are mild with minimal tolerability issues (far less so than with chemotherapy or infused/injected treatments). Just under half the patients we've heard from cited negative side effects from ibrutinib, including joint/muscle pain, fatigue, diarrhoea, dry/cracked fingers, rashes, light-headedness. A majority of patients noted positive side effects, including lymph node reduction, increased energy, no nausea, no loss of appetite, no neuropathy, no hair loss and no back pain.

Most patients with experience of ibrutinib are also very positive about the prospects for their long-term health and wellbeing. As one patient put it:

"Yes, I would highly recommend it. Ibrutinib kept my lymphoma stable for 2 years."
[Man, aged 65-74; previous treatments inc R-chop;

vincristine; stem cell transplant; radiotherapy; bendamustine + rituximab]

Carers and patients' families also benefit from the use of ibrutinib. The fact that it is an oral treatment that can be taken at home makes for a number of advantages in terms of administration and monitoring of the treatment.

The milder side effects and improved efficacy mean patients can regain a good quality of life, have fewer hospital visits/less travel and contribute more to society. This has a corresponding impact on carers and patients' families and reduces the level of difficulties associated with living with WM.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

- Ease of use and oral administration has had a transformational effect on quality of life, not least the time spent in treatment, particularly with current extended rituximab infusion times, travelling to remote centres and staying for extended periods. Most infusion-based regimes also need blood tests (with kidney and liver function) the day before. 8-10 hours per session is not unusual.
- Avoiding traditional chemotherapy enables the ibrutinib patient to be active almost immediately and return to normal life and work sooner, needing less care from side effects and unplanned admissions and worry of relapse, which are common at present.
- As a targeted therapy related to WM specific MYD88 and CXCR4 mutations, ibrutinib is superior in every way to established chemotherapies, and its action and widespread reimbursement in health systems in Europe and Canada is well known by UK patients, who see the transformational effect on the treatment landscape of WM.
- Avoidance of traditional and life-long damaging side effects are virtually eliminated, while if resistance becomes a feature in the long term, then treatment with other evolving small molecule inhibitors is not precluded. There is no current evidence of long term immunosupression and increasing evidence that ibrutinib crosses the blood/brain boundary unlike other common chemotherapy, and thus it would be useful in treating Bing-Neel syndrome.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

We are not aware of any significant differences of opinion, although there are a small number of WM patients for whom ibrutinib will be less effective due to the combinations of the MYD88 L256p and CXCR4 mutations. This is usually identified early on in treatment.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

The only disadvantages are the side effects noted above (although these are much more tolerable than existing treatments), along with the high list price.

Please list any concerns patients or carers have about current NHS treatments in England.

Please see our answer to question 3. Ibrutinib would avoid most, if not all, of the difficulties listed. The side effects such as bruising and need for cessation during surgery are tolerable and most appear to reduce with time or through short term dose reduction.

Current treatments used and designed for other lymphomas have unacceptably low response rates, relapses, considerable long term side effects and poor quality of life.

Please list any concerns patients or carers have about the treatment being appraised.

The only fundamental concerns that patients have about ibrutinib and its appraisal is that it won't be recommended for use on the NHS and that they will be denied access to an effective treatment in England, that can be part of turning WM into a chronic disease.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

We're not aware of any differences of opinion.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

- Younger patients with families and those who have more aggressive forms/poorer prognosis WM.
- Patients who are Rituximab intolerant who currently have *no* options. Increasing rituximab intolerance during treatment seems to be a particular feature of WM patients.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

- Those with prexisting conditions such as atrial fibrillation or other contraindications precluding treatment with ibrutinib that cannot be handled with temporary dose reductions.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

X Yes ☐ No

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

- Ibrutinib is not yet funded in the NHS, so there is no NHS treatment experience in WM. However the 2016 WMUK patient survey found that those treated with Ibrutinib privately found it less challenging than even *watch and wait* for themselves and their families.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

- Yes, from the published data, via feedback from patients in North America, and through online for a, the trials experience is representative of actual practice. It has now been routinely used for up to 4 years with few adverse events and turned it into a chronic disease. The trial was so short as the result was so emphatically positive.
- Bearing in mind that the trial took place in the major USA tertiary centre catering for problematic WM cases, in a heavily pre-treated population (up to 9 lines of treatment), the results were remarkable and have been unchallenged.
- We are concerned that the data may be regarded as insufficient by NICE in terms of its Phase 2 status, maturity, small sample size and lack of quality of life data. In essence we fear that WM, as a rare disease, but not rare enough for treatment under HST, will be appraised against mainstream diseases and fall between two stools. It is well-know and inevitable that rarer diseases will generate

less certain trial results, and allowance must be made, as this disadvantages patients with rarer diseases.

- It seems inexplicable to patients and most clinicians that a drug that works so effectively and quickly, transforming treatment elsewhere, may be penalised because the median PFS has not been reached. The fact that very few patients die or relapse and the Kaplan-Meir curve is thus virtually flat should be a hugely positive factor, and the 'uncertainly' model adopted by NICE for more conventional chemotherapy should be recognised as inappropriate here.

- Common sense says that the model is inappropriate for such a transformational drug in WM, rather than the data being deficient.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

- N/A

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

X Yes ☐ No

If yes, please provide references to the relevant studies.

- As mentioned previously, the WMUK May/June 2016 treatment survey summary, which we understand they have supplied in full as part of their submission.

8. Equality

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Current treatments inevitably disadvantage older patients with co-morbidities – for instance just chlorambucil may be offered if old or frail. With some exceptions, ibrutinib could be used in these patients and reduce age inequalities. Increasingly, age of diagnosis is lowering, and we are in contact with younger patients of working age and with young families. These families who could continue to function near normally if offered Ibrutinib on relapse.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

- Ibrutinib being an oral medication effectively removes all elements of inconvenience that are such a strong factor in current treatment regimes.

9. Other issues

Do you consider the treatment to be innovative?

X Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

- The treatment is innovative in that it has a new mode of action and is well-tolerated. It will transform relapsed treatment through targeted therapy. Patient experience will be significantly improved. The current high cost of the treatment will be offset, at least in part, by cost savings, including a reduced burden on chemotherapy facilities, the increased availability of the latter for other patient groups and reduced time costs for healthcare professionals. There is less short and long term damage to body of the patient, and quality of life hugely improved.

Are there any other issues that you would like the Appraisal Committee to consider?

No.

10. Key messages

Key Messages **In no more than 5 bullet points, please summarise the key messages of your submission.**

- WM is complex disease that is not well-served in terms of the currently available treatments, which have significant side effects in many cases and high toxicity profiles, and limited effectiveness.
- Ibrutinib is the first targeted therapy for WM, with apoptosis of WM cells via MYD88 mutations in the BTK pathway targeted by ibrutinib. These mutations are not found in any quantity in other NHLs, and makes relapsed WM an ideal target in this very small population.
- Ease of oral administration is a significant advantage and reduces the burden on patients and carers almost immediately. Costs of medication and unplanned admissions balanced by reduced burden on chemo suites, families and society.
- Ibrutinib is an innovative treatment and is far better tolerated than existing chemotherapy-based regimes .

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)
Ibrutinib for treating Waldenström's macroglobulinaemia [ID884]

1. About you and your organisation

Your name:
Name of your organisation: WMUK (Waldenström's Macroglobulinaemia UK)
Your position in the organisation: Chair of Trustees, expert patient

Brief description of the organisation:

- Charity supporting patients, carers and doctors, through website, telephone, online forum, newsletters, doctor/patient meetings and research funding. Our board 50/50 doctors and patients, reflecting our integrated aim to improve treatment. We have closely knit community of 900, including 45 doctors. We provide a secretariat to WMUK Doctor Forum.

- Currently sponsors research in genetics of WM at Leeds University, the University College London Hospital WM Biobank and the independently run Rory Morrison UK Clinical WM Registry.

- Income is mainly from patients, carers and sponsored events run by individuals. We have a fundraising link with media through our patron, broadcaster Charlotte Green. We have no paid employees.

- Work closely with the IWMF- the USA based World WM organisation and the European WM network, where we provide 2 board members. In 2014 we co-hosted the world-doctor patient WM meeting in London with over 200 delegates.

- I'm a 66 year old WM patient of 13 years undergoing my 5th line of treatment and one of two expert patients. I'm a board member of the European WM network and attended 3 world physician meetings on WM. This submission contains patient views. Clinical input was jointly stated in our scoping submission and also separately given to the Committee by expert clinicians.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: NONE

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

- Unique features of WM make it difficult to live and treat compared with many lymphomas. Presenting in many different ways, with constant threat of relapse in different forms after partial responses. This puts a huge burden on patients, carers and the NHS. Numerous disease symptoms include IgM peripheral neuropathy, hypergammaglobulinaemia, confusion, weakness, hyperviscosity, tinnitus, cryoglobulinemia, cold agglutinin disease and later transformations.

- Current chemotherapy side effects are very substantial and often permanent such as peripheral neuropathy, tinnitus and digestive tract dysfunction.

- Patients are concerned with potential transformations, including many treatment induced – Richter's (usually to DLBCL), Melanomas, Bing-Neel syndrome and Amyloidosis and the need to use stem cell sparing therapies avoiding purine analogues such as fludarabine in case of later ASC transplant. Other complications such as hyperviscosity lead to eye problems and may need repeated apheresis.

- Treatment and WM immunocompromises patients, leading to unplanned hospital visits and change in lifestyle (such as limiting travel or appearance in public places). Long term effects of treatment and disease cause general deterioration in the immune system, leading to adventitious infections and organ failure. Expensive IVIG infusions may be needed to support failing immune systems.

- Even reasonably effective treatment may leave constant profound fatigue - almost ubiquitous in WM.

- Although classed as indolent NHL, for a substantial minority it is far from indolent, with 38% higher grade patients at diagnosis (EBMT data 2015[2]), particularly in increasing numbers of younger working patients with poor genetic prognostics. We are now seeing patients diagnosed in their 30s.

- Since the removal of Bortezomib by CDF for no clinical reason in 2015 (then the only UK funded therapy for WM), clinicians depend on 'trickle down'/off-label uses from related B-cell diseases such as CLL. This is totally unsatisfactory, the CDF actually reducing WM treatment options to save money is bizarre.

- Some non-specialist clinicians fail to tell patients that they have WM, or even recognise the disease as a distinct entity - and fail to ICD10code as 88.0, leading to inaccurate PHE statistics and patients lacking appropriate support. Having a WM indication approved would reduce this uncertainty.

- WM suffers as a rare disease - above the threshold of specialised commissioning, but lacking the clinical data generated for more common cancers, leading to no specific indications or disease algorithm. This is clearly inequitable in WM which now deserves a proper indicated treatment.

WMUK conducted patient **treatment surveys** to assess unmet need in 2014 and 2016. Summary 2016 results are presented as addendum A to support this submission and patient statements in Appendix B. They both demonstrate unmet treatment need and the depth of feeling towards the lack of effective, long lasting treatments, together with hidden costs to both patients, carers, the NHS, and society.

3. *Current practice in treating the condition*

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Patients and carers in this tiny, integrated community are rightly fearful of the inevitable treadmill of treatment, relapse and retreatment that dominates their lives, leading to reduction in their immune systems and consequent infections. They are keenly aware of the lack of any specific treatment or standard of care for WM, despite BSH guidelines. Appendix A shows the relative importance of treatment outcomes to patients, lack of effective options and harshness of existing treatments. The level of reported family disruption due to chemotherapy is particularly distressing.

- **What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?**

  - Available 'off label' treatments have substantial drawbacks in terms of depth/ length of remission and side effects. Many induce slow responses during which symptoms persist- up to 9 months common. Many patients and carers feel they never get clear of the treatment treadmill.

  - Evidence is gained from close contact with patients and clinicians, doctor/patient meetings, WM doctor forum, our database and information gained from the May-June 2016 patient treatment survey, gaining 280 responses in 14 days; a totally extraordinary response for this small community.

  - Patients find current chemotherapy far less acceptable and more disruptive than clinicians. For example FCR which is common and regarded as 'tolerable' by clinicians, appears to be unacceptable with 20% reporting it as intolerable or not completing target number of cycles - both

for psychological and physical effects[1]. The severe mood-altering properties of corticosteroids which accompany most chemotherapy are underestimated Concern for neutropenia often dominates the time between cycles, and may need GCSF support administered by GPs or community nurses.

- Choice of relapsed treatment seems random, almost postcode prescribed, particularly in smaller centres where clinician's choice or hospital policy determines treatment. Patients were offered a treatment choice in only 18 % of cases[1]. Ibrutinib approval would create a standard of treatment.

- Unplanned admissions or GP visits *directly related* to treatment was 54%[1]. Many events are neutropenia related. Can this be an effective use of NHS resources, and is it costed by NICE?

- Auto SC transplants are not offered in some areas, but common in London but seem to have local funding problems. We note that this option was removed for some reason from the scope, despite being 8%[1] of treatment responses. In Europe, 546 WM patients were transplanted over the last 10 years. (EBMT Data[2]). **The fact that this very harsh treatment- termed by patients the 'nuclear option' is still acceptable, points to the lack of effective low impact alternatives in relapse.**

- Multiple treatments and relapses mean clinicians may run up against lifetime chemotherapy limits for liver and kidney functions.

- 96% UK patients questioned agreed that there was a need for more treatment options for WM [1]

4. *What do patients or carers consider to be the advantages of the treatment being appraised?*

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

- All of the above! Ease of use and oral administration has a transformational effect on quality of life where available, reducing time spent in chemotherapy, particularly with extended rituximab infusion times, travelling to remote centres and staying for extended periods. Most infusion-based regimes also need blood tests (kidney and liver function) the day before. 8-10 hour sessions are not unusual[1].

- Avoiding traditional chemotherapy enables the ibrutinib patient to be active almost immediately and return to normal life and work, needing less care from side effects, unplanned admissions and worry of relapse, which are common at present.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

- As a targeted therapy related to WM-specific MYD88 and CXCR4 mutations, ibrutinib is clearly superior in every way to 'hand me down' chemotherapies, and its action and widespread reimbursement in health systems in Europe and Canada is well known by UK patients, who see the transformational effect on the treatment landscape of WM. 78% of patients surveyed (including untreated) had heard of ibrutinib treatment and its advantages.[1]

- Avoidance of traditional and life-long damaging side effects virtually eliminated, whilst if resistance becomes a feature in the long term, treatment with other evolving small molecule inhibitors is not precluded. There is no current evidence of long term immunosuppression and increasing evidence that ibrutinib crosses the blood/brain boundary unlike other common chemotherapy, and thus be useful treating Bing-Neel syndrome.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

- No. There are a small minority of patients of whom ibrutinib will be less effective due to combinations the MYD88, L256p and CXCR4 mutations. This is usually identified very early in treatment.
- Most patients expect this drug to be available as they have seen the transformational effect in the USA and many speak online through fora to USA patients.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

- **No disadvantages,** with the exception to those having contraindicated conditions such as atrial fibrillation, which usually fade with time or with temporary dose reduction.

Please list any concerns patients or carers have about current NHS treatments in England.

- **See 3 above.** (and all of the disadvantages on the panel in 4 above). Ibrutinib would avoid most, if not all, of the difficulties listed above. The side effects such as bruising and need for cessation during surgery are tolerable and most appear to reduce with time or short term dose reduction.

- Current treatments used, handed down from other lymphomas have unacceptably low response rates, relapses, considerable long term side effects and poor quality of life. Chemotherapy causes immense disruption to family life and work.

Please list any concerns patients or carers have about the treatment being appraised.

- There are grave concerns that the treatment, which clearly works for a vast majority of patients, turning WM into a chronic disease, will be denied to them in England due simply to funding.
- Delay in approving Ibrutinib in England after its European licensing in July 2015 after fast-tracking by EMA and FDA is of particular concern to relapsed patients. Patients know it is already funded in Denmark, Greece, Spain, Germany, Netherlands, USA and Canada and by IFAs in other EU states.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

- No, none raised in any of 280 responses[1].

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

- Younger patients with families and those who have more aggressive forms/poorer prognostics. Older patients with co-morbidities who cannot tolerate chemotherapy.

- Patients who are Rituximab intolerant (up to 20%, Personal Communication, Dr Steven Treon) who currently have *no* effective options. Increasing Rituximab intolerance during treatment seems to be a particular feature of WM patients.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

- Those with pr-existing conditions such as persistent atrial fibrillation or other contraindications precluding treatment with ibrutinib that cannot be handled with temporary dose reductions.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

X Yes ☐ No

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

- Ibrutinib is not yet funded in the NHS, so no NHS treatment experience in WM. However the WM patient survey [1] found that **those treated with Ibrutinib privately or on trial found it less challenging than even *watch and wait* for themselves and families**.

- With our submission we include details of two English patients who have long term experience of Ibrutinib, one on the Dana-Farber/Treon trial and one funded by insurance. Both cases mirror results shown in the Dana-Farber trial with few or no long term side effects.

- Dana Farber (personal communication) reports those treated long term with Ibrutinib (up to 4 years now in USA) show no different outcomes from the original trial.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

- Yes, from the published data, personal recent contact with USA patients, and through online fora trials experience is representative of actual practice. It has now been routinely used for up to 4 years in USA with no new adverse events and has turned WM into a chronic disease. The trial was so short and peer-reviewed published so soon, as the result was so emphatically positive.

- **Bearing in mind that the trial took place in the major USA tertiary centre catering for problematic WM cases, in a heavily pre-treated population (up to 9 lines of treatment), the results were remarkable and have remained unchallenged.**

- ***We are most concerned in the light of other indicated applications that data may be regarded as insufficient by NICE*** *in terms of its Phase 2 status, maturity and small sample size.* WM is a rare disease, but not rare enough for treatment under HST, so we fear that will be assessed under mainstream disease criteria and fall between two stools. We have strenuously pointed out previously in consultation that rarer diseases inevitably generate less certain results, and allowance must be made, as it disadvantages WM patients. This inequity bias against rarer diseases was emphatically acknowledged by Sir Andrew Dillon in his February 2015 Channel 4 interview.

- It seems inexplicable to patients and most clinicians that a drug that works so effectively and quickly, transforming treatment elsewhere may be penalised because say, the median PFS has not been reached. The fact that very few patients die or relapse and the Kaplan-Meir curve is thus abnormally flat should be a hugely positive factor, and the 'uncertainly' model adopted by NICE for conventional chemotherapy should be recognised as inappropriate here.

- Common sense says that such a transformational drug in WM should be judged solely on its merits and cost effectiveness, rather than the data being seen as lacking in some way.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

- N/A

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

X Yes ☐ No

If yes, please provide references to the relevant studies.

- WMUK May/June 2016 treatment survey summary (Annex A) provides unmet need evidence and poor quality-of-life data for existing treatments. A similar Canadian survey which successfully resulted in national funding showed similar results.

- We believe that further supporting data from a wider WM population may be published in later 2016 by Dr Meletios Dimopoulos at ASH. We do not believe this is a reason for further delay, however.

8. Equality

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Current treatments strongly disadvantage older patients with co-morbidities – for instance just Chlorambucil may be offered if older or frail. With some exceptions, ibrutinib could be used in these patients and reduce age inequalities. Increasingly, age of diagnosis is lowering, and we now deal with active patients with jobs and children. These families could continue to function normally if offered Ibrutinib on relapse.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

- Ibrutinib being an oral medication effectively removes all elements of inconvenience and access that are such a strong factor in current treatment regimes.

9. Other issues

Do you consider the treatment to be innovative?

X Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

- It will transform relapsed treatment through a targeted therapy increasing a specific WM cell death pathway. Patients' lives will be significantly impacted for the better. Cost of medication for this small group will be offset at least in part, by fewer burdens on chemotherapy facilities and increased availability for other patient groups. There is less short and long term damage to body and immune system of patients, and quality of life hugely improved. This external gain needs to be factored in.

Are there any other issues that you would like the Appraisal Committee to consider?

- WMUK raised funding from many sources for a professionally hosted, independently managed UK WM **clinical data registry** with integrated data mining tools and in-depth quality of life data, hosted by internationally registry firm Dendrite Clinical Systems. This operates within the NHS IT environment. It now has some 300 initial cases logged. This was driven by a very patchy WM outcomes record in various cancer registries and links with WM UK Biobank DNA results.

- **Registry data layers were updated in step with NICE/CDF evolution** so that data for conditional access under the new CDF within the 24 month timeframe (if required) can easily be extracted

under agreement. If this was agreed between manufacturer and CDF the rubric would specify registry data entry (a simple process) for each centre using ibrutinib. WMUK policy is to encourage centres of excellence, usually in large hospitals treating large numbers of WM patients. Ideally larger centres would treat a majority of Ibrutinib users, but it would be also easier for accounting purposes, as they use e-prescribing.

- We suggest that testing for MYD88 and CXCR4 mutations be part of the data, to refine the level of responses related to the nature of these mutations. Larger teaching hospitals already test in anticipation of relating targeted therapies to clinical outcomes.

10. Key messages

***Key Messages* In no more than 5 bullet points, please summarise the key messages of your submission.**

- **Ibrutinib is the first targeted WM therapy**. WM cell apoptosis via MYD88 mutations affecting the BTK pathway are targeted by ibrutinib. These are not found in any quantity in other NHLs. Thus relapsed WM is an ideal target for ibrutinib in this very small population - 92 English patients a year (based on the scoping document, as only 29.7% survey patients are relapsed[1]), with resulting low financial impact. Move to such personalised medicine is a key NHS objective. ***It just works in the vast majority of cases***, turning WM into a chronic disease where funded. This view is supported by most UK clinicians specialising in WM.

- **WM is a distinct rare entity** with unique problems and side effects. No standard of relapsed care, so 'postcode treatment' with high patient impact and modest responses common. Off-label treatments handed down from other B-cell conditions are the norm with responses that are slow to maximise depth of remission and very hard on patients and carers.

- **Oral administration** reduces the burden on patients and carers immediately. Costs of medication are abated by reduced burden on chemo suites, unplanned admissions, families and society. Ibrutinib treatment far better tolerated than harsh regimes, with few permanent side effects.

- **WMUK is concerned, in the absence of a published SOP,** this assessment will be scored against mainstream disease criteria, and not as a rare disease with appropriate lower data thresholds as was Bortezomib when removed from the old CDF.

- **WM Registry:** WMUK has invested substantial resources in a professionally hosted clinical data UK registry which is up and running. If ibrutinib were approved, the registry will monitor treatment responses to give feedback to clinicians. If only conditionally approved it can provide the anonymised clinical data demanded by NICE over the 24 month period.

[1] **Annexe A:** UK treatment survey May-June 2016 n=280 cases over 14 days.
Annexe B: WM patient statements (3) uploaded 17/06/2016
[2]**EBMT**= European Bone Marrow Transplant Registry
Annexe C: Letters of support from IWMF, Leukaemia Care and WMUK Doctors' Forum uploaded 17/06/2016

Annexe A WM Treatment Questionnaire Results - Preliminary analysis

The survey of 35 questions was open for 14 days closing the 9th June, open only to UK resident patients. It was designed to capture a snapshot of WM treatment in the UK and assess unmet treatment needs. 280 anonymous responses were received, the largest ever UK survey response in WM. Only demographic questions were compulsory. Some questions allowed further text response, generating over 2000 comments, and some typical ones are shown. 30% were answered by their partner/carer in conjunction with patient unable to attempt own response, using patient demographics. Only a selection of questions relevant to the appraisal are included.

1) Demographics

Average age of patients **58.8** Median age **59**

62% were male, **38%** female

Average time since diagnosis **10.5** yrs

Comment: this is a lower figure than nationally accepted, due to a bias in IT knowledge, but the age profile is reducing, bearing in mind the lag time since diagnosis.

Under 18 years old	0.0%
18-24 years old	0.0%
25-34 years old	0.0%
35-44 years old	2.9%
45-54 years old	12.4%
55-64 years old	28.1%
65-74 years old	41.3%
75 years or older	15.3%

2) Treatment

15% had been diagnosed with the precursor condition **MGUS**- Monoclonal Gammopathy of Unknown significance.

29% had relapsed after treatment- the population target of this assessment.

Average visit time for day **chemotherapy treatment 5 hrs** (excluding transplants)

22% found it difficult or somewhat difficult to access treatment. (distance to specialist centre, cost, parking etc)

9% had been treated privately

51% had unplanned admission or GP visits directly related to treatment complications.

5 patients had been on Ibrutinib. 4 funded privately and I on trial.

Tolerability of common treatments

Answer Options	Very tolerable 1	2	3	4	5	6	7	8	9	Intolerable 10	11 Discontinued	Rating Average	Response Count
FCR Fludabarine/Rituximab/Cyclophosphamide	4	6	3	8	5	4	5	7	0	3	8	5.94	53
Chlorambucil	17	2	1	4	5	0	0	4	0	0	5	4.00	38
Bortezomib (Velcade)+ Ritiximab	2	3	0	2	0	0	2	2	1	0	5	6.47	17
DRC Dexamethasone/Rituximab/Cyclophosphamide	4	3	6	3	3	3	5	3	4	1	5	5.83	40
BR Bendamustine/Rituximab	8	8	11	4	4	3	3	0	3	1	5	4.48	50
BDR Bortezomib/Dexamethasone followed by Rituximab	1	1	0	1	0	0	0	1	1	0	2	6.57	7
R-CHOP Rituximab,Cyclophosphamide, Doxyrubicin,Vincristine,Prednisolone	2	1	5	3	4	2	3	6	3	2	3	6.24	34
R-ESHAP or other conditioning regime for autologous stem cell transplant - but did not complete transplant - if completed,score below.	0	1	1	0	1	0	0	3	3	1	0	7.10	10
Autologous Stem Cell transplant (own cells)	0	1	1	2	1	0	0	2	4	3	1	7.40	15
Allogeneic Transplant (donor cells) ?	0	1	0	0	1	0	1	0	0	0	0	4.67	3
Rituximab Maintenance	7	10	2	2	3	2	0	3	0	1	1	3.65	31
Ibrutinib	2	1	0	0	1	0	0	1	0	0	0	3.40	5
Watch and Wait prior to treatment	42	14	11	8	6	3	1	6	1	4	1	3.07	97
Other (please specify and score).													82

The 'other 'category of 82 included a further 16 not treated (i.e watch and wait) and a mixture of the above, often forced by Rituximab intolerance (i.e FC) or' unusual' local clinical choices.

Comment: R-CHOP, FCR, BCR scored poorly. BR seemed acceptable. ASCT with harsh conditioning regimes were most unacceptable. Acceptance by patients as intensive salvage therapy shows the lack of options. **Small Ibrutinib sample scored better than watch and wait**- or 'watch and worry' so called. Rituximab maintenance common and tolerable, even though not in BSH guidelines . **8%** had had ASCT- **deleted from final scope** but reasonably common in relapse.

3) Treatment Options

Only 18% had been offered a **treatment option**.

When considering treatment for your Waldenström's Macroglobulinaemia, how important is it for you and your specialist to have multiple options when deciding which drug to take, based on known side effects and expected outcomes of treatment? 1 (Not important as long there Is at least one treatment option) to 10 (Extremely important to have more than one treatment option)

Answer Options	Not Important1	2	3	4	5	6	7	8	9	Extremely Important10	Response Count
Importance of Having Treatment Options	6	2	7	1	20	8	14	28	18	126	230
										d question	230

Comment: clearly lack of treatment options is currently a problem to patients (and to clinicians?)

59% agreed that 'their current treatment is **unable** to manage their WM to some extent'.
10% had been on trials Mostly ACP196 or R2W
70% considered the 'treatment of WM to be inequitable' compared with other cancers.

Quotation 180

"Having access to less intrusive medications would be a huge step forward in the treatment of WM. With the right medication I feel that the disease could be managed even if not cured".

96% considered there' was unmet need in current treatment'.

Quotations 201,155

"Watch and wait was stressful, as was DRC treatment due to worry about risks and response. I had a rituximab flare"

"Due to have 6 FCR treatments but haematologist discontinued after 4 treatments due to side effects: drop in red blood cell count needing 2 units of blood Pulmonary embolisms 2 X neutrapenic sepsis infections requiring hospital admissions via A & E"

Comment: The high response to questions on *unmet need, treatment unable to manage their disease* and *inequity of treatment*, presents a picture of general disquiet about current treatment and substantial unmet need.

4) Effects on Patient and Family of the disease

For each of the following symptoms associated with Waldenström's Macroglobulinaemia, please rate how much each symptom has impacted your Quality of Life on a scale from 1 (No Impact) to 10 (Very Significant Impact).

Answer Options	Not applicable to me	No Impact1	2	3	4	5	6	7	8	9	Very Significant Impact10	Response Count
Weakness	22	21	16	16	8	19	19	17	23	7	24	192
Headaches	38	60	25	17	5	12	13	7	5	4	5	191
Confusion, loss of coordination, dizziness	34	44	26	21	10	15	12	13	7	4	9	195
Vision problems	45	57	29	10	11	19	2	9	5	1	7	195
Tiredness or lack of energy	11	15	9	10	7	14	9	22	29	21	47	194
Shortness of breath	28	30	20	15	12	19	10	20	16	11	15	196
Excessive bleeding, nosebleeds, bleeding gums	64	53	20	17	6	6	6	6	8	1	5	192
Unexplained weight loss, loss of appetite	59	61	18	10	7	4	5	9	5	4	10	192
Joint or muscle pain	25	32	25	16	14	15	12	12	18	9	15	193
Fevers	58	54	19	13	10	7	8	7	3	6	6	191
Heavy night sweats	30	42	19	14	11	12	8	14	16	10	14	190
Swollen lymph nodes	55	68	16	6	10	6	4	4	6	8	9	192
Swollen abdomen (belly)	63	65	10	8	6	11	7	3	4	3	9	189
Frequent infections	33	39	21	19	8	10	9	14	6	12	21	192
Tingling or numbness in feet or legs	39	40	20	9	9	6	13	11	18	10	17	192

Comment: Deep tiredness, lack of energy and frequent infections characterises WM patients. In many cases carers had taken over many functions

Quotations 020, 138:
" I have lost strength in my hands and fingers so simple tasks like unscrewing a bottle cap are not possible, The magnitude of hospital appointments/admissions have meant that I have been unable to fulfill my job role and had to finish work. We had to rely on my wife's small income for the last five years. Confinements in hospital,(treatments and numerous infections) have meant a much reduced contribution to family obligations".

"Fatigue forced early retirement which we could not really afford. I had children aged 7 and 11 (now a few years older) on retirement. Uncertainly about future of illnesss and possibility of death before children grow up has led to mental health problems. Consequences to partner and children, both practically and emotionally, are significant."

5) Potential new Treatments

If you were to consider having treatment with a new drug approved by NICE for the treatment of your Waldenström's Macroglobulinaemia, to what extent would you be willing to tolerate side effects? 1 (Will Not Tolerate Any Side Effects) to 10 (Will Tolerate Significant Side Effects).

Answer Options	Will Not Tolerate Any Side Effects1	2	3	4	5	6	7	8	9	Will Tolerate Significant Side Effects10	Response Count
Side Effects	2	9	18	17	39	16	31	39	8	44	223
										answered question	**223**

Patients clearly will accept substantial side effects if remission is deep and long lasting

Quotation 085:

"If a new drug will help to prolong life then side effects are a small price to pay. Unless you have been faced with the thought of losing someone and living for over a decade with a death sentence hanging over you, you may not understand the importance"

On a scale from 1 (Not important) to 10 (Very Important), how important is it for a new drug to be able to control the following aspects of Waldenström's Macroglobulinaemia?

Answer Options	Not Important1	2	3	4	5	6	7	8	9	Very Important10	Response Count
Bring about a remission	2	1	1	1	4	2	3	12	10	195	231
Control disease symptoms	1	0	2	1	7	4	2	26	19	169	231
Allow me to live longer	3	1	1	0	9	4	3	14	7	187	229
Improve blood counts	1	1	2	0	9	8	7	21	19	163	231
Improve quality of life	1	1	1	0	4	6	4	14	19	181	231
Reduce strain on carer/partner	7	1	3	3	5	4	4	16	9	176	228
										answered question	**233**

Comment: There is no doubt that all of these are highly important to WM patients!

6) Ibrutinib **76%** heard about ibrutinib before survey. They were asked for knowledge of the drug.

Quotations 138,75,98,221,19

"Less invasive than some therapies such as VCR and RCHOP. Longer life expectancy and remission"

"I have been on it for a year with no side effects"

"It will hopefully extend my remission and remove the necessity of a stem cell transplant"

"I follow IWMF and other WM online discussions. I am in BLOG contact with patients who have / are on Drug Trials. I am aware that Inbrutinib is already approved in Canada. Consultants in both Australia and U.K. have drawn my attention to the possibility of the drug becoming available in U.K. and being 'trialled' in Australia"

"That it is taken by pills daily. That it can often give better results that existing IV treatments. That it may not cause a relapse later. That it has its own set of side effects"

Comment: There was a remarkably high degree of knowledge about this drug

SUPPORT • EDUCATION • RESEARCH
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June 16, 2016

Chair, WMUK
44 Beresford Road
London E4 6EE

Dear

Thank you for asking me to assess the impact of ibrutinib (Imbruvica) in relapsed Waldenström's macroglobulinemia (WM) from our international perspective as the world's largest WM support and research funding organization.

Since designation as a breakthrough therapy and subsequent approval by the Food and Drug Administration in the US, ibrutinib has become the drug of choice for relapsed WM. It has transformed the treatment landscape, which was previously characterized by "hand-me-down" therapies from other B-cell lymphomas, some of which had relatively low response rates or unacceptable toxicities in WM. Ibrutinib is also approved for front-line use in the US and is increasingly being used as initial therapy.

Ibrutinib is the first small molecule drug to specifically target the BTK cellular pathway, which is downstream from MYD88, a signalling protein that is very important in B-cell growth and survival. Mutations in MYD88, especially L265P, are present in over 95% of WM patients but are relatively uncommon in other lymphomas. This means that its downstream pathways, including BTK, are especially effective therapeutic targets in WM.

This was revealed by the world's leading WM expert, Dr Steven Treon at Dana-Farber Cancer Institute in Boston, who conducted the original Phase II trial of ibrutinib in WM. This was so clearly a success that the vast majority of physicians and researchers no longer question its long-term efficacy.

A previously unmet therapy need has been largely filled by ibrutinib. Most patients have found the drug very tolerable. It is also currently the only real non-chemotherapy option for patients who have rituximab intolerance – relatively common in WM with an incidence of up to 20%.

Ibrutinib has well known side effects, but these generally decrease with time or through temporary dose reductions. In the huge majority of cases, patients are able to return to normal life and work, sometimes in days, without the chronic fatigue that characterizes WM patients. Ibrutinib also largely removes the uncertainty over relapse and reduces the need for chemotherapy. We understand that if resistance develops, therapy on ibrutinib will not prejudice further therapies of small molecule inhibitors as they become available. It is funded in the US by all insurance companies and through Medicare and Medicaid.

Patients here have now been treated for over four years, and there appear to be no new long-term adverse effects. It has been recently approved for reimbursement in Canada following a comprehensive survey by Lymphoma Canada that showed overwhelming patient support for its

effectiveness, and we understand that it is gaining rapid reimbursement approval in European public health systems following its approval by the EMA in 2015.

Through feedback from our many UK members, the International Waldenstrom's Macroglobulinemia Foundation understands their concerns about falling behind the rest of Europe and North America and hopes for their sake that ibrutinib will be funded in the very near future.

Sincerely yours,

44 Beresford Road, Chingford, London E4 6EE

17/06/2016

Annexe C : NICE Appraisal 884 :Ibrutinib in relapsed WM

Dear NICE Appraisal Committee,

We write to express our strong support for the funding of Ibrutinib for relapsed patients with WM. We are the WMUK Doctors' Forum of haematologists and scientists with expertise in WM in the United Kingdom, who also represent a range of stakeholders in this technology appraisal namely the British Society for Haematology, the Royal College of Pathologists and the Royal College of Physicians.

We are grateful that an STA of Ibrutinib in this rare disease has been tabled for discussion in September. We recognise the difficulties faced by NICE in appraising novel therapies for cancer patients. This is more challenging in the setting of rare diseases, for which there is limited high quality evidence. We are working hard to build on the evidence that will permit a more informed appraisal over time, with the set up of prospective instruments for data accrual including a national registry and bio bank for WM.

WM is a disease entity with unique clinical and biological characteristics. One of the key clinical challenges pertains to the production of a monoclonal IgM paraprotein which can cause both hyperviscosity and immunological complications such as peripheral neuropathy. These complications can limit the usefulness of conventional chemo/immunotherapy in these patients but can be overcome by the use of agents such as Ibrutinib that has an excellent toxicity profile in these respects, and can result in a brisk improvement in blood rheology with little or no neurological toxicity.

Much has been achieved in recent years through effective research across the world and how to target it using biological therapies. Such therapies include Ibrutinib, for which there is a sound biological rationale. WM remains an incurable disease so far, and once chemotherapy/ immunotherapy combinations have been exhausted, there remains an unmet need. Ibrutinib is well tolerated and can control this disease effectively, as demonstrated by the evidence provided.

Its proposed use for relapse represents an important development for these patients. The availability of this agent would offer not only additional life but importantly its tolerability and convenience means that patients have a good quality of life away from hospital for a long period of time.

Yours sincerely

Dr Guy Pratt
Chair, WMUK Doctors Forum
Consultant Haematologist
Queen Elizabeth Hospital, Birmingham

Dr Nilima Parry-Jones
Consultant Haematologist
Nevill Hall Hospital, Wales

Dr Ashutosh Wechalekar
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Dr Saad Rassam
Consultant in Haematology and Haemato-Oncology
Kent Oncology Centre, Maidstone

Dr Reuben Benjamin
Consultant Haematologist
Kings College Hospital, London

Dr Jonathan Wallis
Consultant Haematologist
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Newcastle-Upon-Tyne

Dr Lalita Banerjee
Consultant Haematologist
Kent Oncology Centre, Maidstone

Dr Helen McCarthy
Consultant Haematologist
Royal Bournemouth Hospital, Bournemouth

Dr Shirley D'Sa
Consultant Haematologist
University College London Hospital, London

Dr Sunil Iyengar
Consultant Haematologist
Royal Marsden Hospital, London

Dr Jane Tighe
Consultant Haematologist
Aberdeen Royal Infirmary, Aberdeen

Dr Fergeal McNichol
Consultant Haematologist
Belfast City Hospital, Belfast

Dr Chara Kyriakou
Consultant Haematologist
Northwick Park Hospital, Harrow

Dr Jindriska Lindsay
Consultant Haematologist
Kent and Canterbury Hospital, Canterbury

Dr Andrew Davies
Cancer Research UK Senior Lecturer in Medical Oncology and Honorary Consultant
Southampton General Hospital, Southampton

Dr Helen Barker
Consultant Haematologist & Clinical Lead Haematology
Sheffield Teaching Hospitals, Sheffield

Dr Jaimal Kothari
Consultant Haematology
Oxford University Hospitals, Oxford

Dr Adrian Bloor
Consultant Haematologist
Christie Hospital, Manchester

Dr Rebecca Auer
Consultant Haematologust
St Bartholomew's Hospital, London

Dr Roger Owen
Consultant Haematologist
Leeds Teaching Hospitals, Leeds

Dr Mark Offer
Consultant Haematologist
Wexham Park Hospital, Slough

Prof Simon Wagner
Consultant Haematologist
Leicester Royal Infirmary, Leicester

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ibrutinib for treating Waldenström's macroglobulinaemia [ID884]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]
Name of your organisation: Royal College of Pathologists

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

No funding links with the tobacco industry.

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Waldenstrom Macroglobulinaemia (WM) is a rare B-cell lymphoproliferative disorder. Patients are typically elderly (median age approx 70 years at presentation) and symptoms occur as a consequence of anaemia and infection as well specific syndromes relating to the IgM monoclonal protein. These include peripheral neuropathy and hyperviscosity syndrome. WM typically follows a relapsing and remitting course over many years and as a consequence patients will receive many different forms of chemotherapy. Responses in this disorder are rarely complete and duration of responses are typically short, at least in the relapsed / refractory setting. Clinical symptoms are highly variable and in some cases can persist despite apparent adequate response to therapy. Treatment is reserved for patients with symptomatic disease only. Criteria for the initiation of therapy are well established in national and international guidelines.
At present there is no consensus on the standard of care for initial therapy in WM. There is a paucity of randomised phase III data but national and international guidelines support the use of rituximab-based chemoimmunotherapy as initial therapy. It is accepted that it is difficult to propose one regimen over another and a variety of factors such as age, co-morbidity, disease-related clinical features and renal function can all potentially impact. The recommendations made in the British Committee for Standards in Haematology published in 2014 remain broadly applicable to UK practice (Owen *et al,* Br J Haematol 2014; 165:316-333).

Chemo-immunotherapy regimens used in WM include the following

DRC – dexamethasone, rituximab, cyclophosphamide
Pros: tolerability and toxicity profile, applicable to virtually patients, cost
Cons: published data would suggest that PFS and duration of response is likely to be inferior to purine analogue combinations

The CVPR combination of cyclophosphamide, vincistine, prednisolone, rituximab is also in widespread use across the UK and would be considered broadly equivalent to DRC

FR+/-C – fludarabine, rituximab with or without cyclophosphamide
Pros: Published data would suggest high response rates and prolonged disease free intervals. Likely to be superior to DRC in terms of efficacy.
Cons: short term haematological and infectious toxicities are significant. Many patients do not complete the course of treatment and many require growth factor and transfusion support. Prophylactic cotrimoxazole and antivirals are also needed due to risk of pneumocystis and herpes zoster infections. Fludarabine has limited applicability in older patients and in those with sub-optimal renal function. Late onset

toxicities include autoimmune cytopenias and there remain concerns regarding secondary myelodysplasia and acute myeloid leukaemia (MDS/AML). Many of these toxicties have been confirmed in the recent UK trial, R2W.

BR – bendamustine, rituximab
Pros: Data would suggest similar level of efficacy to FCR but possibly less haematological and infectious toxicity. Bendamustine is safer in patients with renal impairment and as a consequence is applicable to a greater proportion of patients.
Cons: Published data in WM is limited. Only available via CDF currently. Haematological and infectious toxicity is not insignificant – likely to be less than with FCR but greater than with DRC. Long term safety data in terms of MDS/AML is more limited.

CR – cladribine, rituximab
Efficacy and toxicities broadly comparable to fludarabine regimens.

The above regimens are also used in patients with recurrent / progressive disease. Bortezomib based therapies have been advocated in the setting of relapsed disease in both national and international guidelines based on the results of a number of phase II studies. Unfortunatley bortezomib is no longer available via the Cancer Drugs Fund. As a consequence of this therapeutic options in WM are limited to combinations of alkylating agents, purine analogues and rituximab.

Autologous stem cell transplantation is an option for patients at relapse. In practice it is only applicable to limited proportion of patients (no more than 10% overall) given that it is only considered in younger patients with a short duration of first response.

It is recognised that a minority of patients will not be considered candidates for chemo-immunotherapy on account of frailty / co-morbidities and that single agent chlorambucil, single agent rituximab and best supportive care are all options in this context. Clinical decisions in this setting will be influenced by co-morbidities, disease features and patient choice. Defining patients considered unfit is of course highly subjective. However in my own practice only a limited number (<10%) of patients would be considered in this category at initial presentation. Best supportive care could consist of corticosteroids, transfusion support and intermittent plasma exchange.

I do not consider that there are any major geographical variations in practice and that overall practice in the UK will broadly follow the BCSH guidance.

Clinical trial activity in WM has been very good in the UK. Data relating to the recently completed R2W trial will be presented in a plenary session of international WM workshop in October 2016.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

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A well-established prognostic scoring system is available (IPSS WM, Morel *et al,* Blood 2009; 113:4163-4170) which can delineate 3 prognostic groups based on simple laboratory parameters as well as age. The main role of this scheme is to allow comparison of clinical trial data and it is not currently recommended that treatment decisions for individual patients be made entirely on the basis of the IPSS WM.

WM is characterised by the L265P point mutation in the MYD88 gene (approx. 90% of patients). This mutation was first described by Treon and colleagues in the US but the high prevalence of the mutation has been confirmed by a number of additional studies in many countries including the UK (Treon *et al* N Engl J Med 2012; 367:826-833). The presence of this mutation does appear to predict for response to ibrutinib as significantly inferior response rates are documented in WM patients lacking the mutation (Treon *et al,* N Engl J Med 2015; 372:1430-1440). It may therefore be appropriate to consider ibrutinib only for those patients known to have the MYD88 L265P mutation. Simple and inexpensive assays are available for its detection in bone marrow aspirate samples. It may ultimately be possible to perform this assay in the peripheral blood. There are two potential limitations to this approach are

1. Availability of mutation screening across the whole of the UK
2. The presence of alternative MYD88 mutations in a minority of patients lacking the L265P mutation (Treon *et al,* N Engl J Med 2015; 373:584-586)

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

The technology should, in my opinion, be used in the secondary care setting. I don't believe that there are any additional requirements to consider. Ibrutininb is a well tolerated oral medication and as such is likely to have a positive effect on resource utilisation in haematology day care / chemotherapy units. Hospital admissions with infectious complications could also decrease. Many haematologists will have experience of managing patients on ibrutinib for other B-cell disorders such as CLL.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Not currently used in WM. Widespread use in CLL both within clinical trials as well routine use via CDF prescribing. No additional issues to consider.

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

There are several published guidelines available in WM.

Most relevant to UK practice are those developed by the British Committee for Standards in Haematology. Although published in 2014 they remain broadly

applicable to UK practice (Owen *et al,* Br J Haematol 2014; 165:316-333).

There are further international guidance documents produced by the

International WM Workshop (Dimopoulos *et al* Blood 2014; 124:1404-1411 and recently updated, Blood epub)

National Comprehensive Cancer Network (NCCN; www.nccn.org/professionals/physician_gls/f_guidelines.asp) and European Society for Medical Oncology (ESMO; Buske *et al,* Ann Oncol 2013; 24 Suppl 6:vi155-9)

Additional guidelines on diagnostic work up which describe the value of MYD88 genetic screening have been developed by the International WM Workshop (Castillo *et al,* Brit J Haematol 2016; in press).

The advantages and disadvantages of the technology
NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?
If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.
If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?
What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The pivotal study demonstrated the following key points (Treon *et al,* N Engl J Med 2015; 372:1430-1440).

1. Excellent response rates – an overall response rate of 90.5% and major response of 73% is unprecedented in the setting of relapsed / refractory disease. This is likely to translate into considerable progression free survival benefit and early data in this regard is very encouraging. Confirmatory response data is also available from Arm C of the INNOVATE study which was presented at the recent EHA meeting with ORR 84% and MRR 68% and 1 year PFS of 93% (Dimopoulos *et al,* abstract p652)

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2. Rapid responses – this is an important consideration for many patients particularly those with hyperviscosity. This is not always seen with conventional therapies were delayed IgM responses are frequently seen and plasma exchanges need to continue during therapy.

3. Low toxicity and ease of administration – haematological toxicity is low. There are some specific toxicities such as bruising / bleeding and atrial fibrillation that should be noted. Oral therapy is a real benefit.

4. Demonstration of clinical benefit – there is a clear relationship between IgM response and clinical benefit (improvement in haemoglobin). This is a very important factor to consider and should not be underscored. This data has been poorly captured in some previous studies. It is well recognised that in some instances following standard chemo-immunotherapy that satisfactory IgM responses are not always associated with haemopoietic improvement and clinical benefit.

5. Potential effect of tumour genetics on response and overall outcome. The MYD88 L265P mutation is central to the biology of the disease and is an ideal biomarker for those likely to benefit most from therapy.

In my view there is a clear role for ibrutinib in patients with relapsed / refractory WM. This is an unmet clinical need given the limited range of agents currently available to patients. This situation being exacerbated by the loss of bortezomib from the CDF.

Ibrutinib has unprecedented single agent activity and targeted nature of action. In this setting it will provide real benefit to patients given the excellent toxicity profile and oral administration. There are, however, some specific toxicity issues to consider and these include atrial fibrillation. Given the small number of patients included in the pivotal study it may be appropriate to consider the toxicity data across all B-cell malignancies and there are “real world” data available in CLL and mantle cell lymphoma.

It could be envisaged, although I suspect that formal quantitative data is lacking, that ibrutinib would have a real positive impact on certain resource areas with real tangible reductions in the following

Day case attendances
Acute hospital admissions with sepsis
Growth factor and supportive medicine use
Transfusion support
Plasma exchange

Ibrutinib has also been approved for use in de novo patients considered unsuitable for standard chemo-immunotherapy. This is more contentious as this patient cohort is difficult to reproducibly define. It is difficult to support use in the upfront setting at this time as there are no data yet available. Given the continuous nature of ibrutinib therapy and likely long duration of response in the front line setting as well as cost compared to conventional therapies it is essential that randomised trials are performed. These should include detailed QoL measures given the likely prolonged

duration of therapy. A trial comparing Ibrutinib+rituximab versus DRC in previously untreated patients is proposed in the UK.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- **Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;**
- **Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;**
- **Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities**

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

There are no relevant equality issues.

Any additional sources of evidence
Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

The majority of published studies in WM are small phase 2 studies which have included previously untreated as well as relapsed / refractory patients. Robust outcome data particularly in the relapsed / refractory setting is limited. The European Consortium for WM (ECWM) has conducted a pan-European chart review and have delineated outcomes in relapsed patients. This analysis demonstrated short median PFS for second and third line therapy; 23 and 16 months respectively. This has been presented at the recent European Haematology Association meeting (Buske *et al,* abstract E1275). This data will be used in the Janssen submission and is an appropriate comparator.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments

that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within
3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

No additional resources or staff training required. Likely positive impact on haematology day care facilities and acute hospital admissions as detailed above.

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Single Technology Appraisal (STA)

Ibrutinib for treating Waldenström's macroglobulinaemia [ID884]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name

Name of your organisation
University College Hospitals NHS FT

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ☑
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ☑
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? ☑- [but not as a paid employee. I am the Chair of the WMUK Doctors' Forum- part of the WMUK Doctor-Patient Charity (UK Point of Contact for WM) and a trustee of the charity]
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:
No

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

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The current treatment of Waldenström's macroglobulinaemia (WM) in the UK comprises chemotherapy combined with the monoclonal antibody, Rituximab administered until maximal response in the day case setting (6-8 cycles spanning 4-6 months).

There is no single accepted treatment for WM. Agents are drawn from a group of familiar cytotoxics: alkylating agents such as Cyclophosphamide (oral or IV) or Chlorambucil (oral), purine analogues such as Fludarabine (oral) or Cladribine (SC) or Bendamustine (IV) which is felt to have alkylator /purine analogue characteristics.

Current available options are summarised below:

Rituximab, a monoclonal anti-CD20 antibody, is recommended in the treatment of all WM patients, in combination with other agents or as monotherapy. For many patients, the low toxicity profile and substantial response rates as a single agent make Rituximab suitable for minimally symptomatic WM patients or those with IgM-related neuropathy, haemolytic anaemia, or mild cytopenias. The overall response rate (ORRs) is 50% to 60% in treatment-naïve and relapsed/refractory patients, with a median progression-free survival (PFS) approaching 2 years. (Gertz, *et al* 2009, Treon, *et al* 2005). It has been noted however that a proportion of patients with WM exposed to single agent rituximab or rituximab-containing regimens had to discontinue rituximab due to worsening infusion-related reactions (IRRs) as treatment with rituximab has continued (Castillo, *et al* 2016). Approximately 7% of WM patients in whom IRRs intensified with each infusion, to the point that Rituximab had to be discontinued. Half were Rituximab-naive. Intolerance developed in the single agent and combination settings, and seen at any level of serum IgM. Approximately 30% of rituximab-intolerant patients went on to receive Ofatumumab,

which was tolerated and produced a response in 80% of these cases. This agent is an alternative and costlier monoclonal antibody than Rituximab.

Bendamustine and Rituximab (BR) in treatment-naïve patients with WM demonstrated an ORR of 100% and complete response (CR) of 53% in a Phase II trial (Rummel, *et al* 2013). The primary adverse effect was myelosuppression (leukopenia Grade ≥3: 16%; thrombocytopenia Grade ≥3: 3%). A Phase III trial of BR vs R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) in patients with indolent lymphomas, including 41 with WM, showed a similar ORR (95%) in both treatment arms. BR, however, had a significantly longer median PFS (70 vs 28 months; hazard ratio 0.33; P=0.003), fewer relapses and adverse events.

A Phase II trial of **Dexamethasone, Rtuximab, and Cyclophosphamide (DRC)** in treatment-naïve patients demonstrated an ORR of 83%, and CR rate of 7% with less than 9% rate of Grade ≥3 adverse reactions (Dimopoulos, *et al* 2007). DRC is a non-stem-cell toxic treatment option in WM.

The above combinations are reported as being well tolerated. However, a survey of patients 280 patients by the UK charity, WMUK has identified a significant chemotherapy-induced burden that is not reflected by clinical trials. Most WM patients spent 3-6 hours in hospital per chemotherapy cycle/visit. Some spent much longer due to reactions to chemotherapy, transplant procedures and outpatient time. A significant proportion of patients feel that chemotherapy treatments undermine their ability to attend to household chores, ability to concentrate, work and contribute financially to household expenses, to exercise, to fulfil family obligations and to spend time with family and friends.

A number of WM-centric toxicities have been identified with commonly used therapies:

Rituximab: the IgM flare induced in 40-60% which may result in a hyperviscosity crisis, aggravation of IgM-related peripheral neuropathy (PN) and cryoglobulinaemic symptoms, hypogammaglobulinaemia with resulting infections

Nucleoside analogues: Severe T cell depletion resulting in opportunistic infections and a reported rate of second malignancies of 10-15% (especially acute leukaemia and myelodysplasia)

Bortezomib: grade 2 and 3 PN.

Autologous stem cell transplant (ASCT) in WM is deemed safe and effective in multiple retrospective studies. The largest cohort of patients with WM who underwent ASCT included 158 patients and showed a transplant-related mortality of 3.8% at 1 year (Kyriakou, *et al* 2010). ASCT achieved an ORR of approximately 95% and a major response rate (MRR) of 78%–80%, with an estimated 5-year OS of 69% and 5-year time-to-next-therapy of 48%. Survival was affected by number of prior treatment regimens and disease chemosensitivity at the time of transplant. Funding for ASCT in WM patients in the UK is currently suspended pending the high court appeal surrounding PrEP funding.

The 2014 British Committee for Standards in Haematology guidelines recommends treatment with a combination regimen with rituximab and either cladribine, bendamustine, dexamethasone (plus cyclophosphamide) or fludarabine (with or without cyclophosphamide) (Owen, *et al* 2014). Chlorambucil monotherapy is also recommended for those people who cannot tolerate other treatments. Choice of treatment depends on a variety of clinical factors including grade of disease, kidney function, co-morbidities and whether a person is suitable for stem cell transplantation.

There are no major differences in opinion as regards front line therapy. There are international consensus criteria for response to treatment (Owen, *et al* 2013), and if there is deemed to be an inadequate response to therapy, second line therapy is deployed.

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Second and subsequent line combinations are drawn from the same list as first line combinations- if the response to treatment has been sufficiently long (typically 2- 5 years on average) then the same combination may be reused. Otherwise, most physicians would turn to an alternative combination.

Once treatment is complete and has been deemed effective, the patient reverts to outpatient-based clinical monitoring usually seen every 3 to 6 months as long as clinically stable.

The natural history of the condition is for chemoresistance to develop and diminishing returns accrued from ongoing treatments. During this phase of the disease, patients' well-being is reduced, with higher levels of fatigue, reduced blood counts and IgM-related complications become evident once again. In addition, there is a steady accrual of immune deficiency due to progressing lymphoma and repetitive treatments. This leads to a depleted physical state and increased infections which ultimately lead to increased admissions to hospital for transfusions and inpatient management.

The discovery of the L265P mutation in MYD88 has considerably improved the understanding of WM pathogenesis (Treon, *et al* 2012). The MYD88 L265P mutation has been found in approximately 90% of all WM and 100% of familial WM. The gain-of-function MYD88 L265P mutation strongly promotes WM cell growth and survival through downstream activation of the above-mentioned pathways, with the transcription of NF-κ.

Ibrutinib is an oral, small-molecule, selective, irreversible inhibitor of BTK that triggers apoptosis in WM cells with the MYD88 L265P mutation. A Phase I trial of ibrutinib in 56 patients with relapsed/refractory B-cell lymphomas, including four patients with WM, showed an objective response in 60% of the patients and a median PFS of 16 months (Advani, *et al* 2013).

The encouraging results and acceptable tolerability led to a pivotal Phase II trial of ibrutinib in *previously treated* WM patients (Treon, *et al* 2015a). A total of 63 consecutive patients received daily ibrutinib, 420 mg, until disease progression or unacceptable adverse effects. The ORR was 90%, with median treatment duration of 19 months. Patients with WM who have the MYD88 L265P mutation and wild-type CXCR4 have the most benefit from ibrutinib, with an ORR of 100% and MRR of 91. (Treon, *et al* 2015b).

Preliminary results of a multicentre Phase III trial demonstrated activity of ibrutinib in *rituximab-refractory* WM patients. With an ORR rate of 84%, single-agent ibrutinib shows activity in heavily pre-treated rituximab-refractory WM patients (Dimopoulos MA 2015).

No special training of NHS staff is needed for this drug, and no additional resource requirement is anticipated, either in hospitals or in the community. On the contrary, most other treatments for WM are intravenous, and require time and space in the hospital setting. Given the available data for Ibrutinib, it is anticipated that a greater proportion of patients with WM treated with Ibrutinib would spend more time feeling well as a result of spending more time in remission.

The most recently published British (BCSH) Guidelines for WM and ESMO guidelines predate the recent developments outlined above. The Treatment Recommendations for Waldenström Macroglobulinemia from the 8th International Workshop on WM (Leblond, *et al* 2016) note that the approval of the BTK-inhibitor ibrutinib in the US and in Europe represents a novel and effective treatment option for both treatment–naïve and relapsing patients.

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Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

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There are currently fewer options than ever available for UK patients with WM, following the removal of Bortezomib from the CDF and suspension of funding for ASCT. Ibrutinib will provide an important targeted non-chemo option to treat WM. Given the strong biological rationale for its use, its ability, to lower the IgM promptly and effectively (an unprecedented median time to response, 4 weeks), it will represent a whole new option for this patient group. In the pivotal phase 2 trial, all patients in whom treatment was initiated for hyperviscosity symptoms required no additional plasma exchange after two cycles of therapy (Treon, *et al* 2015b). This will lead to a reduction in the need for this complex and costly intervention. Costs include those associated with professional services, hospitalisation, albumin, laboratory tests and catheter costs and treating side-effects, which are difficult to capture as they occur as part of the hubbub of clinical activity.

Ibrutinib as single agent has activity in WM comparable to that with combination therapies; however, no head-to-head trials have been conducted. The clinical effects of the IgM protein in the setting of WM often dominates the clinical picture cannot be underestimated. This sets WM aside from other B NHL. Swift and well tolerated control of monoclonal IgM produces demonstrable benefits in this patient group.

In terms of ease of use, being an oral medication which is taken once a day, the ease of use is undeniable. Other standard treatments for WM require cytotxic reconstitution in the chemotherapy pharmacy, administration in a hospital setting, and the use of additional symptomatic treatments such as anti-emetics.

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No additional tests are required for the prescription and dispensation of Ibrutinib. Standard blood tests (FBC, U&E, LFT) needed prior to each cycle is no different to the requirements for chemotherapy. If anything, the frequency of blood tests and hospital attendance is likely to be reduced with the use of Ibrutinib.

Unlike other treatments, which are administered for a fixed number of cycles, Ibrutinib is used indefinitely until disease progression. Although drug costs form a conspicuous portion of treatment costs in cancer patients, disease-related healthcare costs are significantly driven by disease complications, which result in inpatient hospitalisations, hospital readmissions, and medical procedures, which should be taken into account.

No additional testing would be required to select patients who are suitable for this treatment. Genetic testing for MYD88 L285P and CXCR4 is not standard in all laboratories and although the results suggest subgroups which may especially benefit from Ibrutinib, the result would not be a prerequisite for using this treatment. Clinical trials are ongoing to further define the role of these mutations on the results of therapy. The information available so far is highly suggestive of a benefit in the MYD88 L265P, CXCR4 WT subgroup, which constitutes the majority of WM patients.

Starting and stopping criteria are well established and based on the consensus criteria (Owen, *et al* 2013) and can be easily applied in this setting.

Ibrutinib is already in widespread use in UK hospitals and the use in the clinical setting has not thrown up any unexpected side effects compared to those reported in the pivotal clinical trials. As outlined above, since this treatment is orally administered and easy to prescribe and use, there have been no additional requirements noted over and above that reported in clinical trials. In practice, and as trials have progressed through the phases, the initially noted side effects have proven to be less of a concern than originally thought.

Regarding outcome measures, in the Phase I trial of ibrutinib in 56 patients with relapsed/refractory B-cell lymphomas, including patients with WM, an objective response (partial response or above) was noted in 60% of the patients and a median PFS of 16 months. The encouraging results and acceptable tolerability led to a pivotal Phase II trial of ibrutinib in previously treated WM patients. A total of 63 consecutive patients received daily ibrutinib, 420 mg, until disease progression or unacceptable adverse effects. The ORR was 90%, with median treatment duration of 19 months. These outcome measures were appropriate and clinically relevant in this patient group.

Ibrutinib is well tolerated. Grade 3 or higher neutropenia and thrombocytopenia were seen in 14% and 13% of the patients, respectively. Most of these patients received three or more prior types of therapy. Grade 2 or higher bleeding complications were seen in 6% of the patients, all of which were associated with concomitant use of fish oil supplements. Atrial fibrillation was reported in 5% of patients, all of whom had a history of paroxysmal atrial fibrillation, which resolved after ibrutinib was withdrawn.

Notably, in the experience of physicians involved in clinical trials of BTK inhibitors in the UK, there has been universal observation of a rapid and sustained improvement in well-being and quality of life which has been impressive. In particular, the improvement in the level of anaemia and symptoms of fatigue have been unprecedented and welcomed.

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Single Technology Appraisal (STA)

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NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- **Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;**
- **Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;**
- **Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities**

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

>>
I do not think these statements apply here

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

>>
No

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

>>

Regarding resource utilisation, there is already considerable experience of using Ibrutinib within NHS hospitals as it has been in use for several years for conditions such as MCL and CLL. It is not yet available for use in WM. In the setting of WM, trial data has demonstrated that responding patients rapidly return to better health and functioning as their IgM levels fall in response to BTK inhibition. The use of this agent in the WM setting is not expected to cause additional resource requirements as the drug is simply dispensed by the pharmacy for oral consumption. It is already dispensed in Haematology clinics across the UK and does not require a specialist (tertiary) setting.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Ibrutinib ID884

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: [redacted]
Name of your nominating organisation: WMUK
Do you know if your nominating organisation has submitted a statement?

X☐ Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

X☐ Yes ☐ No **but see addendum in 5 below**

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

X Yes ☐ No

- a carer of a patient with the condition?

☐ Yes X☐ No

- a patient organisation employee or volunteer?
-

Y☐ Yes ☐ No

Do you have experience of the treatment being appraised?

X☐ Yes ☐ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.) **See 5 below as an addendum to the WMUK submission**.

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
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- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

The recent disruption and withdrawal (8/16) of Haematopoietic Stem Cell Transplants for relapsed/refractory WM patients (roughly 14 a year) by NHS Specialised Commissioning , despite BSBMT recommendation, has yet further reduced treatment options for part the target group of potential Ibrutinib patients who have no effective alternatives.

Please list any concerns you have about the treatment being appraised.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating

discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Is there anything else that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Patient expert statement

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-

☐ Yes ☐ No

Do you have experience of the treatment being appraised?

☐ Yes ☐ No

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Please list the benefits that you expect to gain from using the treatment being appraised.

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Please list any concerns you have about current NHS treatments in England.

Please list any concerns you have about the treatment being appraised.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

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9. Other issues

Do you consider the treatment to be innovative?

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If yes, please explain what makes it significantly different from other treatments for the condition.

Is there anything else that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

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WMUK
UK Point of Contact for Waldenström's Macroglobulinaemia

Patient A: Ibrutinib Trialist, Diagnosed with Waldenström's Macroglobulinaemia – 2009

My life and that of my family changed in 2009 when diagnosed with Waldenström's Macroglobulinaemia-a rare lymphoma.

Initial Treatment – CHOP - 2009
The first chemo was CHOP and after a few days the joints started to ache, the sickness was controllable, but I felt pretty bad. I couldn't concentrate on my business and pretty much left it to run itself. The second week I was in a lot of pain, very tired and shaky. Then came the steroids that made me very aggressive and short tempered. While you are having the chemo you can't mix very well with the outside world, just in case you pick up an infection that might stop you from having the next cycle. When it came to my daughter's graduation, I spent most of it observing things from a distance not wanting to shake anybody's hand or get too close just in case I caught something from them.

By now I had received three cycles of CHOP chemotherapy, CVP therapy with GCSF support due to neutropenia. After these four cycles my IgM had reduced to 20 g/L and then Rituximab was commenced in addition. I received a further four cycles of R-CVP therapy and then four further cycles of Rituximab mono therapy. All this treatment ended in March 2010 approximately one year after my first treatment. At the end of the treatment I had a restaging and my IgM was 27grams/L. A bone marrow biopsy showed significant persisting infiltration with WM cells.

ESHAP - Autologous Transplant - 2010
On the advice of Shirley D'Sa I received three cycles of Rituximab and ESHAP chemotherapy through a tunneled central line as salvage. I finished the cycles in October 2010. Restaging in October 2010 showed only a very low level residual lymphoma in the marrow of around 10%. ESHAP is a pretty horrible chemotherapy and it slowly breaks you down mentally and physically and the side effects from the drugs never go away. I then received Cyclophosphamide priming and stem cell collection in November of 2010 and proceeded on the advice of Dr D'Sa to BEAM chemotherapy and autologous stem cell transplant at the end of November 2010. The transplant took place a month before Christmas and just before the stem cells are put back into your body you receive BEAM therapy that strips out your stomach lining. At my 100-day assessment following autogous stem cell transplant in March 2011 I had a total IgM of 5 grams with a monoclonal component of 2.8 grams/L. My bone marrow at this stage was essentially normal with only very small areas of low-grade lymphoma being picked up on immunohistochemistry.

The Transplant was failing – 2011
By December 2011 my IgM Paraprotein was rising and I therefore searched the Internet to find out if there was a treatment available abroad as the only thing available in the UK was more chemo, which clearly was not working. **I Visited Dana-Farber Cancer Institute in Boston, USA - 2012** to see Steve Treon as he was working on a drug that would be available to trial in about 6/12 months time that might help me.

Ibrutinib Trial Starts - 2013
In February 2013 I went down with septicemia thought to be the result of too many cortisone injections for the pain in my elbows. I contacted Steve who told me the trial was full, but he would see me but could not guarantee that I would be accepted as it was now an FDA registration study requiring strict adherence to eligibility criteria; I turned up on a Monday morning in March 2013 at the Dana-Farber Cancer Institute in Boston. My bloods were taken and I then went for a Bone Marrow Biopsy. I met with Steve, he explained the criteria requirements for the trial. He then examined me, got out his scope looked into my eyes (Blood Capillaries in the eye were close to rupturing) and said' Mark you are on the trial as long as you promise me you will not fly home until you have taken the ibrutinib tablets'.

My eyes hurt like hell but within half a day of taking Ibrutinib I noticed the difference. The pain in my back was going, my eyes felt better, I wasn't so tired and my appetite was returning. I remember saying to my wife, 'I have not felt this good for years', I don't think she believed me, most probably thought it was a sort of placebo effect. But on the flight back to the UK my eyes were not sore and my joints were not aching as much from being cramped up on a plane. For the first time in 4 years I was going to get my life back, not looking too far ahead or getting too emotional about the whole thing but taking each day as it comes and making the most of it.

For the first three months I had to commit to visit Dana-Farber in the States every month and then three monthly for the next 36 months. The visits consisted of blood chemistry analysis, bone marrow biopsies, CT scans, discussions with different doctors as to my physical and mental health and checks on how you were coping with the drug. On each and every visit we would run through what problems I had experienced since my last visit, had I stopped taking the tablets for any reason. I would have a daily table that I had to fill in, how I felt any pains, fatigue, colds, temperature and what time that day I took Ibrutinib.

Living with Waldenstrom's is a daily struggle; you never know how you are going to feel when you wake up in the morning. I can still get extreme pains in some of my joints especially the back but luckily for me the knee and elbows are now pain free. I was diagnosed with prostate cancer at Xmas 2014. I was very grateful to the doctors at Dana Farber for making me keep an eye on my psi because that was the only indication I got that there could be a problem and the cancer was caught at an early and treatable stage.

I still have many medical issues, tiredness, forgetfulness, tinnitus, joint aches and pains. These are not the side effects of the ibrutinib but the disease and the scars of heavy chemotherapy. The drug has proved very tolerable. **If ibrutinib were available when I was diagnosed** how much better things would be for me now! What a difference that would have made to me, my family, my business, my 70 staff and their families and the Inland revenue who would be over £8 million better off if my company had traded at the same level today as it did in 2009 when I was running it, before

Patient B 13 years diagnosed, 5 lines of treatment

I was diagnosed in 2003 at 55 after being breathless and tired with peripheral neuropathy and night sweats. IgM was 50 g/l, blood viscosity was 5.4; so plasmapheresed x12 whilst local haematologist worked out treatment - a course of **Chlorambucil** and a prognosis of 5 years. As CEO of a charity, I felt so poorly that I stepped down to fight the disease and the charity was not stuck with someone useless. Friends at CRUK investigated WM, saying I should get a second opinion from a London teaching hospital with a WM clinic, as Chlorambucil suited older, less fit patients.

Advice was to start a course of **Cladribine (2CDa)** immediately and I had 2 monthly cycles with GCSF support, travelling to London from the West Country. My increasing neuropathy was investigated by a specialist as were my eyes . Chemo was tough, giving me a good partial response with a remission of 2.5 years, although I never lost the deep,deep fatigue which accompanies most with WM.

My numbers deteriorated, loosing first neutrophils and then haemoglobin, and IgM rose to 30. The treatment was **R-CHP (no O due to the neuropathy),** again as a travelling outpatient. I found this even harder, with extreme mood and palate changes caused by steroids, more neuropathy, very low neutrophils and tiredness. Constipation caused by neutropenia triggered off rectal bleeding in the middle of a street. Scheduled for 8 cycles, I halted it at 6, when the treatment gave me a very good partial remission, lasting 4 years.

This broke down in 2011, and an **autologous stem cell transplant** was the only solution offered, so entered conditioning in January 2012 with ESHAP Chemo via a PICT line. Side effects included more neuropathy and permanent tinnitus, acid reflux and sinus infections, all of which had to be investigated. Constant line blocking meant many extra hospital visits and weekly district nurse services. The LEAM transplant, firstly in ambulatory care and then as an inpatient went well, although two doses of Plerixafor (£5k each) were needed to mobilise stem cells due to my age and pretreatment with Cladribine. All side effects remained.

My transplant relapsed 4 years on this year (this time platelets led the way) and so I had limited options after 13 years of this disease at the age of 66. As no BTK or Pi3K inhibitor was available, in the end I was offered **Bendamustine + Rituximab** which I am currently undergoing, but treatment has stalled due to neutropenia and with more purine analogues I am concerned at transformation.

I feel lucky beating the original prognosis by delaying treatments for as long as possible, and getting to a disease expert UCLH but direct and indirect costs to the NHS and my family have been huge and I totally fail to understand why WM relies on 'hand me down' treatments from related diseases. I got to know many other WM patients as friends from the outset, but sadly 75% of them have predeceased me.

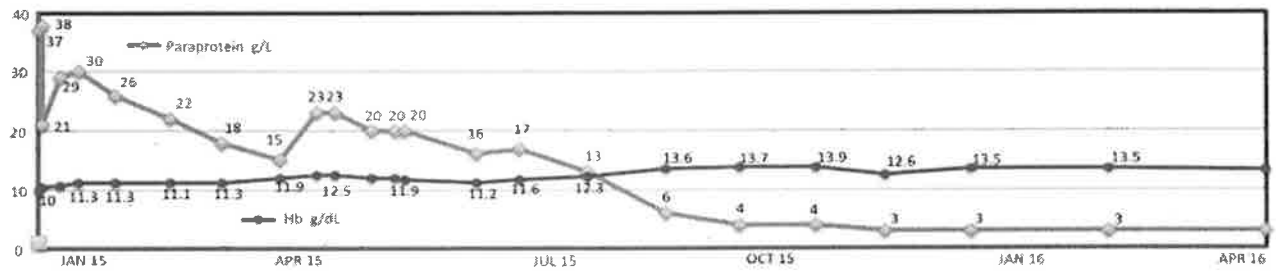
Patient C- Twice relapsed and Rituximab intolerant- now on Ibrutinib

My name is I am a twice-relapsed Waldenstroms patient currently on Ibrutininb and in remission. I am currently 57 and was 52 at diagnosis in October 2011.

When diagnosed I was symptomatic with anemia and hyperviscosity syndrome. I was immediately put on RCVP but found intolerant of Rituximab due to two hospital admissions with >40C fevers and SVT. I also showed no response to this chemo so commenced Velcade, supplied by my medical insurers, in March 2012. At this time I had given up employment due to the amount of time spent in hospital and on-going twice-weekly appointments. I completed my course of Velcade in Oct 2012 and enjoyed partial remission although my paraprotein started rising again after only a couple of months. I was very despondent at the WM conference in 2013 knowing that I would need treatment again soon and most options included Rituximab.

In Feb14 I started ESHAP, with a view to a stem cell transplant, but after three courses the disease in my marrow had hardly reduced so it was decided to try Rituximab once more. Again I suffered SVT and fevers with temps >40C. This resulted in a three-week hospital stay followed by weekly plasmaphersis due to paraprotein spike and cardio ablation for SVTs. I started on Velcade again in Feb15 but this had to be stopped two months later due to increasing PN. At this point I didn't appear to have any promising options having twice failed to respond to cytotoxic chemotherapy and being completely intolerant of Rituximab.

Dr Shirley D'Sa had previously tried to get me on trials for Ibrutinib but my history of heart arrhythmia had ruled me ineligible. In June 2015 Dr D'Sa made a submission to my medical insurers demonstrating that Ibrutinib offered my only real chance of remission and they agreed to supply on a three monthly review basis. I started the drug in July 2015. My paraprotein levels immediately started to fall and were down to insignificant values within three months, where they have remained. In addition I am no longer anemic – for the first time in five years



Not only has Ibrutinib has given me my first real remission, the ease of taking the drug in tablet form has greatly helped my quality of life. I am a single parent with a teenage daughter currently taking her GCSE's. Hospital stays and the added incapacity caused by traditional chemo would leave her without parental support for long periods of time during a hugely important time in her life. Further to this the management of my Waldenstroms means I do have the opportunity to lead a relatively normal life.

Ibrutinib for treating Waldenström's macroglobulinaemia: A Single Technology Appraisal

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Rider on responsibility for report

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Contributions of authors

Christopher Carroll and Emma Simpson summarised and critiqued the clinical effectiveness data reported within the company's submission. Paul Tappenden and Praveen Thokala critiqued the health economic analysis submitted by the company. Ruth Wong critiqued the company's search strategies. John Stevens and Jean Sanderson critiqued the statistical analysis contained within the company's submission. Josh Wright and Rebecca Auer provided clinical advice to the ERG throughout the project. All authors were involved in drafting and commenting on the final report.

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ABBREVIATIONS

2L	Second-line
3L	Third-line
4L	Fourth-line
AE	Adverse event
AIC	Akaike Information Criterion
ASCO	American Society of Clinical Oncology
ASCT	Allogeneic stem cell transplant
ASH	American Society of Hematology
BCSH	British Committee for Standards in Haematology
BIC	Bayesian Information Criterion
BR	Bendamustine plus rituximab
BSC	Best supportive care
BTK	Bruton's tyrosine kinase
CDF	Cancer Drug Fund
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIRS-G	Cumulative Illness Rating Scale-Geriatric
Clad-R	Cladribine plus rituximab
CLL	Chronic lymphocytic leukaemia
CMV	Cytomegalovirus
CR	Complete response
CS	Company's submission
CSR	Clinical study report
CT	Computerised tomography
DARE	Database of Abstracts of Reviews of Effects
DCO	Data-cut off
dL	Decilitre
DOR	Duration of response
DRC	Dexamethasone, rituximab and cyclophosphamide
DSA	Deterministic sensitivity analysis
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
ECR	European chart review
EHA	European Hematology Association
EMA	European Medicines Agency
Embase	Excerpta Medica database
eMC	Electronic Medicines Compendium
EPAR	European Public Assessment Report
EPOC	Effective Practice and Organisation of Care
EQ-5D-5L	Euroqol EQ-5D 5-level
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FACT-Lym	Functional Assessment of Cancer Therapy - Lymphoma
FCR	Fludarabine, rituximab and cyclophosphamide
FR	Fludarabine plus rituximab
GVHD	Graft-versus-host-disease
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
HVS	Hyperviscosity
HZV	Herpes zoster virus
ICER	Incremental cost-effectiveness ratio

IgM	Immunoglobulin M
IPSSWM	International Prognostic Scoring System for Waldenström's macroglobulinemia
IRRC	Independent Response Review Committee
ISPOR	International Society For Pharmacoeconomics and Outcomes Research
ITS	Interrupted time series
IV	Intravenous
IWWM	International Workshop on Waldenström's Macroglobulinemia
K-M	Kaplan-Meier
LPL	Lymphoplasmacytic lymphoma
LPL	Lipoprotein lipase
LYG	Life year gained
MCL	Mantle cell lymphoma
MEA	Managed entry agreement
MEDLINE	Medical Literature Analysis and Retrieval System Online
mg	Milligram
ml	Millilitre
NHL	Non-Hodgkin's Lymphomas
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NR	Not reported
o.d.	Once daily
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme
PC	Physician's choice
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
R/R	Relapsed/refractory
R-CHOP	Rituximab, cyclophosphamide, vincristine and prednisolone
RCT	Randomised controlled trial
RDI	Relative dose intensity
REAL	Revised European American Lymphoma
SAE	Serious adverse event
SCT	Stem cell transplantation
SD	Stable disease
SLL	Small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
SOC	Standard of care
TTP	Time to progression
UK	United Kingdom
ULN	Upper limit of normal
US	United States
VGPR	Very good partial response
WHO	World Health Organization
WM	Waldenström's macroglobulinemia
WTP	Willingness-to-pay

1. SUMMARY

1.1 Critique of the decision problem in the company's submission

Waldenström's macroglobulinemia (WM) is a lymphoproliferative B-cell disorder characterised by infiltration of lymphoplasmacytic cells into the bone marrow and immunoglobulin M (IgM) monoclonal gammopathy. WM is considered to be a lymphoplasmacytic lymphoma (LPL) by both the Revised European American Lymphoma (REAL) and World Health Organization (WHO) classification systems. WM is a rare disease which accounts for less than 2% of all non-Hodgkin's Lymphomas (NHLs). WM typically affects the elderly; the median age at diagnosis is estimated to be >70 years and patients are predominantly male. The incidence of WM appears to be lower in non-Caucasians. Current estimates from the British Committee for Standards in Haematology (BCSH) suggest an incidence rate of WM of 0.55 per 100,000 people per year in the UK; this leads to an estimated 292 new cases in England each year. Whilst WM is incurable, the early stage of the disease is typically asymptomatic and follows an indolent course, and progression to symptomatic disease is typically slow. Based on the International Prognostic Scoring System for WM (IPSSWM), median survival is estimated to be 11.88 years for low-risk patients and 3.63 years for high-risk patients.

The decision problem required an assessment of the clinical effectiveness and cost-effectiveness of ibrutinib compared with rituximab/chemotherapy options in two populations: (i) adults with WM who have received at least one prior therapy, and; (ii) adults with WM who have not received prior therapy and for whom chemo-immunotherapy is unsuitable.

The intervention under appraisal is ibrutinib (Imbruvica®). Ibrutinib is a first-in-class Bruton's tyrosine kinase (BTK) inhibitor. Within its WM indication, ibrutinib is administered orally at a recommended dose of 420mg (three 140mg capsules) once daily (o.d.). Treatment with ibrutinib should be continued until disease progression or until the therapy is no longer tolerated by the patient. Ibrutinib is available in packs of 90 capsules or 120 capsules. As of August 2016, the NHS indicative list price for ibrutinib is £4,599 per pack of 90 capsules or £6,132 per pack of 120 capsules (£51.10 per capsule). A Patient Access Scheme (PAS) is currently in place for ibrutinib: under the PAS, the price for ibrutinib is [redacted] per pack of 90 capsules or [redacted] per pack of 120 capsules ([redacted] per capsule). According to the company's submission (CS), the company is currently in the process of agreeing a further confidential commercial access arrangement with NHS England; details of this arrangement had not been agreed at the time of this assessment.

The CS states that the decision problem addressed is in line with the scope. However, this is not accurate: the CS does not contain any clinical or economic evidence for ibrutinib within the population of treatment-naïve patients for whom chemo-immunotherapy is unsuitable. The company's clinical review reflects patients with relapsed/refractory (R/R) disease; the company's health

economic analysis focusses specifically patients with R/R WM who have received one prior line of therapy.

The comparator considered in the company's health economic model includes a blend of alternative second-line rituximab/chemotherapy options. Specifically, the model includes: (i) bendamustine and rituximab (BR); (ii) dexamethasone, rituximab and cyclophosphamide (DRC); (iii) fludarabine, cyclophosphamide and rituximab (FCR); (iv) cladribine and rituximab; (v) cladribine monotherapy; (vi) rituximab monotherapy; (vii) chlorambucil and rituximab, and; (viii) chlorambucil monotherapy. This set of options is broadly in line with the final NICE scope, with the exceptions that rituximab and fludarabine (without cyclophosphamide) is not considered as a treatment option and chlorambucil is assumed to be given either in combination with rituximab or as monotherapy (rather than only as monotherapy).

The CS presents analyses according to the following outcomes: overall survival (OS); progression-free survival (PFS); response rate; duration of response/remission; adverse events (AEs), and; health-related quality of life (HRQoL). With respect to the relative effectiveness of ibrutinib versus other treatments for WM, a comparison is only made in terms of PFS. OS gains associated with ibrutinib compared with rituximab/chemotherapy can be inferred from the company's health economic model but are not presented comparatively as part of the clinical evidence review within the CS. With the exception of pre-planned subgroup analyses of overall response and major response within Study 1118E, the CS does not contain any subgroup analyses.

The CS does not present an argument that ibrutinib satisfies NICE's End-of-Life criteria within the WM indication. Within the CS, the company requests that ibrutinib is included on the Cancer Drug Fund (CDF) and sets out a proposed managed entry agreement (MEA) including the collection of additional data.

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS identified one relevant single-arm study. In Study 1118E, 63 previously-treated adult patients with WM from across three sites in the USA were allocated to receive the licensed 420mg/day dose. Treatment was administered for a median of 19.1 months (range, 0.5 to 29.7 months) and 43/63 patients (68%) remained on treatment after the final data cut-off (DCO) on 19th December 2014. The median age was 63.0 years (mean age = 64.5 years); the majority of patients were male (76.2%). The median time from diagnosis of WM to study entry was 76 months (range: 6 to 340 months). The median number of prior regimens was 2 (range: 1 to 9).

The principal efficacy outcomes were response and PFS. The reported overall response rate (ORR,

any response) was 90.5% (95% confidence interval [CI] 80.4% to 96.4%), which was achieved by 57/63 patients. Responders were categorised as follows: very good partial response (VGPR): n=10; partial response (PR): n=36; and minor response: n=11. The major response rate (defined as PR or better) was 73% (95% CI 60.3% to 83.4%). Based on data only available in the clinical study report (CSR), the Kaplan-Meier estimate for the event-free rate for all responders at 18 months was 80.9% (95% CI 64.9% to 90.2%), and the corresponding values for major responders were 86.7% (95% CI 67.9% to 94.9%). The CS presents subgroup analyses of ORR and major response rate and reports that response rates were "consistent across most subgroups" (e.g. by age, Eastern Cooperative Oncology Group [ECOG] score at baseline, IPSSWM risk score). The CS reported two slightly different definitions of PFS relating to Study 1118E. The Kaplan-Meier curve estimates the PFS rate at 24 months to be 69.1% (95% CI 53.2% to 80.5%). By the end of data collection (19th December 2014 DCO), 60 of the 63 patients were still alive and the estimated rate of OS was 95.2% (95% CI 86% to 98.4%).

Treatment with ibrutinib resulted in a significant decline in median percentage of bone marrow infiltration from 60% to 25% ($p<0.001$). There was no correlation between serum IgM levels and bone marrow involvement at 6 months ($r=0.03$, $p=0.83$), but there was at 12 months ($r=0.51$, $p<0.001$) and at 24 months ($r=0.56$, $p<0.008$). At baseline, adenopathy and splenomegaly were identified by computed tomography (CT) in 37/63 (59%) and 7/63 (11%) patients, respectively, and the number of patients with lymphadenopathy and splenomegaly were reduced after ibrutinib treatment.

Given the absence of randomised head-to-head evidence comparing ibrutinib versus any other WM treatment, the CS presents an indirect comparison of PFS data from Study 1118E and a matched cohort from a retrospective European chart review. This indirect comparison estimated the hazard ratio (HR) for PFS for ibrutinib versus standard therapies. The company's multivariable Cox model produced an estimated HR for PFS for ibrutinib versus standard therapies of [redacted]). The use of alternative imputation methods produced more favourable HRs for PFS ranging from [redacted]) to [redacted]).

The CS concludes that, in terms of efficacy, the clinical data demonstrated benefit with ibrutinib treatment in 63 patients with R/R WM treated with ibrutinib. Treatment with ibrutinib also resulted in rapid reduction in serum IgM and improvement in haemoglobin, reversing the principal underlying causes of treatment-related morbidities.

On account of the small number of patients (n=63) in the only relevant trial in WM (Study 1118E), the CS also reports some safety results from selected supplementary studies in which patients with

chronic lymphocytic leukaemia (CLL) or mantle cell lymphoma (MCL) received ibrutinib: RESONATE (PCYC-1112), RESONATE-2 (PCYC-1115), PCYC-1102, PCYC-1103 and PCYC-1104. The CS states that in Study 1118E and the supplementary trials, the majority of adverse events (AEs) were mild to moderate in severity, with a low incidence of grade 3/4 AEs. Ibrutinib was therefore well tolerated, with a discontinuation rate of 9.5% following a median treatment duration of 19.1 months.

There is one single ongoing study: PCYC-1127-CA (iNNOVATE - NCT02165397). This is an international (including UK), multi-centre, Phase III trial evaluating the safety and efficacy of ibrutinib in combination with rituximab in patients with WM. Ibrutinib is not currently licensed as a combination therapy. This study includes a third arm of ibrutinib monotherapy, an open-label sub-study for 31 patients who are refractory to rituximab. The study was initiated in July 2014 and the estimated completion date is January 2019. The CS states that interim results are expected in April 2017 at the earliest, but some efficacy and safety data were presented in the CS.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The reviews of the clinical efficacy and safety evidence were poorly reported and there was a lack of high quality evidence. There were no randomised controlled trials (RCTs) or non-randomised controlled trials of ibrutinib in the relevant populations outlined in the final NICE scope. The clinical evidence consisted of one Phase II, single-arm, open-label study of ibrutinib in 63 adult patients with WM who had received at least one prior therapy - Study 1118E (PCYC-1118E). The CS does not contain any clinical evidence relating to the effectiveness of ibrutinib for treatment-naïve patients with WM who are unsuitable for chemo-immunotherapy.

The Evidence Review Group (ERG) has a number of concerns regarding Study 1118E. Whilst the study was generally well-reported, it was at high risk of selection, performance and other bias, not only on account of its study design but also because of inadequate reporting of outcome measurement. The trial had only 63 patients, who were generally younger and had less severe disease than the R/R adults with WM who might routinely present in practice England. The outcome measures used were generally valid and reliable but the response criteria (the primary outcome) were "modified" from international standards. With the exception of complete response (CR), the definitions of minor response, PR and VGPR applied in Study 1118E, as reported in the CS and protocols, appear to differ from internationally recognised response criteria: in Study 1118E, they are limited to serum IgM level only, whilst international standards also require the presence or absence of clinically significant findings or symptoms. The ERG notes that IgM response alone is insufficient as an outcome for WM because clinical benefit might be seen in patients without IgM response, or IgM reduction might not see an improvement of symptoms. It also generally appears to be the case that response rates were

"consistent across most subgroups", although differences in major response are particularly apparent for patients with different levels of ß$_2$–microglobulin, haemoglobin, bone marrow disease involvement and genotype MYD88^{L265P} and CXCR4^{WT}.

With respect to the company's indirect comparison, the ERG has concerns regarding the reliability of the reported estimate of treatment effect, in particular: (i) the potential for unadjusted confounders; (ii) the lack of a unique matched sample from the chart review, and; (iii) the exclusion of patients who had received five or more prior lines of treatment. In addition, the CS does not contain an analysis of the relative survival benefits of ibrutinib versus standard therapies used in the treatment of WM.

AEs of any grade were very frequent in all trials, with up to 100% of patients in any of the included studies experiencing at least one AE and between 42% and 57% experiencing the most frequent event, diarrhoea. Grade 3 and 4 AEs were experienced by 49% and 57% of patients in Study 1118E and RESONATE, respectively. The grade 3 and 4 events that occurred most often in Study 1118E were: neutropenia (14%); thrombocytopenia (13%); pneumonia (8%), and; gastroesophageal reflux (5%). The findings of the supplementary studies were generally consistent with those of Study 1118E in terms of type and frequency of grade 3 and 4 AEs ($\geq$2%). The most frequent grade 3 or 4 AEs were: neutropenia (up to 16% in any study); thrombocytopenia and anaemia (up to 11%), and; pneumonia (up to 7%). In Study 1118E, 6 out of 63 patients (10%) discontinued treatment due to AEs (not including disease progression): possible treatment-related disease transformation; treatment-aggravated thrombocytopenia; infection unrelated to ibrutinib; haematoma post bone marrow biopsy and myelodysplasia and acute myeloid leukaemia related to prior treatments. The other ibrutinib studies reported a rate of between 4% and 11% discontinuation due to AEs. The proportion of deaths within the ibrutinib arms of the included trials ranged from 2% to 11%; according to the studies, none of the deaths were related to ibrutinib.

1.4 Summary of cost-effectiveness submitted evidence by the company

The CS includes a systematic review of published economic evaluations of treatments for WM together with a *de novo* health economic evaluation of ibrutinib versus rituximab/chemotherapy in adult patients with R/R WM. The company's review did not identify any full economic evaluations relating to ibrutinib or any other therapy for WM.

The company's *de novo* economic model adopts a sequence-based Markov approach to estimate the costs and health outcomes for ibrutinib versus rituximab/chemotherapy for patients with R/R WM from the perspective of the NHS and Personal Social Services (PSS) over a 30-year (lifetime) horizon. The company's model includes five health states: (1) second-line progression-free; (2) third-line progression-free; (3) fourth-line progression-free; (4) best supportive care (BSC), and; (5) dead. The

model uses parametric curves fitted to data on PFS, time to progression, pre-progression mortality and post-progression survival to inform transition rates between the health states. Transitions between states are modelled according to a 28-day cycle length (392 cycles). Patients enter the model in the second-line progression-free state and receive treatment with ibrutinib or rituximab/chemotherapy. Within the ibrutinib group, the probability of being progression-free at any time *t* is modelled using a parametric (Weibull) survivor function fitted to the empirical PFS time-to-event data from Study 1118E. Within the ibrutinib group, the probability that a patient leaving the second-line progression-free state dies is modelled using age- and sex-adjusted general population mortality hazards derived from life tables. Within the rituximab/chemotherapy group, PFS in second-line is modelled using the inverse of the HR derived from the multivariable Cox model applied to the ibrutinib PFS curve, whilst the probability that a patient leaving the second-line progression-free state dies is modelled using data derived from the matched European chart review cohort (1-4 prior lines of therapy). Within both treatment groups, progression events in the third- and fourth-line progression-free states were estimated using data from the European chart review for patients who were starting fourth-line treatment, whilst the probability of death in all post-second-line progression-free states was based on data from the European chart review for patients who had progressed from third-line treatment. A proportion of patients transit directly to BSC after progressing from each line of therapy. Health utility is differentiated according to the presence/absence of disease progression, with a higher baseline value applied to each of the progression-free states compared with the BSC state. Disutilities associated with AEs are included only for second-line treatment; AEs associated with active subsequent-line treatment are not included in the model. The company's model includes costs associated with: (i) drug acquisition; (ii) drug administration (applied to the rituximab/chemotherapy regimens only); (iii) routine follow-up; (iv) the management of AEs; (v) BSC, and; (vi) terminal care.

Based on a re-run of the probabilistic version of the company's base case model by the ERG, ibrutinib (including the PAS) is expected to produce an additional [redacted] quality-adjusted life years (QALYs) at an additional cost of [redacted] compared with rituximab/chemotherapy; the incremental cost-effectiveness ratio (ICER) for ibrutinib versus rituximab/chemotherapy is expected to be £58,905 per QALY gained. The results of the deterministic model are similar, with ibrutinib yielding an ICER of £58,630 per QALY gained compared with rituximab/chemotherapy. Assuming a willingness-to-pay (WTP) threshold of £30,000 per QALY gained, the company's base case model suggests that the probability that ibrutinib produces more net benefit than rituximab/chemotherapy is approximately zero. The company's deterministic sensitivity analyses (DSAs) and scenario analyses indicate that the ICER for ibrutinib versus rituximab/chemotherapy is expected to be greater than £47,000 per QALY gained across all analyses.

1.5 Summary of the ERG's critique of cost-effectiveness evidence submitted

The ERG critically appraised the company's economic analysis and partially double-programmed the deterministic version of the model. The ERG's critical appraisal identified several issues relating to the company's economic analysis and the evidence used to inform it. The most pertinent issues included: (i) the absence of any economic analysis of ibrutinib for treatment-naïve patients in whom chemo-immunotherapy is unsuitable; (ii) concerns regarding the company's modelling approach, in particular the use of a sequence-based model, the modelling of death conditional on PFS, and the mismatch between the evidence required for the model and the evidence available for the appraisal; (iii) ambiguity surrounding the data used to inform pre-progression mortality for rituximab/chemotherapy (iv) the use of general population life tables to model pre-progression mortality within the ibrutinib group; (v) the limited evidence to quantify the health gains associated with ibrutinib versus any other WM therapy; (vi) model errors and inconsistencies surrounding costs, and; (vii) the incomplete characterisation of uncertainty.

The ERG undertook ten sets of exploratory analyses using the company's submitted model. The ERG's preferred base case involved re-estimating drug acquisition and administration costs, rectifying an apparent error in the follow-up costs and applying the pre-progression mortality rate observed within Study 1118E to the ibrutinib group. The remaining exploratory analyses focussed on assessing the uncertainty surrounding the utility score for the BSC state, the HR for PFS, the costs of rituximab/chemotherapy, the parametric function used to model pre-progression mortality for rituximab/chemotherapy and removing the modelled survival benefit for ibrutinib. Given the weaknesses of the company's model and the evidence used to inform it, all ICERs reported in the CS and within the ERG's exploratory analyses should be interpreted with caution.

The ERG's preferred analysis resulted in an ICER for ibrutinib versus rituximab/chemotherapy of £61,219 per QALY gained. The other exploratory analysis did not produce markedly different ICERs, with the exception of the scenario in which the survival gain for ibrutinib was removed from the model; within this analysis, the ICER for ibrutinib versus rituximab/chemotherapy was increased to £390,432 per QALY gained. The ERG's threshold analysis around the HR for PFS suggests that under the ERG's base case assumptions, the lowest possible deterministic ICER for ibrutinib versus rituximab/chemotherapy is estimated to be £59,620 per QALY gained (HR~[redacted]). Under the company's more favourable scenario which is based on general population pre-progression mortality rates, the lowest possible deterministic ICER for ibrutinib versus rituximab/chemotherapy is estimated to be £56,917 per QALY gained (HR~[redacted]).

1.6 ERG commentary on the robustness of evidence submitted by the company

Strengths

The ERG considers that the CS includes all relevant clinical evidence relating to the use of ibrutinib for the treatment of WM.

Weaknesses and areas of uncertainty

The ERG notes that the main limitations of the company's submission relate to the following:

- The absence of any RCT or non-randomised controlled trial in the previously-treated WM population
- The absence of any clinical evidence on the treatment-naïve WM population defined in the final NICE scope
- The principal evidence consists of one single–arm, open-label study of 63 patients, which, on account of its design and elements of reporting, is at high risk of selection, performance and other bias
- Uncertainty surrounding the extent to which the population in Study 1118E represents the population likely to present in clinical practice in England
- The response measure in Study 1118E used different criteria from accepted international standards and other details of the assessment were unclear
- An indirect estimate of the effect of ibrutinib versus rituximab/chemotherapy on PFS was based on an adjusted arm-based comparison against a mixed comparator and excluded patients who had previously received at five or more prior lines of treatment
- AEs of any grade were very frequent but were generally mild, although approximately 50% of patients in two studies have reported grade 3 or 4 AEs.
- Given the weaknesses in the company's model and the evidence used to inform it, the true ICER for ibrutinib versus rituximab/chemotherapy is unclear.

The CS requests the inclusion of ibrutinib on the CDF and presents details regarding the establishment of a proposed MEA including additional data collection around clinical outcomes for treatment-naïve and R/R WM patients (including comparative effectiveness), HRQoL, and resource use. The ERG's exploratory threshold analyses suggest that even under the company's assumption of general population mortality rates whilst patients are receiving ibrutinib, the ICER for ibrutinib versus rituximab is not expected to be below £56,917 per QALY gained, irrespective of the HR for PFS. Other things being equal, this represents the best case scenario for the cost-effectiveness of ibrutinib versus rituximab/chemotherapy in the R/R WM setting. The ERG therefore considers it unlikely that further data collection will lead to a more favourable cost-effectiveness profile for ibrutinib.

2. BACKGROUND

This chapter presents a brief summary and critique of the company's description of Waldenström's macroglobulinemia (WM) and treatments currently available for the management of the disease. Where appropriate, the information provided in the company's submission (CS)[1] has been augmented using current clinical guidelines[2, 3] and other literature.[4-6]

2.1 Critique of company's description of underlying health problem

WM is a lymphoproliferative B-cell disorder characterised by infiltration of lymphoplasmacytic cells into the bone marrow and immunoglobulin M (IgM) monoclonal gammopathy.[6] WM is considered to be a lymphoplasmacytic lymphoma (LPL) by both the Revised European American Lymphoma (REAL) and World Health Organization (WHO) classification systems. WM is a rare disease which accounts for less than 2% of all non-Hodgkin's Lymphomas (NHLs).[6] WM typically affects the elderly; the median age at diagnosis is estimated to be >70 years and patients are predominantly male.[2] The incidence of WM appears to be lower in non-Caucasians.[4] Current estimates from the British Committee for Standards in Haematology (BCSH) suggest an incidence rate of WM of 0.55 per 100,000 people per year in the UK; based on a current English population size of approximately 53 million persons, this leads to an estimated 292 new cases in England each year.

Whilst WM is incurable, the early stage of the disease is typically asymptomatic and follows an indolent course, and progression to symptomatic disease is typically slow.[1] Diagnosis requires demonstration of an IgM monoclonal protein and histological evidence of bone marrow infiltration by lymphoplasmacytic cells. Several factors are associated with a poor prognosis, including: (i) advanced age (>65 years); (ii) β2-microglobulin >3mg/L; (iii) anaemia (haemoglobin ≤11.5g/dL); thrombocytopenia (platelet count ≤100 x 109/L) and, (iv) IgM monoclonal gammopathy (IgM >7.0g/dL).[6] The International Prognostic Scoring System for WM (IPSSWM) for newly diagnosed patients with WM has recently been developed based on these risk factors; current estimates indicate a considerable difference in 5-year survival rate according to risk category (see

Table 1). The CS states that this scoring system is used clinically to guide treatment choices once the patient has become symptomatic.[1] Clinical advisors to the Evidence Review Group (ERG) stated that treatment choices are typically guided by overall performance status and the presence of comorbidities.

Table 1: Survival prognosis according to IPSSWM risk category (adapted from Morel *et al*[5])

Risk category	Definition	Median survival (years)	5-year survival
Low-risk	Aged ≤65 years plus not more than 1 adverse characteristic	11.88	87%
Intermediate-risk	2 adverse characteristics or aged >65 years	8.22	68%
High-risk	3 or more adverse characteristics	3.63	36%

Adverse characteristics are aged >65 years; platelet count ≤100 X 109/L; β2-microglobulin >3 mg/L; haemoglobin ≤11.5 g/dL; monoclonal IgM concentration >7.0 g/dL; granulocytes ≤1.5 X 109/L; albumin ≤3.5 g/dL.

Clinical manifestations of WM include cytopenias (anaemia) and lymphadenomegaly resulting from infiltration by lymphoplasmacytic cells and IgM paraprotein-related symptoms such as: cryoglobulinemia; cold agglutinin syndrome; demyelinating neuropathy; amyloidosis (involving kidneys, heart and nervous system); infections, and; symptomatic hyperviscosity (visual disturbance, headache, dizziness, altered consciousness, fatigue and weakness).[6]

There is a dearth of evidence relating to the impact of WM and its treatment on health-related quality of life (HRQoL); the CS[1] highlights that there is no disease-specific instrument for measuring HRQoL in patients with WM. The CS includes brief details relating to a survey of [redacted] patients with WM (of whom, [redacted] of respondents to the question on disease stage had relapsed or refractory (R/R) WM); respondents reported that the symptoms which impacted most on their quality of life were: tiredness or lack of energy; weakness; frequent infections; tingling or numbness in the feet or legs, and; shortness of breath.[1]

The CS highlights that current treatments for WM may also have a significant detrimental impact on patients' HRQoL. In particular, cytopenias resulting from bone marrow infiltration by lymphoplasmacytic cells and the adverse effects of immunoglobulins, can cause painful complications such as cryoglobulinaemia and neuropathy, and patients experiencing hyperviscosity may suffer catastrophic sequelae including irreversible vision loss. The CS notes that patients with WM are also at increased risk of thrombosis and may suffer treatment-related morbidities such as secondary infections, thrombosis and second malignancies including myelodysplastic syndrome, acute myeloid leukaemia, and solid cancers.[1]

2.2 Critique of company's overview of current service provision

There is currently no guidance from the National Institute for Health and Care Excellence (NICE) relating to the diagnosis or treatment of WM. The CS describes the key guidelines on treatment for WM (see CS,[1] pages 31-34) which have been published by the BCSH (Owen *et al*, 2014[2]) and the European Society for Medical Oncology (ESMO) (Buske *et al*, 2013[3]). Both guidelines were

published prior to the European Medicines Agency (EMA) issuing regulatory approval for ibrutinib. It is recognised in the included guidelines,[2, 3] and acknowledged in the CS,[1] that there is a lack of randomised evidence for WM treatments, especially as part of combination therapy. The evidence base for this appraisal is therefore limited.

With respect to the first-line of treatment of medically fit patients, both sets of guidelines advocate a combination of rituximab with chemotherapy, with the deferral of rituximab in cases of "IgM flare." Both guidelines reject the use of rituximab as a maintenance therapy due to limited evidence available to support its use (see
Table 2). The guidelines differ with respect to recommendations on the use of R-CHOP (rituximab, cyclophosphamide, vincristine and prednisolone) and bortezomib (which was delisted from the Cancer Drug Fund (CDF) in 2015, see CS,[1] page 34) and also in terms of statements on the efficacy of chlorambucil relative to other agents.

Table 2: Guideline recommendations for first-line treatment of WM

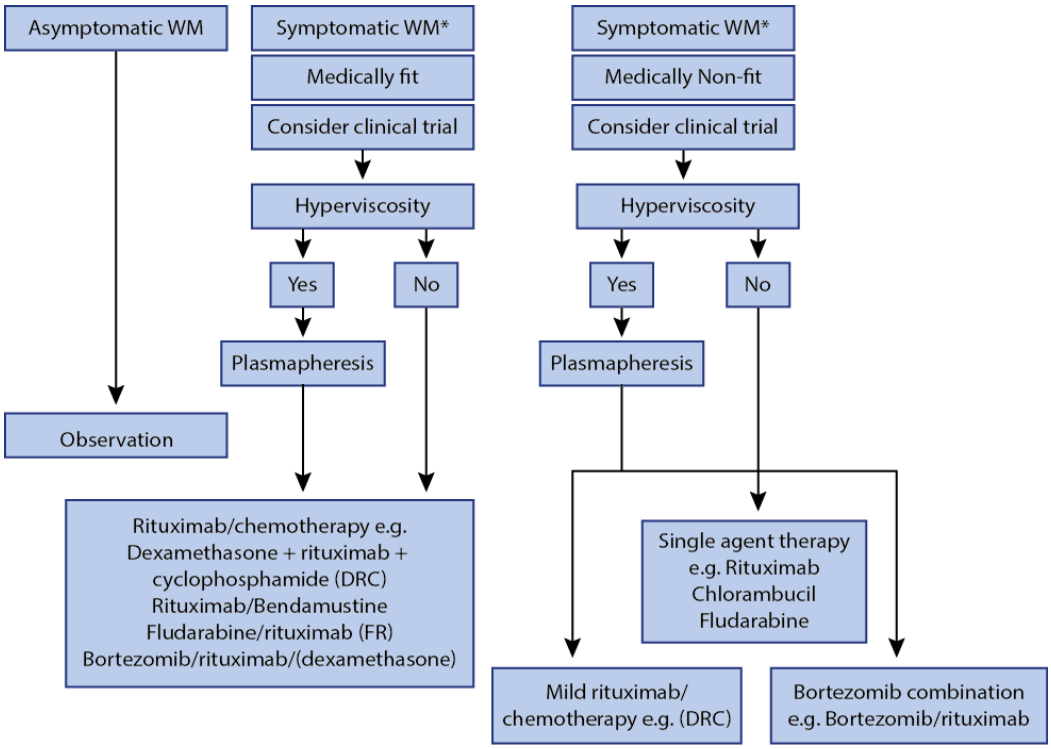
BSCH[2]	**ESMO[3]**
• Patients with symptomatic WM should receive a rituximab-containing regimen, e.g. DRC, BR, FR, FCR or Clad-R. The choice of regimen in individual patients will take into consideration performance status, clinical features including renal function, co-morbidities and potential candidacy for stem cell transplantation (SCT). • Given the risk of IgM flare, careful monitoring of all patients receiving rituximab is required. Rituximab should be deferred in patients at high risk of hyperviscosity. • R-CHOP should not be used as primary therapy in WM. • Chlorambucil remains a suitable therapy in elderly frail patients. • Bortezomib is not recommended as primary therapy outside the context of a clinical trial. • There is insufficient evidence to support the use of maintenance rituximab.	• Options for symptomatic patients who are medically fit are rituximab in combination with alkylating agents are DRC or R-CHOP. • Rituximab can be combined with cladribine, fludarabine, bendamustine or bortezomib (with or without dexamethasone). • In medically non-fit patients (e.g. patients who do not tolerate chemotherapy because of non-lymphoma-related co-morbidities) single-agent rituximab is a treatment option, which avoids chemotherapy-related toxic effects. However, responses are delayed and, particularly in patients with signs of hyperviscosity or patients with high IgM values, there is the danger of so-called 'IgM flare', a transient increase of serum IgM immediately following initiation of rituximab treatment. In these patients, plasmapheresis should precede rituximab application. • Fludarabine as a single-agent is more effective than chlorambucil. • Rituximab maintenance treatment outside of clinical trials is not considered standard today.

DRC – dexamethasone, rituximab and cyclophosphamide; BR – bendamustine plus rituximab; FR – fludarabine plus rituximab; FCR – fludarabine, rituximab and cyclophosphamide; clad-R – cladribine plus rituximab; R-CHOP - rituximab,

cyclophosphamide, vincristine and prednisolone; Immunoglobulin M; SCT – stem cell transplantation; WM - Waldenström's macroglobulinemia.

Figure 1 presents the ESMO algorithm for the first-line treatment of WM.

Figure 1: ESMO algorithm for first-line treatment in WM



With respect to treatment for medically fit patients with R/R disease, both sets of guidelines advocate continuing with a rituximab and chemotherapy combination, albeit using a different regimen from that given as first-line treatment (see Table 3).

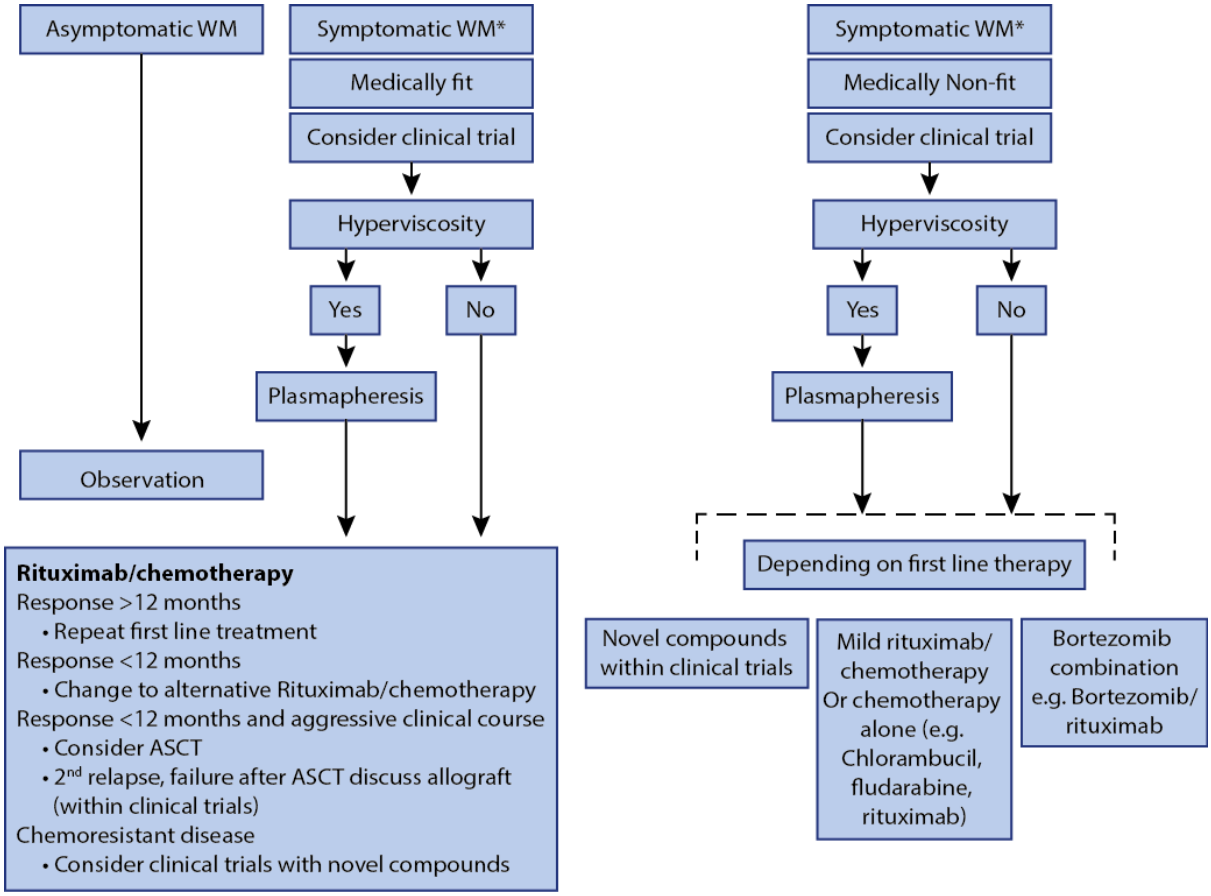
Table 3: Guideline recommendations for the treatment of R/R WM

BSCH[2]	ESMO[3]
• Patients who remain asymptomatic despite serological evidence of progression can be observed until clinical symptoms occur. • Repeat bone marrow aspirate and trephine assessment and CT scanning should be performed prior to the re-introduction of treatment. • The choice of regimen at relapse includes regimens discussed in the first-line treatment section. • Appropriate regimens include FR, FCR, Clad-R, BR and DRC. The choice of regimen in individual patients will take into consideration performance status, clinical features including renal function, comorbidities and potential candidacy for SCT. • Patients should receive a rituximab-containing regimen if CD20 is expressed. • Retreatment with primary therapy may be appropriate in some patients. • Bortezomib-containing regimens are suitable in the relapse setting. Weekly regimens are preferable, given the neurological toxicity associated with the bi-weekly schedules. Prophylaxis against herpes zoster virus (HZV) reactivation is recommended. • Alemtuzumab is a potential option in refractory disease.* Surveillance for cytomegalovirus (CMV) reactivation is recommended.	• There is a consensus that an alternative rituximab/chemotherapy regimen should be used if the relapse occurs within the first year. • The choice of the rituximab/chemotherapy regimen depends on the prior regimen. If the patient was treated initially with rituximab plus alkylating agents, the salvage regimen could be switched to rituximab in combination with nucleoside analogues, rituximab/bendamustine or bortezomib and *vice versa*. • If patients are chemosensitive and eligible for autologous SCT, then myeloablative chemotherapy followed by reinfusion of autologous stem cells is a valid option in these clinically aggressive cases. • Allogeneic transplantation may be considered in young relapsed patients with aggressive clinical course, but preferably within clinical trials.

DRC – dexamethasone, rituximab and cyclophosphamide; BR – bendamustine plus rituximab; FR – fludarabine plus rituximab; FCR – fludarabine, rituximab and cyclophosphamide; clad-R – cladribine plus rituximab; R-CHOP - rituximab, cyclophosphamide, vincristine and prednisolone; R/R WM – relapsed/refractory Waldenström's macroglobulinemia; HZV herpes zoster virus; CMV – cytomegalovirus; SCT – stem cell transplantation.
** Alemtuzumab is now only available on a named-patient basis*

The ESMO algorithm for the treatment of patients with R/R WM is presented in Figure 2.

Figure 2: ESMO algorithm for treatment of WM patients with relapsed/refractory disease



Clinical advisors to the ERG confirmed that the BCSH and ESMO guidelines generally reflect current clinical practice and there is currently no licensed treatment that represents the standard of care for WM. Rather, standard treatment (taking into account the fitness of the patient) tends to be based on treatment options originally developed for other lymphoproliferative diseases including multiple myeloma and chronic lymphocytic leukaemia (CLL). Clinical advisors to the ERG noted that for many patients of advancing age and frailty there are very few effective options for WM, particularly for those with R/R disease. Given this unmet need, ibrutinib has been granted an orphan designation by the EMA.[6]

3. CRITIQUE OF THE COMPANY'S DEFINITION OF THE DECISION PROBLEM

This chapter presents a summary and critique of the decision problem addressed by the CS.[1] A summary of the decision problem as outlined in the final NICE scope[7] and addressed in the CS[1] is presented in Table 4.

Table 4: Company's statement of the decision problem (adapted from CS Table 1)

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from final NICE scope
Population	• 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.		The decision problem addressed is in line with final NICE scope
Intervention	Ibrutinib		The decision problem addressed is in line with final NICE scope
Comparator (s)	<u>For adults with WM who have received at least one prior therapy:</u> • rituximab and bendamustine • rituximab, dexamethasone and cyclophosphamide • rituximab and fludarabine with or without cyclophosphamide • cladribine with or without rituximab • rituximab • chlorambucil <u>For adults with WM who have not received prior therapy and for whom chemo-immunotherapy is not suitable:</u> • chlorambucil • rituximab • best supportive care (BSC)	<u>For adults with WM who have received at least one prior therapy:</u> The physician's choice (PC) comparator encompassed the following treatments: • rituximab and bendamustine • rituximab, dexamethasone and cyclophosphamide • rituximab and fludarabine *with* cyclophosphamide • cladribine with or without rituximab • rituximab • chlorambucil *with* or without rituximab <u>For adults with WM who have not received prior therapy and for whom chemo-immunotherapy is not suitable:</u> • chlorambucil • rituximab • BSC	<u>For adults with WM who have received at least one prior therapy:</u> The PC comparator aims to accurately reflect the fact that there is currently no licensed (other than ibrutinib) or funded treatment for these patients, and there is no clear standard of care for patients with WM. PC is comprised of the comparators listed within the final NICE scope with the exception of rituximab in combination with fludarabine and without cyclophosphamide based on clinical opinion. Furthermore, chlorambucil with rituximab was included within the PC composition. The selection of PC as the key comparator, as well as its composition, was validated by UK clinical opinion.[8, 9] <u>For adults with WM who have not received prior therapy and for whom chemo-immunotherapy is not suitable:</u> As per scope.
Outcomes	• Overall survival (OS) • Progression free survival (PFS) • Response rate • Duration of response / remission • Adverse effects of treatment • HRQoL	• OS • PFS • Response rate • Duration of response / remission • Adverse effects of treatment • HRQoL	As per scope

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from final NICE scope
Economic analysis	• The cost-effectiveness of treatments is expressed in terms of incremental cost per quality-adjusted life year (QALY) • The time horizon for estimating clinical and cost effectiveness is sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs are considered from a National Health Service (NHS) and Personal Social Services (PSS) perspective.	• The cost-effectiveness of treatments is expressed in terms of incremental cost per QALY • The time horizon for estimating clinical and cost effectiveness is sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs are considered from an NHS and PSS perspective.	As per scope
Subgroups to be considered	None detailed	No subgroup is considered in the CS	The decision problem addressed is in line with final NICE scope
Special considerations including issues related to equity or equality	None detailed	The population targeted by this submission is in line with that for which the EMA granted ibrutinib a license and for which ibrutinib has been scoped, i.e. WM patients who have received prior therapy, and have not received prior therapy and for whom chemo-immunotherapy is unsuitable. As such, the targeted population is broader than the one studied in the pivotal trial (Study 1118E), and includes patients with R/R WM.	Given that there is no treatment licensed and/or funded for WM patients, the addition of ibrutinib to the treatment pathway will address equity issues regarding the lack of effective treatments for patients with WM.

WM - Waldenström's macroglobulinemia' BSC – best supportive care; OS – overall survival; PFS – progression-free survival; HRQoL – health-related quality of life; QALY – quality-adjusted life year; NHS – National Health Service; PSS – Personal Social Services; EMA – European Medicines Agency; R/R – relapsed/refractory; PC – physician's choice; CS – company's submission

3.1 Population

The marketing authorisation for ibrutinib in the WM indication states that 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."*[10]

The final NICE scope[7] refers to two populations: (i) adults with WM who have received at least one prior therapy, and; (ii) adults with WM who have not received prior therapy and for whom chemo-immunotherapy is unsuitable. Whilst the CS[1] (Table 1, page 10) states that the decision problem addressed within the CS is in line with the scope, this is not accurate: the CS does not contain any clinical or economic evidence for ibrutinib in the population of treatment-naïve patients for whom chemo-immunotherapy is unsuitable.

The CS (page 22) highlights that the EMA European Public Assessment Report (EPAR) variation, dated 21st May 2015, includes discussion of the license to include untreated patients who are unsuitable for treatment with chemo-immunotherapy:[6]

"During the assessment the CHMP raised a major objection about the indication needing to be further discussed, with reference to first line setting. Based on historical comparisons of results obtained with ibrutinib in the R/R (Refractory/Relapsed) setting with efficacy and safety/tolerability for single drugs and combination therapies in the first line setting, the indication has been revised to include adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy. The restricted indication was considered acceptable as there is no reason to expect inferior efficacy or a worse safety profile in the first line setting, and for the group of patients unsuitable for chemo-immunotherapy, limited treatment options are currently available." (Committee for Medicinal Products for Human Use [CHMP] assessment report,[6] 21st May 2015).

The CS states that whilst Study 1118E[11] enrolled R/R WM patients only, the EMA approved ibrutinib for the treatment of WM patients both in the R/R and in the first-line setting, provided that first-line patients are ineligible for chemo-immunotherapy.

3.2 Intervention

The intervention under appraisal is ibrutinib (Imbruvica®). Ibrutinib is a first-in-class Bruton's tyrosine kinase (BTK) inhibitor. Within its WM indication, ibrutinib is administered orally at a recommended dose of 420mg (three 140mg capsules) once daily (o.d.). Ibrutinib has a separate orphan designation for WM under the category of "treatment of lymphoplasmacytic lymphoma"

which was granted by the EMA on 29th April 2014. Ibrutinib received a positive opinion for the treatment of WM from the CHMP on the 21st May 2015; marketing authorisation was subsequently granted by the European Commission (EC) on the 3rd July 2015. Ibrutinib also holds a European marketing authorisation for the treatment of adult patients with CLL and for the treatment of adult patients with R/R mantle cell lymphoma (MCL).[10]

The Summary of Product Characteristics (SmPC) recommends that treatment with ibrutinib should continue until disease progression or until the therapy is no longer tolerated by the patient.[10] According to the SmPC, ibrutinib should be withheld for any new onset or worsening grade ≥3 non-haematological toxicity, grade 3 or greater neutropenia with infection or fever, or grade 4 haematological toxicities. Following resolution of toxicity to grade 1 or baseline, ibrutinib may be reinitiated at the starting dose. If the toxicity reoccurs, the o.d. dose should be reduced by one capsule (140mg). A second reduction of dose by 140mg may be considered as needed. If these toxicities persist or recur following two dose reductions, treatment should be discontinued.[10] The dose of ibrutinib should be lowered to 140mg o.d. when used concomitantly with moderate CYP3A4 inhibitors. The dose of ibrutinib should be lowered to 140mg o.d. or withheld for up to 7 days when used concomitantly with strong CYP3A4 inhibitors.[10]

Ibrutinib is available in packs of 90 capsules or 120 capsules. As of August 2016, the NHS indicative list price for ibrutinib is £4,599 per pack of 90 capsules or £6,132 per pack of 120 capsules (£51.10 per capsule).[12] A Patient Access Scheme (PAS) is currently in place for ibrutinib: under the PAS, the price for ibrutinib is [redacted] per pack of 90 capsules, or [redacted] per pack of 120 capsules ([redacted] per capsule). According to the CS,[1] the company is currently in the process of agreeing a further confidential commercial access arrangement with NHS England; details of this arrangement had not been agreed at the time of this assessment.

The SmPC notes that the safety and efficacy of ibrutinib has not been established in paediatric patients and that no data are available.[10] No specific dose adjustment is required in elderly patients. The SmPC also notes that there are no data in patients with severe renal impairment or in patients on dialysis. Dose adjustments are recommended for patients with mild and moderate hepatic impairment. It is not recommended to administer ibrutinib to patients with severe hepatic impairment. The SmPC also notes that patients with severe cardiovascular disease were excluded from clinical studies of ibrutinib.

Contraindications to ibrutinib treatment include hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 of the SmPC and the use of preparations containing St. John's Wort.[10]

3.3 Comparators

The CS states that ibrutinib is the only licensed therapy for WM and that there is no clear standard of care for patients with WM. The comparator considered in the CS is referred to as "physician's choice" (PC) and, within the company's health economic model, is assumed to be comprised of a blend of alternative second-line rituximab/chemotherapy options including: (i) bendamustine and rituximab (BR); (ii) dexamethasone, rituximab and cyclophosphamide (DRC); (iii) fludarabine, cyclophosphamide and rituximab (FCR); (iv) cladribine and rituximab; (v) cladribine monotherapy; (vi) rituximab monotherapy; (vii) chlorambucil and rituximab, and; (viii) chlorambucil monotherapy. This set of options is broadly in line with the final NICE scope,[7] with the exceptions that rituximab and fludarabine (without cyclophosphamide) is not considered and chlorambucil is assumed to be given either in combination with rituximab or as monotherapy (rather than only as monotherapy).

The CS does not contain any direct head-to-head comparisons of ibrutinib versus any other therapy for WM. Instead, the CS reports the methods and results of an adjusted arm-based indirect comparison which compares outcomes from Study 1118E[11] against those derived from a retrospective European observational study[9] (the "European chart review") conducted in collaboration with the European Consortium for Waldenström's Macroglobulinemia. This indirect comparison was used to estimate a hazard ratio (HR) for the effect of ibrutinib versus standard therapies on PFS (see Sections 4.3 and 4.4).

Whilst health outcomes associated with second-line rituximab/chemotherapy within the company's health economic model were based on the subset of patients included in the matched European chart review cohort (n=175), the proportionate use of each rituximab/chemotherapy regimen was instead based on expert opinion (see Section 5.2).

3.4 Outcomes

The CS presents analyses of Study 1118E for the following outcomes:

- Overall survival (OS)
- Progression-free survival (PFS)
- Response rate
- Duration of response / remission
- Adverse events (AEs)
- HRQoL.

With respect to the relative effectiveness of ibrutinib compared with standard therapies, a comparison is only made in terms of PFS. OS gains associated with ibrutinib compared with

rituximab/chemotherapy can be inferred from the company's health economic model but are not presented comparatively as part of the clinical evidence base within the CS.

3.5 Economic analysis

The CS[1] includes the methods and results of a *de novo* model-based health economic analysis to assess the incremental cost-effectiveness of ibrutinib versus a blended comparator of rituximab/chemotherapy regimens for the second-line treatment of adults with R/R WM. As stated in Section 3.1, no economic analysis is presented for the first-line treatment of adults with WM for whom chemo-immunotherapy is unsuitable. The company's health economic analysis is detailed and critiqued in Chapter 5.

3.6 Subgroups

With the exception of pre-planned subgroup analyses of overall response and major response within Study 1118E (see CS[1] pages 47-48), the CS does not contain any subgroup analyses.

3.7 Special considerations

The CS notes that WM is a disease of the elderly and that the current most effective therapies are generally more suitable for younger fitter patients. Given that such treatments are toxic or immunosuppressive, these may be unsuitable for patients with a poor performance status and/or significant comorbidities. The CS also highlights that patients are currently managed with off-label treatments that do not target disease-specific abnormalities, but which are generally aimed at managing disease symptoms.

The CS does not present an argument that ibrutinib satisfies NICE's End-of-Life criteria within the WM indication. Within the CS, the company requests that ibrutinib is included on the CDF and sets out a proposed managed entry agreement (MEA) including additional data collection; this is discussed further in Section 5.5.

4. CLINICAL EFFECTIVENESS

This chapter presents a summary and critique of the reviews submitted by the company on the efficacy and safety of ibrutinib in adult patients with WM who have received at least one prior therapy, and as first-line treatment for patients who are unsuitable for chemo-immunotherapy. The ERG's critique was performed following the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and checklist.[13]

4.1 Critique of the methods of reviews

The CS[1] reports the methods and results of three reviews:

(i) A review of the efficacy and safety evidence from non-randomised and non-controlled studies (see CS, Sections 4.1 and 4.10);

(ii) A review of the efficacy evidence from randomised, non-randomised and non-controlled studies for the purposes of an indirect comparison (see CS, Sections 4.1 and 4.11), and;

(iii) A review of safety evidence from randomised and non-randomised studies, including five additional trials of ibrutinib in different populations (see CS, Section 4.12).

At the time at which the CS was submitted to NICE, there were no published randomised controlled trials (RCTs) or non-randomised controlled studies of ibrutinib in the relevant population. The company's review of efficacy evidence therefore consisted of the description of a single-arm open-label, non-controlled Phase II trial (PCYC-1118E, i.e. Study 1118E[11]), which was designed to assess the efficacy and safety of ibrutinib in R/R WM in patients with at least one prior therapy. This study formed the principal clinical evidence contained within the CS. A quality assessment of Study 1118E was not included in the CS, but was later provided in the company's clarification response (question B13).[14]

Following a request for clarification from the ERG regarding certain process elements adopted by the company, especially in terms of study identification and selection (see clarification response,[14] questions B5 - B12), the ERG considers the company's systematic review of efficacy and safety evidence for ibrutinib to be mostly sound, although the inclusion and exclusion criteria appear at times to be arbitrary.

The review undertaken to inform the company's indirect comparison (see CS, Section 4.11, and Sections 4.3 and 4.4 of this report) included only one source of data, a retrospective European chart review.[9]

The review of the safety evidence was not considered by the ERG to be a systematic review because it was unclear from the original submission how the evidence on populations other than WM was selected (the searches reported in Section 4.1 of the CS were restricted to WM). It was unclear how the trials PCYC-1102, PCYC-1103, PCYC-1112 (RESONATE), PCYC-1115 (RESONATE-2) (CLL populations) and PCYC-1104 (MCL population) were identified and selected; there were no detailed inclusion or exclusion criteria or details of data extraction for these trials, and a list of potentially relevant excluded studies was not provided. In response to a request for clarification by the ERG (see clarification response,[14] question B31), the company reported that the identification and selection process for these additional studies was reported in the submissions for two other NICE appraisals (CLL - ID749 and MCL - ID753).

4.1.1 Searches

The company conducted an up-to-date search (until May 2016) to identify relevant published clinical studies of patients with WM (methods detailed in CS Section 4.1 and CS Appendix 1). The initial and updated searches were carried out in the following databases:

- MEDLINE (via PubMed) and MEDLINE In-Process (via PubMed)
- Embase (via Embase.com) and Embase In-Process (via Embase.com)
- Cochrane Collaboration Central Register of Clinical Trials (CENTRAL, via the Cochrane Library).

Recent and published systematic reviews were also searched between 2011 and 2015. The company carried out supplementary searches in several conference proceedings websites and a trials registry (in the last three years):

- American Society of Clinical Oncology (ASCO) 2013–2015 (via Embase)
- American Society of Hematology (ASH) 2013–2015 (via Embase)
- European Hematology Association (EHA) 2013–2015 (via Embase)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 2013–2015 (international and European meetings): http://www.ispor.org/
- International WM workshop (IWWM) 2012 and 2014: http://www.wmworkshop.org/
- Clinicaltrials.gov (only studies for which results are available were searched).

The strategies were fully reported in Appendix 1 of the CS. The company adopted a broad search approach using the population terms (Waldenström's macroglobulinaemia) combined with terms for study design (including randomised controlled trials, non-randomised clinical trials and systematic reviews) in the PubMed and Embase search strategies (Appendix 1, Tables 3 and 5). As "population only" terms retrieved approximately five or six thousand records, the ERG agrees that it was

appropriate that the company only searched for WM without any specific named intervention or comparator terms. In addition, the company searched more widely for grey literature that was completed but unpublished in trial registries, society and association websites.

The ERG did not identify any significant errors within the company's search strategies. However, there was an inconsistency in the translation of study design terms between the Embase and PubMed searches: statements 5 and 6 of the Embase clinical search (CS Appendix 1, page 7), contain terms for clinical trials and systematic reviews, whilst statement 5 of the PubMed clinical search (CS Appendix 1, page 8) includes additional terms for observational studies, "classical articles", comparative studies and technical reports. Therefore, it is unclear whether it was the company's intention only to identify clinical trial and systematic review evidence.

Separate adverse event (AE) evidence searches were not undertaken for either the intervention or comparators; this review relied solely on evidence in the trials and systematic reviews and evidence identified within other appraisals (see clarification response,[14] question B31). The ERG considers that the company's searches for the named intervention and comparators should have been combined with an AE filter in MEDLINE and Embase. Potentially relevant AE data could therefore have been missed (data issues addressed in clarification responses B31, B32, B33 and B35).

With respect to reporting, the ERG re-ran the company's PubMed search and found that the values reported and actual number of records retrieved from the search were consistent with those reported in the CS (Appendix 1, Table 5).

4.1.2 Inclusion criteria

The inclusion criteria for the clinical review of ibrutinib were not described in Section 4.1 of the CS, but were detailed in Appendix 1 of the CS (Table 2). These criteria are reproduced in Table 5. These criteria required the inclusion of "prospective interventional trials" measuring the efficacy and safety of ibrutinib compared with an extensive range of comparator treatments, including best supportive care (BSC) in adult patients with WM. This process identified four publications of ibrutinib in this population, but the submission excluded three of these because they *"were only available in abstract format without accompanying full-text publications"* (CS,[1] Section 4.1, page 38 and CS Appendix 2, page 13). This exclusion criterion was not in the eligibility criteria list in CS Appendix 1 Table 2. In response to a request for clarification (see clarification response,[14] question B9), the company indicated that two of the three abstracts reported on the included Study 1118E.[11] The third excluded abstract reported the ongoing iNNOVATE trial;[15] this trial was excluded from the company's review, but was described in the CS (Section 4.14) with respect to ongoing studies.

The inclusion criteria for the review of safety evidence were not specified in the CS. The safety review included the single-arm, open-label Study 1118E and five trials of ibrutinib in different populations: RESONATE[16], RESONATE-2[17], PCYC-1102[18] and PCYC-1103[19], all in CLL, and PCYC-1104[20] in MCL. However, as noted above, the methods by which these non-WM studies were identified and the criteria by which they were selected, and others were excluded, were not reported.

Table 5: Inclusion and exclusion criteria for the clinical efficacy systematic review of ibrutinib in WM (adapted from CS, Appendix 1, Table 2)

	Inclusion criteria	**Other delimiters and exclusion criteria**
Population	WM	Patients without WM or LPL (LPL alone was rejected at the full-text screening level)*
Intervention(s)†	Ibrutinib monotherapy Ibrutinib combination therapy	No treatment of interest (for example, radioimmunotherapy alone)
Comparator(s)	Alemtuzumab monotherapy Allogeneic stem cell transplant (ASCT) Bendamustine ± rituximab (BR) Bortezomib + dexamethasone Bortezomib + dexamethasone + rituximab Bortezomib ± rituximab Carfilzomib + rituximab + dexamethasone Chlorambucil + ofatumumab Chlorambucil ± rituximab Cladribine ± rituximab (Clad-R) Cyclophosphamide + doxorubicin[hydroxydaunomycin] + vincristine + prednisone ± rituximab (CHOP/R-CHOP) Dexamethasone + rituximab + cyclophosphamide (DRC) DRC+ bortezomib Everolimus Enzastaurin Fludarabine + cyclophosphamide + rituximab (FCR) Fludarabine ± rituximab Idelalisib Lenalidomide Obinutuzumab Ofatumumab Perifosine Rituximab + cyclophosphamide + vincristine + prednisone (RCVP) Rituximab + cyclophosphamide + prednisone Rituximab + high-dose methyl prednisone/steroids (R+HDMP) Rituximab monotherapy	Non-randomised, comparative clinical efficacy and safety studies reporting on only one treatment of interest

	Thalidomide ± rituximab "Watchful waiting"/no treatment/prophylactic therapy/palliative care	
Outcome(s)	Efficacy Overall Survival (OS) Progression Free Survival (PFS) Response to treatment (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], very good partial response [VGPR], minor response [MR]) TTFR Improvement in haematological parameters, including haemoglobin, IgM paraprotein serum viscosity, and platelet count Treatment-free interval Safety: AEs of treatments	Publications that do not report safety and/or efficacy outcomes for WM specifically Articles investigating *in vitro*, animal, foetal, molecular, genetic, pathologic, or pharmacokinetic/pharmacodynamic outcomes without outcomes of interest reported
Study design	Prospective interventional trials	Narrative publications, non-systematic reviews, case studies, case reports, and editorials Non-English, full-text articles or articles without an English abstract Comparative studies with fewer than 10 patients with WM per treatment group in at least two treatment arms or single-arm studies with fewer than 10 patients. Observational and retrospective trials

WM - Waldenström's macroglobulinaemia; LPL - lipoprotein lipase; AE - adverse events
** LPL disease designation was accepted at the abstract screening level; outcomes had to be reported separately for WM patients within the full text.*
† Interventions were considered as inclusion criteria for data extraction and summarization only. Studies were not excluded based on interventions (any specific chemotherapeutic agent) until after full-text screening was complete.

4.1.3 Critique of study selection and data extraction

The ERG is satisfied that standard systematic review good practice was followed in terms of study selection and data extraction for the review of Study 1118E: relevant papers were independently selected for inclusion at title, abstract and full-text stages by at least two reviewers, with any discrepancies between reviewers resolved through discussion or the intervention of a third reviewer (see CS,[1] page 37) and data were extracted by one reviewer, checked by a second, and any issues resolved with reference to a third reviewer, where necessary (see CS Appendix 1,[1] pages 6-7).

Following clarification, discrepancies and inadequacies in some of the numbers reported in the PRISMA flowchart were acknowledged and addressed by the company, and an updated PRISMA flowchart was provided (see clarification response,[14] question B10).

4.1.4 Quality assessment

No relevant RCTs were identified, hence quality assessment of this study design (RCT) could not be performed by the company. However, no quality assessment was conducted for the included single-arm, open-label Study 1118E.[11] This could have been performed using a relevant checklist for this type of study design, for example, the Downs and Black checklist.[21] The ERG's quality assessment of Study 1118E using this checklist is presented in Section 4.2.1.1.

During clarification, the ERG requested that the company perform a quality assessment. The company's clarification response[14] (question B13) included an assessment based on Cochrane's Study Quality Guide for non-RCT studies, which applies criteria for the evaluation of interrupted time series (ITS) studies (see Table 6). The ERG did not consider the two questions relating to blinding to be applicable as the Study 1118E was a single-arm study, but agreed with the company's assessment for the other three questions considered.

Table 6: Quality assessment of Study 1118E (reproduced from clarification response Table 2)

Study	**Treon *et al*, 2015[11]**
Was the intervention independent of other changes?	Low risk
Was the shape of the intervention effect pre-specified?	Low risk
Was the intervention unlikely to affect data collection?	Low risk
Blinding of participants and personnel	Unclear
Blinding of outcome assessment	Unclear

The ERG notes that there are additional questions recommended by the selected quality assessment instrument which were not considered within the company's quality assessment:

- *"Were incomplete outcome data adequately addressed?"* The ERG considered this to be low risk of bias.
- *"Are reports of the study free of suggestion of selective outcome reporting?"* Planned outcomes from the protocol (Treon protocol[11]) were overall response rate (ORR), safety and tolerability, PFS, time to next therapy. Currently ORR and PFS data have been published, as well as safety data, although only for grade 2+ AEs.[11] However, the final data-cut of the study is estimated to take place in October 2018 (see clarification response,[14] question A3), hence it would be prudent to defer judgment on this item at this stage.
- *"Was the study free from other risks of bias?"* As a single-arm study, there is a risk of bias due to absence of a control group and blinding. The primary outcome used "modified" criteria, affecting external validity.

The quality assessment of Study 1118E is discussed further in Section 4.2.1.1.

4.1.5 Evidence synthesis

The synthesis for the review of clinical efficacy was a basic descriptive summary of the published evidence from the single-arm, open-label study, Study 1118E.[11] This study reported the following efficacy outcomes: ORR and PFS. Given that Study 1118E was a single-arm study that does not provide a relative estimate of a treatment effect, and there were no other relevant RCTs, a conventional meta-analysis was not applicable. An adjusted arm-based indirect comparison of Study 1118E and the European chart review cohort[9] was performed by the company (see Sections 4.3 and 4.4).

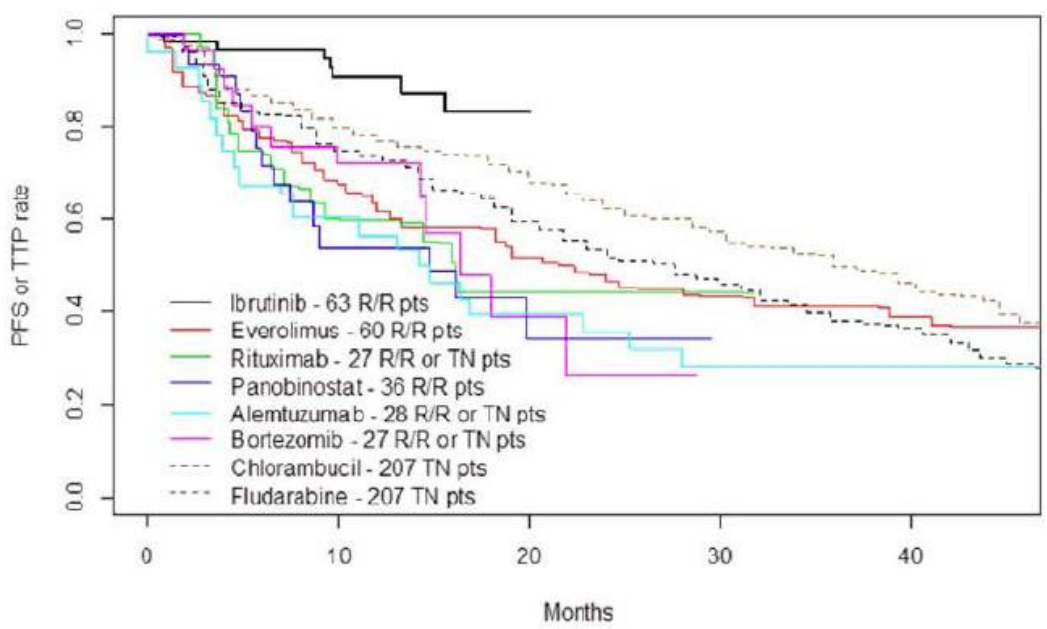
4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 Summary of relevant ibrutinib trial evidence on clinical efficacy

There are no RCTs or non-randomised controlled studies of ibrutinib in any population with WM. The CS excluded three studies of ibrutinib in adults with WM because they were published only as abstracts. Only details of the iNNOVATE study were provided by the company.[22, 23] In response to a question on this point by the ERG, the company reported that the other two studies were abstracts reporting early data from Study 1118E and were therefore superseded by the full publication[14] (question B9). The CS therefore only provided a detailed description of the one Phase II, single-arm, open-label study identified by the company as satisfying certain requirements of the final NICE scope,[7] i.e. ibrutinib in adult patients with WM who have received at least one prior therapy. This evidence is reported in CS Section 4.10.

There were also no RCTs, non-RCTs or single-arm studies of ibrutinib for the second indication specified in the final NICE scope, that is, as first-line treatment for adult patients with WM for whom chemo-immunotherapy is unsuitable.[7] Given the absence of comparative evidence in this population, the company submitted a figure which presents the results of a naïve indirect comparison of PFS outcomes from Study 1118E for the R/R WM population (ibrutinib, 63 patients) and selected trials of other monotherapies for treatment-naïve and R/R WM populations (see Figure 3).

Figure 3: Naïve comparison of PFS in patients with WM (single-agent use) (reproduced from CS, page 16, Figure 1)



The CS argues that this naïve comparison demonstrates how ibrutinib might perform relative to other treatments in the treatment-naïve subgroup specified in the final NICE scope *"given the clinical view (generally, across oncology) that treatment options perform better the earlier they are prescribed within the treatment pathway, it is not clinically implausible that ibrutinib will perform even better when given in the treatment-naive setting"* (clarification response[14], question B2). However, the ERG notes that, first, no evidence was submitted to substantiate this claim on the relative efficacy of treatments in treatment-naïve and R/R populations and, second, it is unclear how the trial evidence presented in the figure was identified and selected, whether any other relevant trials were excluded, and whether the same definition of PFS was applied in all trials. The identity and details of the single-agent trials included in the figure is unclear from the information provided in the CHMP assessment report.[6]

The clinical evidence for ibrutinib therefore consists of one prospective, multi-centre, US, Phase II, single-arm, open-label study of ibrutinib in adult patients with WM who had received at least one prior therapy: Study 1118E (PCYC-1118E). The inclusion criteria and basic characteristics of this study are presented in

Table 7. The exclusion criteria applied in Study 1118E appear to be consistent with the SmPC for ibrutinib.[10] Clinical advisors to the ERG commented that these criteria would also likely reflect how ibrutinib would be used in clinical practice.

The study required that ibrutinib be administered orally at 420mg (three 140mg capsules) daily for 26 four-week cycles. Patients were evaluated for response and tolerance to ibrutinib on Day 1 of cycles 2 and 3, then every 3 cycles for up to a total of 26 four-week cycles or until disease progression.

Table 7: Summary of trial design of Study 1118E (from CS Table 12 and Treon *et al,* 2015)

Parameter	Description
Location	United States
Trial design	Prospective, multicentre, Phase II trial.
Enrolment	63 patients were enrolled from May 23, 2012 to June 13, 2013.
Key Eligibility criteria	• Age ≥18 years. • Measurable disease, defined as the presence of serum IgM with a minimum IgM level >2 times the institutional upper limit of normal (ULN). • Clinicopathological diagnosis of WM. • Necessity of treatment based on IWWM guidelines. • At least 1 prior therapy for WM. • ECOG performance status of ≤2. • Adequate hematologic, renal, and hepatic function. • No active therapy for other malignancies with the exception of topical therapy for basal cell or squamous cell skin cancers.
Exclusion criteria	• Warfarin anticoagulation therapy. • Diagnosed lymphoma of the central nervous system. • Clinically significant cardiovascular disease. • Medications that could prolong the QT interval.
Trial drugs	Ibrutinib was administered orally at 420mg (three 140mg capsules) daily for 26 four-week cycles until the disease progressed or unacceptable toxic effects developed. Patients without disease progression could provide a second informed consent and continue therapy beyond 26 cycles.

WM - Waldenström's macroglobulinemia; ULN – upper limit of normal; IWWM - International Workshops on WM; IgM - immunoglobulin M; ECOG - Eastern Cooperative Oncology Group

The efficacy outcomes for Study 1118E reported in the CS[1] are generally consistent with those listed in the final NICE scope:[7] response rate and PFS. However, Study 1118E did not include the measurement of HRQoL. Median OS and duration of response had not been reached in Study 1118E at time at which the CS was submitted to NICE (see CS,[1] Table 15). Safety data from Study 1118E are described in Section 4.12 of the CS.

The response outcomes, and their definitions, taken from the CS and the original protocols and publications, are summarised in Table 8. Although Treon *et al*[11] report that *"Responses were defined according to criteria adopted from the 3rd International Workshop on Waldenström's Macroglobulinemia"* (IWWM), with the exception of complete response (CR), the definitions of response applied in Study 1118E, as reported in the CS, the CSR[24] (Table 3) and trial protocols, appear to differ from the internationally recognised criteria. The IWWM criteria are not limited to serum IgM level only, but also include the presence or absence of clinically significant findings or symptoms. The ERG notes that IgM response alone is insufficient as an outcome for WM because clinical benefit might be seen in patients without IgM response, or IgM reduction alone might not result in an improvement of symptoms.[2,25] This is consistent with the consensus statements, which

require more than the measurement of IgM serum levels in any assessment of response, e.g. the assessment of bone marrow involvement.[2,26]

The CS includes major response, which does not appear in other published criteria, but appears to consist of any response greater than minor response. Overall response rate (ORR) is a measure that also appears in Study 1118E and encompasses minor response or better (≥25% reduction in serum IgM levels). The CS employs the same "MR" abbreviation for both minor response and major response, rendering the reporting of outcomes difficult to follow. In the CS, Section 4.10, Table 12, minor response does not appear, major response has two different thresholds, and CR is not defined. These errors were later clarified by the company (clarification response,[14] question B17).

The company's clarification response[14] (question B14) also cited Gertz *et al*[27] to justify the use of ORR as an outcome in WM. Gertz *et al* report that, in a study of rituximab treated WM patients, a reduction of greater than 25% in serum IgM levels was clinically meaningful.

Table 8: Primary efficacy response outcomes for Study 1118E (as reported across CS, Section 4.10, including Table 13, and relevant publications)

Response categories	CS Section 4.10, Table 13*	Company's clarification response question B17	Treon *et al*, Study 1118E NEJM Protocol	Study 1118E NCT01614821 protocol	IWWM response criteria
Overall Response Rate (ORR)	≥25% reduction in serum IgM levels	ORR includes minor response, PR, VGPR rate, CR	>25% reduction in disease burden (Sections 1.2 and 13.1)	>25% reduction in serum IgM levels	Not listed as a category
Minor response	≥25% reduction in serum IgM levels. Required 2 consecutive measurements of IgM	Minor Response (≥25% reduction in serum IgM levels; Required 2 consecutive measurements of IgM)	25-49% reduction in serum IgM levels (Section 9.1.2)	Not included	A >25% but <50% reduction of serum IgM. No new symptoms or signs of active disease
Partial response (PR)	≥50% reduction in serum IgM levels. Required 2 consecutive measurements of IgM	PR (≥ 50% reduction in serum IgM levels; Required 2 consecutive measurements of IgM)	>50% reduction in serum IgM levels (Section 9.1.2)	Not included	A >50% reduction of serum IgM and decrease in adenopathy/ organomegaly (if present at baseline) on physical examination or on CT scan. No new symptoms or signs of active disease
Very Good Partial Response (VGPR)	≥90% reduction in serum IgM levels. Required 2 consecutive measurements of IgM	VGPR rate (≥ 90% reduction in serum IgM levels or IgM levels within normal range; Required 2 consecutive measurements of IgM)	>90% reduction in serum IgM levels (Section 9.1.2)	Not defined	A >90% reduction of serum IgM and decrease† in adenopathy/ organomegaly (if present at baseline) on physical examination or on CT scan. No new symptoms or signs of active disease.

Response categories	CS Section 4.10, Table 13*	Company's clarification response question B17	Treon *et al*, Study 1118E NEJM Protocol	Study 1118E NCT01614821 protocol	IWWM response criteria
Major response	≥50% reduction in serum IgM levels	PR or better	>50% reduction in disease burden (Sections 1.2 and 13.1)	>50% reduction in serum IgM levels	Not listed as a category
Complete Response (CR)	Resolution of all symptoms, normalisation of serum IgM levels, required 2 consecutive measurements of IgM and negative serum immunofixation. Resolution of any adenopathy or splenomegaly by central radiology	CR (Resolution of all symptoms, normalisation of serum IgM levels, required 2 consecutive measurements of IgM and negative serum immunofixation. Resolution of any adenopathy or splenomegaly by central radiology)	Resolution of all symptoms, normalisation of serum IgM levels with complete disappearance of IgM paraprotein by immunofixation, and resolution of any adenopathy or splenomegaly (Section 9.1.2)	Not defined	IgM in normal range, and disappearance of monoclonal protein by immunofixation; no histological evidence of bone marrow involvement, and resolution of any adenopathy/ organomegaly (if present at baseline), along with no signs or symptoms attributable to WM.

ORR – overall response rate; PR – partial response; VGPR – very good partial response; CR – complete response; IgM – immunoglobulin M; CT – computerised tomography
**Errors in table corrected; ** Responses were defined according to criteria adopted from the Third International Workshop on WM*
†This has more recently been amended to "complete resolution" rather than "decrease"[2];[25]

The main secondary efficacy outcome reported in Study 1118E was PFS, which was defined as *"the duration of time from start of treatment to time of objective disease progression (including initiation of new therapy or death)"* (Treon protocol Section 9.1.4, published as supplementary material to Treon 2015[11]) or *"the duration of time from start of treatment to time of objective disease progression, death or last follow-up"* (CS,[1] page 43). According to the study protocol, progressive disease (PD) is defined as occurring *"when a greater than 25% increase in serum IgM level occurs from the lowest attained response value or progression of clinically significant disease related symptom(s)."* According to the protocol, *"death from any cause or initiation of a new anti-neoplastic therapy was also considered to be a progression event"* (Treon protocol,[11] Section 9.1.2). The definitions of stable disease (SD) and PD within Study 1118E and according to internationally recognised criteria are summarised in Table 9.

Table 9: Definitions of stable disease and progressive disease (reproduced from CS Table 12 and relevant publications)

Outcome	Treon *et al*, protocol[11]	6th IWWM response criteria[26]
Stable disease (SD)	A < 25% change in serum IgM levels, in the absence of new or increasing adenopathy or splenomegaly and/or other progressive signs or symptoms of WM	A <25% reduction and <25% increase of serum IgM without progression of adenopathy/organomegaly, cytopenias or clinically significant symptoms due to disease and/or signs of WM
Progressive disease (PD)	A > 25% increase in serum IgM level occurs from the lowest attained response value or progression of clinically significant disease related symptom(s). Death from any cause or initiation of a new anti-neoplastic therapy will also be considered a progression event.	A >25% increase in serum IgM by protein electrophoresis confirmed by a second measurement or progression of clinically significant findings due to disease (i.e. anaemia, thrombocytopenia, leukopenia, bulky adenopathy/organomegaly) or symptoms (unexplained recurrent fever 38.4°C, drenching night sweats, 10% body weight loss, or hyperviscosity (HVS), neuropathy, symptomatic cryoglobulinemia or amyloidosis) attributable to WM.

WM - Waldenström's macroglobulinemia; IWWM - International Workshops on WM; IgM - immunoglobulin M; HVS - hyperviscosity

4.2.1.1 Quality assessment

The CS does not include a critical appraisal of the key study. However, the company's clarification response did provide a brief assessment by the company (see Table 6 in this report).

Table 10 presents a quality assessment conducted by the ERG using the Downs and Black checklist,[21] which assesses quality of reporting (10 items); external validity (3 items); bias (7 items); and confounding (6 items).

Based on this quality assessment, the ERG considers that Study 1118E is a well-reported single-arm study. Clinical advisors to the ERG noted that patients enrolled into the study were generally younger and had less severe disease than patients with R/R WM who might routinely present in practice in England. In terms of internal validity, the criteria relating to blinding were not relevant to this study design, but the statistical tests (within Study 1118E) appear appropriate, and analyses by subgroup were performed to evaluate the effect of potential confounders on two key outcomes (ORR and PFS, although only the results for ORR were reported in the CS). The outcome measures used were generally valid and reliable but the response criteria (the primary outcome) were "modified" (see CS,[1] Table 13, page 43, and ERG report Table 8): except for CR, the response criteria were limited to IgM serum levels only and did not include symptoms or adenopathy/organomegaly, which are listed in the published standards.[2, 26, 28]

There is a high risk of bias with studies of this design due to the absence of a control group; there is also a high risk of selection bias because of the absence of randomisation, and a high risk of performance and detection bias because of the absence of blinding. Inadequate reporting is also an issue because neither the CS nor the Study 1118E publication or its protocol[11] specified what methods were used to assess response: it has been reported elsewhere[2, 26] that different methods for assessment of response (e.g. nephelometry or densitometric assessment of paraprotein concentration) can produce different values and that the assessments must be conducted in a single laboratory. None of this information was reported in the CS or in the publications relating to Study 1118E. The CS does however acknowledge that *"the phase 2 non-comparative nature of the study may not meet the rigour of evidence generally expected"* (CS,[1] page 66).

Table 10: ERG risk of bias assessment (Downs & Black checklist): Study 1118E

Reporting: "Yes=1," "No=0"		**Response**
1	Is the hypothesis /aim /objective of the study clearly described?	Yes
2	Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes
3	Are the characteristics of the patients / samples included in the study clearly described?	Yes
4	Are the interventions of interest clearly described?	Yes
5	Are the distributions of principal confounders in each group of subjects to be compared clearly described? "Yes=2," "Partially=1," "No=0"	N/A
6	Are the main findings of the study clearly described?	Yes
7	Does the study provide estimates of the random variability in the data for the main outcomes?	Yes
8	Have all important adverse events that may be a consequence of the intervention been reported?	Yes
9	Have the characteristics of patients lost to follow-up been described?	Yes
10	Have actual probability values been reported (e.g. 0.035 rather than <0.5) except where the probability value is less than 0.001?	Yes
External validity: "Yes=1," "No=0," "Unable to determine=0"		
11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Unable to determine
12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Unable to determine
13	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Unable to determine
Internal validity - bias: "Yes=1," "No=0," "Unable to determine=0"		
14	Was an attempt made to blind study subjects to the intervention they have received?	N/A
15	Was an attempt made to blind those measuring the main outcomes of the intervention?	N/A
16	If any of the results of the study were based on "data dredging" was this made clear?	No
17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes, Kaplan-Meier method used for time-to-event analyses with censoring
18	Were the statistical tests used to assess the main outcomes appropriate?	Yes
19	Was compliance with the intervention reliable?	Unable to determine
20	Were the main outcome measures used accurate (valid and reliable)?	Unable to determine: Other than for CR, the response criteria appear to differ from international standards, e.g. regarding symptoms and adenopathy and organomegaly
Internal validity - confounding (selection bias): "Yes=1," "No=0," "Unable to determine=0"		
21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	N/A

22	Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	N/A
23	Were study subjects randomized to intervention groups?	No
24	Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	N/A
25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Unable to determine; analyses by subgroup were performed rather than multiple regression analyses
26	Were losses of patients to follow-up taken into account?	Yes
Power: "No=0", "Yes, one measure=1" "Yes, two or more measures=2"		
27	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? Sample sizes have been calculated to detect a difference of x% and y%	Unable to determine: required response rate and thresholds are given but not justified

N/A: Not applicable

4.2.2 Results

4.2.2.1 Participants' baseline characteristics in Study 1118E

Sixty-three participants across three sites in the USA were due to receive the licensed 420mg/day dose in Study 1118E. Treatment was administered for a median of 19.1 months (range 0.5 to 29.7 months) and 43/63 patients (68%) remained on treatment after the final data cut-off (DCO) of 19th December 2014. Baseline characteristics of study participants are reported in

Table 11. The median age of patients was 63.0 years (mean = 64.5 years); the majority (76.2%) of patients were male. The median time from diagnosis of WM to study entry was 76 months (range 6 to 340 months). The median number of prior regimens received by patients was 2 (range 1 to 9 lines).

Table 11: Baseline patient characteristics in Study 1118E (adapted from CS, Table 14)

Characteristic	Ibrutinib (N=63)
Demographic characteristic	
Age	
Median (range), years	63.0 (44 to 86)
Mean (SD), years	64.5 (10.7)
Gender	
Male, n (%)	48 (76.2)
Female, n (%)	15 (23.8)
Race	
White, n (%)	60 (95.2)
Other, n (%)	3 (4.8)
Clinical characteristics	
Time since initial diagnosis	
Median (range), months	76 (6 to 340)
IPSSWM risk* at baseline, no. (%)	
Low	14 (22)
Intermediate	27 (43)
High	22 (35)
Serum IgM (mg/dL)	
Median (range)	3,520 (724 to 8,390)
>4,000, no. (%)	26 (41)
Haemoglobin level	
Median (range), g/dL	10.5 (8.2 to 13.8)
Median haematocrit (range), %	30.8 (24.5 to 41.5)
ß$_2$-microglobulin level, no. (%)	
Median (range), mg/L	3.9 (1.3 to 14.2)
>3 mg/L, n (%)	45 (71)
>3.5 mg/L, n (%)	35 (56)
Prior WM treatment	
Time from last treatment (days)	
Median (range)	170 (1 to 3,276)
Number of regimens	
Median (range)	2 (1 to 9[†])
Number of regimens, no. (%)	
1	18 (28.6)
2	14 (22.2)
3	8 (12.7)
4	7 (11.1)
≥5	16 (25.4)
Previous therapy, n (%)	
Monoclonal antibody	57 (90)
Glucocorticoid	42 (67)
Proteasome inhibitor	33 (52)
Alkylating agent	32 (51)
Nucleoside analogue	15 (24)
mTOR inhibitor	13 (21)
Immunomodulator	7 (11)
Anthracyclines	7 (11)
Autologous SCT	4 (6)
Other, including experimental therapy	13 (21)
Refractory to most recent therapy, n (%)	25 (40)

IgM: immunoglobulin M; mTOR: mammalian target or rapamycin; IPSSWM: International Prognostic Scoring System for Waldenström's Macroglobulinemia; SCT: stem cell transplantation; SD: standard deviation; WM: Waldenström's macroglobulinaemia.

**IPSSWM assesses the following five prognostic factors: age >65 years; haemoglobin ≤11.5 g/dL; platelets ≤100 x 10^9/L; β-2 microglobulin >3 mg/L; and serum IgM monoclonal protein concentration >7 g/dL. Risk at baseline categories are defined as follows: low risk, if ≤1 adverse factor except age; intermediate risk, if 2 adverse characteristics or age >65 years; high risk, if ≥3 adverse characteristics (Note: the ERG has corrected errors in the original CS, Table 14, regarding the IPSSWM system).*

The CS[1] (page 43) reports that the EMA deemed the population of Study 1118E to be representative of the general WM population with previously treated disease. However, Study 1118E did not include any UK patients and there appear to be some differences between UK WM populations and the US WM population in Study 1118E. The CS (Section 4.11) reports on a retrospective, European chart review of 454 patients with WM who had been treated with one or more lines of therapy (taken principally from the company's own data on file[1, 3, 9]). Seventy-two of these patients were from the UK. A comparison of the baseline characteristics of these patients and the patients in Study 1118E is presented in

Table 12. In terms of characteristics without missing data, in Study 1118E patients were slightly younger (median age 63 years compared with 65 years in the UK chart review cohort); there were proportionally more men (76% compared with 61% the UK chart review cohort); the baseline median serum IgM level was lower (3,520mg/dL compared with 4,100mg/dL in the UK chart review), and the proportion of patients with haemoglobin of ≤11g/dL was lower (59% compared with 89% in the UK chart review).

Table 12: Patient baseline characteristics: Study 1118E population and the UK chart review cohort (adapted from CS Table 14 and Table 21)

Characteristic	Study 1118E (n=63)	UK chart review (N=72)
Age at initiation of first-line treatment		
Years, median	63	[redacted]
Years, range	44-86	[redacted]
Percent ≥65 (n)	NR	[redacted]
Percent male (n)	76 (48)	[redacted]
Median number of previous treatment regimen (range)	2 (1-9)	[redacted]
IPSSWM risk at initiation of front-line treatment*, % (n)		
Low	22 (14)	[redacted]
Intermediate	43 (27)	[redacted]
High	35 (56)	[redacted]
Serum antibody levels		
IgM		
Median (range) — mg/dL	3,520 (724-8,390)	[redacted]
Percent >4000 mg/dL (n)	41 (26)	[redacted]
Median IgG (range) — mg/dL	26 (0-125)	[redacted]
Median IgA (range) — mg/dL	381 (49-2,770)	[redacted]
Median β2-microglobulin, range*	3.9 (1.3-14.2)	[redacted]
Any cytopenia*, % (n)	NR	[redacted]
Percent Haemoglobin ≤11 g/dL (n)	59 (37)	[redacted]
Percent Platelets ≤100 × 109/L (n)	11 (7)	[redacted]

*NR: not reported. *Missing data are not included in calculations.*

Clinical advice received by the ERG suggests that patients in Study 1118E were generally younger and had less severe disease than the adults with R/R WM who might routinely present in clinical practice in England. In terms of loss to follow-up, 20 of the 63 patients (32%) had discontinued

treatment within the study period (maximum of 29.7 months) by the December 2014 DCO. Reasons for discontinuation are summarised in Table 13.

Table 13: Reasons for discontinuation during treatment period in Study 1118E (reproduced from CS Table 25 and Treon *et al*)

Reason for discontinuation	Number of cases (n=20)
Disease progression	7
Possible treatment-related disease transformation	2
Patient choice to use commercially-obtained ibrutinib	2
Non-response	1
Treatment-aggravated thrombocytopenia	1
Infection unrelated to ibrutinib	1
Haematoma post bone marrow biopsy	1
Treatment for rectal carcinoma	1
Medication incompatible with ibrutinib	1
Difficulty with travel	1
Alternative therapy	1
Myelodysplasia and acute myeloid leukaemia related to prior treatments	1*

**This is listed as 2 patients in the CS, but only 1 patient in the publication.*

4.2.2.2 Response rates

The key results from Study 1118E are presented in

Table 14. Response data are based on the serum IgM level at the time of best response.[11] In 57 of the 63 previously-treated patients, ibrutinib showed high rates of ORR and major response. Six of the 63 patients still had a serum IgM level of 3,000mg/dL or higher post-treatment (Treon *et al*.[11] and CS, Table 16) and are assumed to have had either SD or PD. In the clinical study report (CSR,[24] provided following clarification), no patient was reported as having achieved a CR. The median times to minor response or PR were 4 weeks and 8 weeks, respectively (see CS, page 48). It is assumed that the reported response rates were assessed by investigators. For an earlier data cut, response rates were lower than presented in the CS, and the ORR and major response rate were lower when assessed by an Independent Response Review Committee (IRRC) than by investigators (CSR,[24] page 39, Table 13).

Table 14: Response rates in Study 1118E (reproduced from CS, pages 45-46 and Table 15)

Category of response	**Number of patients**	**Results**
	Total = 63	
Overall response rate (ORR)	57	90.5% (95% CI 80.4 to 96.4)
Minor response	11	Not reported
Partial response (PR)	36	
Very good partial response (VGPR)	10	
Major response (PR+VGPR+CR)	46	73% (95% CI 60.3 to 83.4)
Complete response (CR)	Not reported	

CI – confidence interval

The CS states that response, as measured by ORR and major response rate, was durable (CS,[1] page 48). Based on data only available in the CSR,[24] the Kaplan-Meier estimate of the probability of being event-free (alive and progression free) for all responders at 18 months was 80.9% (95% confidence interval [CI], 64.9% to 90.2%), and the corresponding value for major responders was 86.7% (95% CI, 67.9% to 94.9%).

4.2.2.3 Other measures of response

The median absolute serum IgM concentration at baseline for subjects treated with ibrutinib decreased from 3,520 mg/dL at baseline to 2,350mg/dL at 8 weeks (see Table 15). There was a significant increase in haemoglobin level among patients who responded (n=57/63) from 10.5g/dL at baseline to 12.0g/dL at 8 weeks and 13.8g/dL at the time of best response (p<0.001).

Table 15: Serum antibody levels in Study 1118E (reproduced from CS, Table 16)

Characteristic	**Value**
Median Serum IgM level over time — mg/dL	
Baseline	3520
8 weeks	2350
At time of best response	880
Patients with a serum IgM level ≥3000 mg/dL, % (n)	
Baseline	73 (46)
After therapy	10 (6)
Median haemoglobin level among respondent patients — g/dL	
Baseline	10.5
8 weeks	12.0
At time of best response	13.8

IgM - immunoglobulin M, mg/dL: milligrams per decilitre, g/dL: grams per decilitre

Treatment with ibrutinib resulted in a significant decline in median percentage of bone marrow infiltration from 60% to 25% (p<0.001).[1] There was no correlation between serum IgM levels and bone marrow involvement at 6 months (r=0.03, p=0.83), but there was at 12 months (r=0.51,

$p<0.001$) and 24 months ($r=0.56$, $p<0.008$).[11] However, details of the assessment method are not reported for Study 1118E and it is not clear who was conducting the assessment. The literature suggests that this assessment should be conducted by "central review" every 4-6 weeks in trials because the most appropriate time-point for assessment is unknown,[26] whereas in Study 1118E bone marrow biopsies were taken at cycles 6 (i.e. 24 weeks), 12 (48 weeks) and 24 (96 weeks) and annually thereafter.[11]

At baseline, adenopathy and splenomegaly were identified by computed tomography (CT) in 37/63 (59%) and 7/63 (11%) patients, respectively (see Table 15). The numbers of patients with lymphadenopathy and splenomegaly were reduced after ibrutinib treatment (see Table 16).

Table 16: CT-identified adenopathy and splenomegaly in Study 1118E (reproduced from CS, Table 17)

Clinical characteristic	**(n=63)**
Adenopathy	
Baseline lymphadenopathy (>1.5 cm)	35*
Decreased	25
Remained stable	9
Increased	1
Splenomegaly	
Baseline splenomegaly (≥15 cm)	7
Decreased	4
Remained stable	2
Could not be evaluated due to elective splenectomy	1

** two patients discontinued before repeat imaging was required*

The Treon publication reported that no IgM flare was reported for any of the 63 patients during the treatment period.[11] Four patients received ibrutinib who were also receiving plasmapheresis due to symptomatic hyperviscosity (HVS) related to PD. All four patients had a response (level not reported), and none required additional plasmapheresis by the end of cycle 2. One patient required plasmapheresis for acquired factor VIII deficiency, but had a response to ibrutinib therapy and did not require further plasmapheresis. The spontaneous bleeding events that prompted therapy also resolved, and the patient continued to receive ibrutinib (Treon *et al*,[11] not reported in the CS).

4.2.2.4 Subgroup analyses based on response

The CS reports subgroup analyses of ORR and major response rate (see Figure 4 and Figure 5 below). The CS reported that both measures of response were *"consistent across most subgroups"* (e.g. by age, Eastern Cooperative Oncology Group [ECOG] score at baseline, IPSSWM risk score) (CS,[1] page 46). While this generally appears to be the case for ORR (see Figure 4), differences in major response

are particularly apparent for patients with different levels of ß$_2$-microglobulin, haemoglobin, bone marrow disease involvement and genotypes MYD88^{L265P} and CXCR4^{WT} (see Figure 5). The ERG would have preferred the use of a single model involving a covariate for each factor as this would allow for the mutual adjustment of covariates as well as the identification of confounding between factors. In addition, given the absence of a control group, whether the treatment effect depends on subgroup is not estimable.

Figure 4: Subgroup analysis of overall response rate in Study 1118E (reproduced from CS Figure 7)

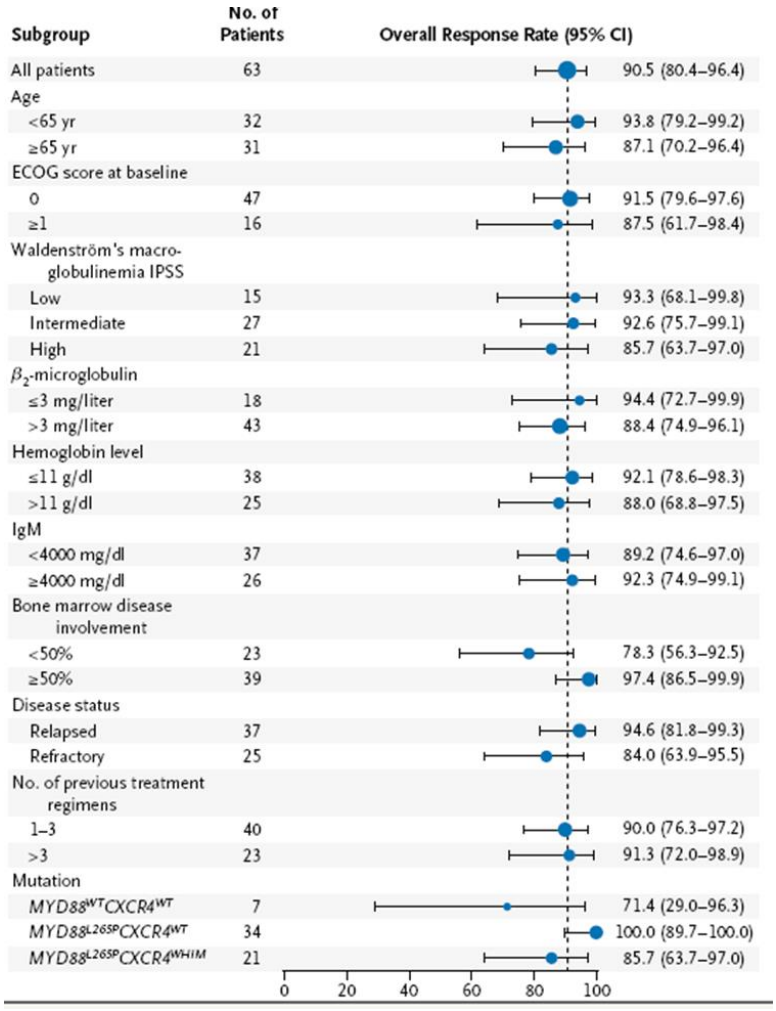
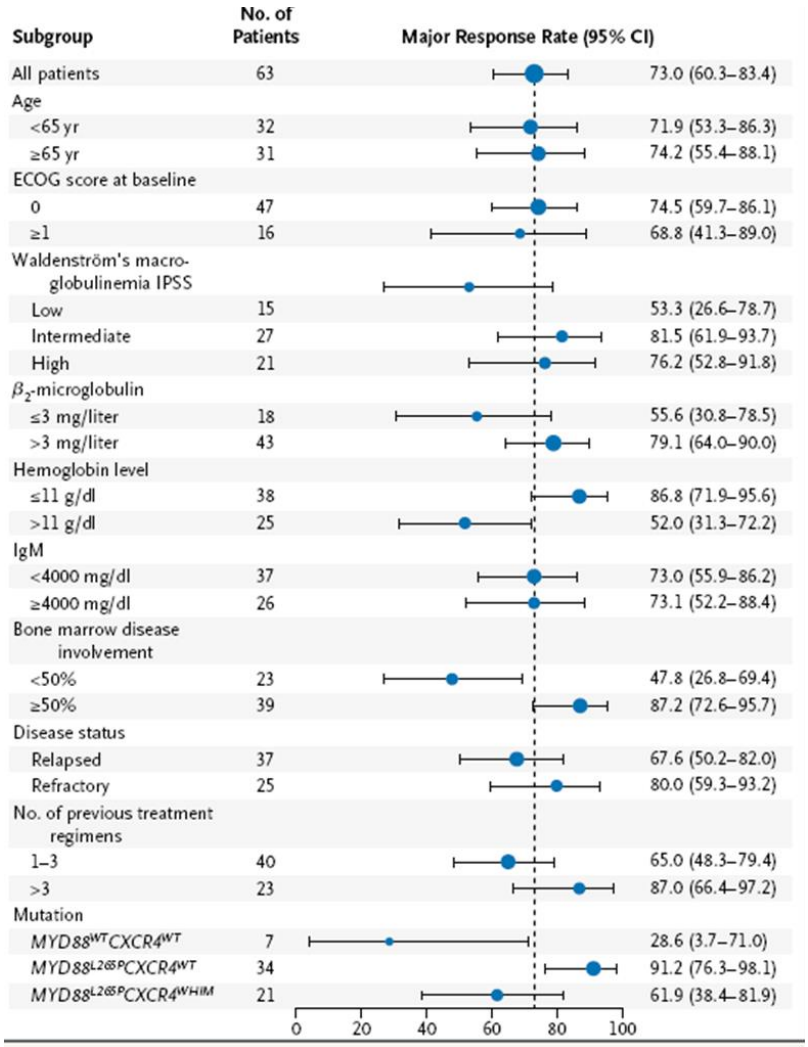


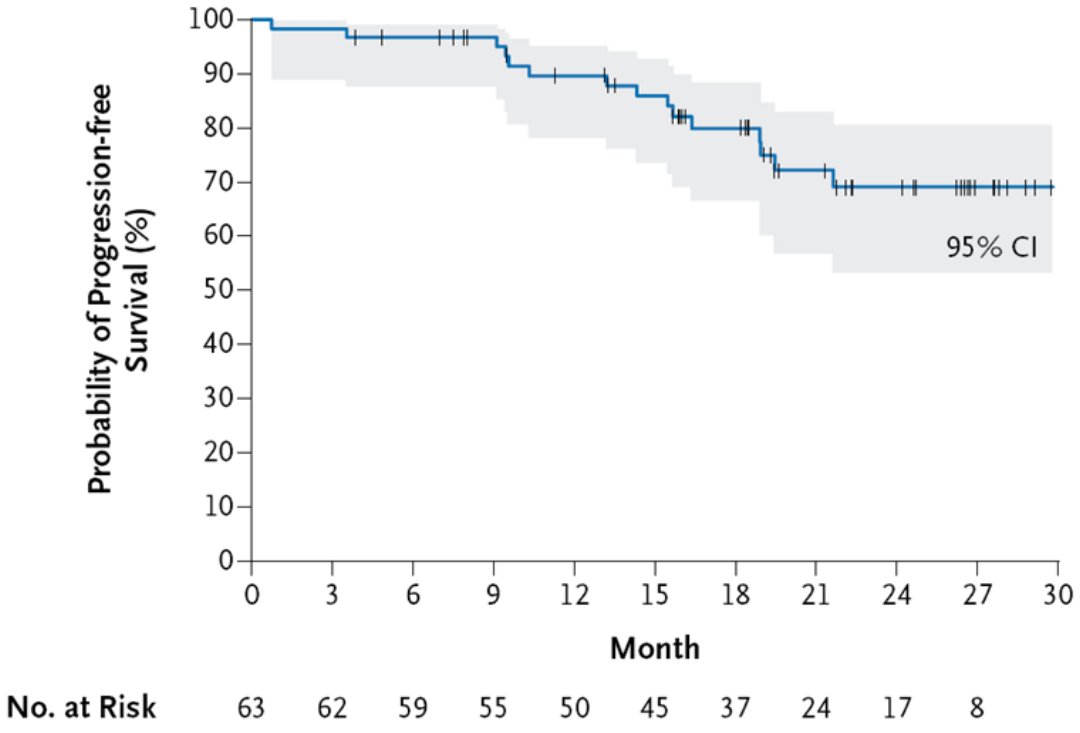
Figure 5: Subgroup analysis of major response rate in Study 1118E (reproduced from CS Figure 8)



4.2.2.5 Progression-free survival

By the end of data collection (19th December 2014), 60 of the 63 patients were still alive. The Kaplan-Meier curve for PFS is shown in Figure 6. At 24 months, the estimated probability of being alive and progression-free was 69.1% (95% CI 53.2% to 80.5%).

Figure 6: Kaplan-Meier curve of PFS in Study 1118E (reproduced from CS Figure 10)

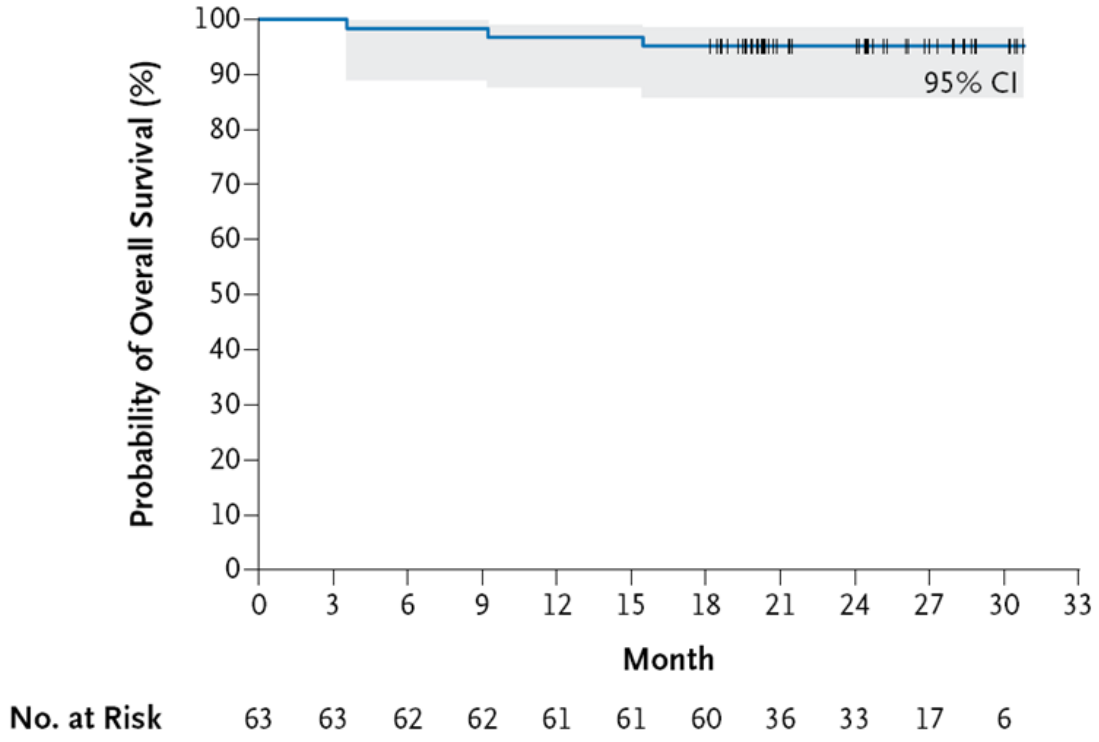


Treon *et al*[11] also report that, for those patients with PD, the median time to progression was 9.6 months (range 3.5 to 19.4 months) if data on transformation events were censored, and 9.5 months (range 3.5 to 19.4 months) if data on transformation events were included.[11] Subgroup analysis found that lower rates of PFS were associated with a high IPSSWM score at baseline, more than three previous treatment regimens, and the $MYD88^{WT}$ $CXCR4^{WT}$ genotype.[11]

4.2.2.6 Overall survival

By the December 2014 DCO, only 3 patients had died (details not reported). Therefore, at 24 months, the estimated probability of being alive was 95.2% (95% CI 86% to 98.4%, see Figure 7). The ERG notes that given the short follow-up and the small number of events, the long-term survival trajectory for patients receiving ibrutinib is highly uncertain.

Figure 7: Kaplan-Meier curve of OS in Study 1118E (reproduced from CS, Figure 11)



4.3 Additional study used to inform the company's indirect comparison

The CS includes an adjusted arm-based indirect comparison of patient-level data from Study 1118E and a European chart review study; the CS reports data from this study based on a published poster[29] and the company's data on file.

The European chart review was an analysis of retrospective observational data. Physicians retrospectively produced electronic records for WM patients. The inclusion criteria for the study were:

- Confirmed WM (International Workshop on WM (IWWM)-2 criteria[30]);
- Symptomatic disease at treatment initiation;
- Front-line treatment initiated January 2000 - January 2014;
- Availability of complete clinical/biologic evaluation at diagnosis/initial therapy.

The full chart review included 454 patients. Of these, patients were from: France (n=92); the UK (n=72); Germany (n=66); Spain (n=60); Italy (n=56); Greece (n=25); the Netherlands (n=25); Poland (n=21); Austria (n=19); and the Czech Republic (n=16). Baseline characteristics for the overall cohort and the UK cohort are summarised in Table 17.

Table 17: Chart review study - patient baseline characteristics at initiation on front-line treatment (reproduced from CS Table 18)

Characteristic	Overall (N=454)	UK (n=72)
Age at initiation of 1L treatment		
Years, median	65	[redacted]
Years, range	29-89	[redacted]
Percent ≥65 (n)	[redacted]	[redacted]
Percent Male (n)	61 (278)	[redacted]
Median number of lines started (range)	[redacted]	[redacted]
IPSSWM risk*, % (n)		
Low	[redacted]	[redacted]
Intermediate	[redacted]	[redacted]
High	[redacted]	[redacted]
Serum antibody levels		
IgM		
Median (range) — g/L	[redacted]	[redacted]
Percent >4000 mg/dL (n)	[redacted]	[redacted]
Median β_2-microglobulin, range*	[redacted]	[redacted]
Median β_2-microglobulin-- mg/L*	[redacted]	[redacted]
Any cytopenia*, % (n)	[redacted]	[redacted]
Percent Haemoglobin ≤11 g/dL	[redacted]	[redacted]
Percent Platelets ≤100 × 109/L	[redacted]	[redacted]

**Missing data are not included in calculations.*

PFS and OS endpoints were reported in the 2015 abstract by Buske *et al*.,[29] and in Section 4.11 of the CS. Median PFS for first-, second- and third-line treatment was 29 months, 23 months and 16 months, respectively (see

Table 18).

Table 18: Median PFS in first-, second- and third-line settings EU-overall and by country (adapted from CS Table 19)

Country	Number of cases	Median PFS, months (95% CI)		
		First-line	Second-line	Third-line
EU-overall	454	29 (25-31)	23 (20-26)	16 (10-18)
France	92	29 (22-32)	30 (20-37)	16 (9-32)
UK	72	32 (25-36)	20 (11-35)	13 (9-33)
Germany	66	36.5 (29-44)	24 (16-29)	8 (3-16)
Spain	60	18 (15-25)	16 (12-24)	11 (9-24)
Italy	56	31 (20-39)	30 (18-42)	17 (4-21)
Eastern European*	37	33 (26-38)	20 (16-26)	21 (4-38)
Smaller European**	71	23 (18-29)	16 (13-25)	16 (7-26)

CI – confidence interval

Median OS for the 454 patients in the overall cohort was 123 months (CS,[1] page 56). Median OS was lower in patients aged 75 or over (75 months), and patients with high-risk IPSSWM risk score (91

months). These were reported as being significantly different, although *p*-values were not reported (Buske *et al*.[29] and CS[1]). No further data relating to these analyses are presented in the CS.

The data selected for use in the indirect comparison were taken from 175 patients selected to form a "matched" cohort. This "matching" process involved selecting patients from the European chart review such that the selected cohort had similar numbers of prior lines of therapy to those patients enrolled in Study 1118E[11] (see CS,[1] page 56). Patients in the "matched" cohort had the following numbers of prior lines of therapy: [redacted] with 1 prior line; [redacted] with 2 prior lines; [redacted] with 3 prior lines, and; [redacted] with 4 prior lines. Baseline characteristics of the "matched" cohort are shown in Table 19. The CS states *"In addition, patients from Study 1118E that had 5 or more prior lines of therapy were excluded from the analyses given that patients from the chart review had received at most four prior treatments. Therefore, a total of 47 patients from Study 1118E were included in the analysis"* (CS,[1] page 57).

Table 19: Patient baseline characteristics: overall chart review matched, vs. Study 1118E vs. UK chart review cohorts (adapted from CS Table 21)

Characteristic	Overall chart review matched (N=175)	Study 1118E (n=63)[23]	UK chart review (N=72)	Study 1118E patients 1-4 treatments (n=47) (clarification response Table 6)
Age at initiation of first-line treatment				
Years, median	[redacted]	63	[redacted]	[redacted]
Years, range	[redacted]	44-86	[redacted]	[redacted]
Percent ≥65 (n)	[redacted]	NR	[redacted]	[redacted]
Percent Male (n)	[redacted]	76 (48)	[redacted]	[redacted]
Median number of previous treatment regimen (range)	[redacted]	2 (1-9)	[redacted]	[redacted]
IPSSWM risk at initiation of front-line treatment*, % (n)				
Low	[redacted]	22 (14)	[redacted]	[redacted]
Intermediate	[redacted]	43 (27)	[redacted]	[redacted]
High	[redacted]	35 (22)	[redacted]	[redacted]
Serum antibody levels				
IgM				
Median (range) — mg/dL	[redacted]	3,520 (724-8,390)	[redacted]	[redacted]
Percent >4000 mg/dL (n)	[redacted]	41 (26)	[redacted]	[redacted]
Median IgA (range) — mg/dL	[redacted]	26 (0-125)	[redacted]	[redacted]
Median IgG (range) — mg/dL	[redacted]	381 (49-2,770)	[redacted]	[redacted]
Median β2-microglobulin, range *	[redacted]	1.3-14.2	[redacted]	[redacted]
Median β2-microglobulin, mg/L *	[redacted]	3.9	[redacted]	[redacted]
Any cytopenia*, % (n)	[redacted]	NR	[redacted]	[redacted]
Percent Haemoglobin ≤11 g/dL (n)	[redacted]	59(37)	[redacted]	[redacted]
Percent Platelets ≤100 × 109/L (n)	[redacted]	11 (7)	[redacted]	[redacted]

CS - company's submission; NR - not reported

**Missing data are not included in calculations*

Progression in the chart review was defined as: *"25% increase in serum IgM from lowest nadir; progression or re-appearance of clinical features; progression or reappearance of hematopoietic insufficiency"* (CS,[1] Table 20, page 56). This was stated in the CS to be comparable to the definition of progression in Study 1118E *"> 25% increase in serum IgM level occurs from the lowest attained response value or progression of clinically significant disease related symptom(s); based on the consensus panel criteria of IgM response."* It is unclear whether the differences between these definitions of progression between the two studies introduce bias into the indirect comparison.

The company's clarification response[14] (question B16) states that within the chart review *"PFS is defined as duration in months from the start date of a given line of treatment for WM to the following occurrence of disease progression/relapse (month/year) or start of the next line of treatment (month/year) or death within the current treatment period, whichever occurs first. Subjects who initiated the current line of treatment and who did not have an event were censored at the last available date during the current therapy."*

The clarification response notes that the definition of PFS in Study 1118E was different: *"Progression-free survival was defined as the time between the initiation of therapy and the date of disease progression, death, or last follow-up"* (Clarification response,[14] question B16).

The company used a multivariable Cox proportional hazards model to estimate an HR for PFS for ibrutinib versus standard therapies including the following covariates: age; gender; haemoglobin ≤11g/L; platelet ≤100 x 10^9/L; β-2 macroglobulin ≤3mg/L; IgM <40g/L, and; low/intermediate risk. These are similar but not identical to the criteria used to assess prognostic risk (i.e. advanced age [>65 years], haemoglobin ≤11.5g/dL, platelet ≤100 x 10^9/L, β-2 microglobulin >3mg/L and IgM >7g/DL. However, it effectively includes covariates twice because the analysis also includes IPSSWM risk.

4.4 Critique of the indirect comparison

4.4.1 Results of the company's indirect comparison

The results of the company's indirect comparison are presented in Table 20. The Kaplan-Meier estimates from the subset of 47 patients from Study 1118E who had received less than five prior lines of therapy and from the 175 matched European chart review cohort are presented in Figure 8.

The company's Cox model produced an estimated HR for the effect of ibrutinib versus standard therapies on PFS of [redacted]. The CS states that this reflects the univariate HR (as no

other covariates except treatment were significant [p>0.05]), however, the company later clarified that this HR was based on the full multivariable model (see clarification response,[14] question B26).

Table 20: Cox regression on PFS data - primary analysis (adapted from CS Table 22)

Covariates	HR	*p*-value
Ibrutinib treatment (versus SOC)	[redacted]	[redacted]
Beta macroglobulin ≤3mg/L	[redacted]	[redacted]
Haemoglobin ≤11 g/L	[redacted]	[redacted]
IgM <40 g/L	[redacted]	[redacted]
Platelet v100x10^9/L	[redacted]	[redacted]
IPSSWM: high risk	[redacted]	[redacted]
IPSSWM: intermediate risk	[redacted]	[redacted]
Female	[redacted]	[redacted]
Age	[redacted]	[redacted]

HR – hazard ratio; SOC – standard of care; IPSSWM - International Prognostic Scoring System for Waldenström's Macroglobulinemia

Figure 8: PFS curves of ibrutinib* vs. matched chart review cohort (reproduced from CS Figure 14)

[redacted]

**patients who had received ≤4 prior lines of therapy, n=47*

The CS also presents two sensitivity analyses using the Cox model based on alternative imputation approaches: (i) no imputation (n=89), and; (ii) imputation, no individual clinical measurement. These two sensitivity analyses produced slightly more favourable HRs of [redacted] and [redacted].

4.4.2 Critique of the company's indirect comparison

The ERG acknowledges that that there are no RCTs in this patient population and that a conventional network meta-analysis is not possible. Consequently, in order to make inferences about relative treatment effects, it is necessary to consider alternative methods of analysis. To this end, the company made use of evidence from the European chart review[9] and attempted to adjust for important prognostic factors that could have affected the treatment effect. The ERG has a number of concerns regarding the company's indirect comparison.

(i) The indirect comparison method may not adjust for all potential confounders

The CS highlights that there was considerable variation in PFS between the countries included in the European chart review (see CS,[1] Table 19). In addition, whilst the matching process was based on matching the number of lines of therapy received by the cohort to Study 1118E, the multivariable Cox model does not include line of treatment as a factor. Overall, the ERG considers that other confounders may remain, hence the company's approach may not consider all sources of uncertainty that contribute towards an unbiased estimate of treatment effect.

(ii) Creation of the matched European chart review cohort

The methods used to select patients in the European chart review cohort are not clear. According to the CS, two criteria were employed in the creation of the matched dataset: *"(i) the same patient from the chart review was not allowed to be in two lines at the same time, and; (ii) the distribution across lines of therapy of the final subset of patients selected from the chart review matched the distribution of patients from Study 1118E"* (CS,[1] page 56). However, the ERG notes that the criteria applied to the matched European cohort do not define a unique sample of patients; there may be many combinations of patients who meet the company's matching criteria. In response to a request for clarification (question B30),[14] the company presented a sensitivity analysis using an alternative sample of patients who also met the matching criteria defined above. This analysis produced an HR of [redacted] this is less favourable than the HR presented in the CS and the confidence interval is wider. The ERG thus has concerns regarding the reliability of this treatment effect estimate and whether it reflects the true uncertainty surrounding the treatment comparison.

(iii) Different definitions of disease progression in Study 1118E and the European chart review

The definition of progression differed between Study 1118E and the European chart review. The impact of this on the estimated treatment effect is unclear.

(iv) Reduced sample size for Study 1118E cohort

The CS notes that 16 patients in Study 1118E received five or more prior lines of treatment. The company's indirect comparison excluded these patients. Consequently, inferences should be made only with respect to this restricted patient population rather than all patients unless the treatment benefit can assumed to be independent of the number of prior lines of treatment. The ERG also notes that excluding patients from the analyses will lead to increased uncertainty surrounding the estimated treatment effect.

(v) Mismatch between the estimated treatment effect and its application in the health economic model

The evidence used to inform the effect of ibrutinib versus rituximab/chemotherapy on PFS has been derived from cohorts of patients who had received between one and four prior lines of therapy. However, within the company's health economic model, this treatment effect is applied to patients receiving second-line therapy (see Section 5.2). The assumption underlying the use of this HR in the model is that the number of prior lines of therapy received is not a treatment effect modifier; this assumption is however contradicted in the use of evidence to inform progression rates in the subsequent states of the model (see Section 5.3).

(vi) Use of the proportional hazards assumption

By definition, the company's Cox model assumes that the PFS hazard in the ibrutinib group is proportional to that in the matched European chart review cohort. This is a potentially strong assumption. In response to a request for clarification from the ERG (see clarification response,[14] question B27), the company confirmed that whilst not discussed in the CS, the proportional hazards assumption was tested between the PFS of ibrutinib in Study 1118E and the PFS of the matched European chart review cohort. The company's clarification response states that all statistical tests (visual examination of the log of negative log of estimated survivor functions and the Epanechnikov Kernel-smoothed hazard function, and the Kolmogorov-Smirnov test) showed that the proportionality assumption should not be rejected. However, the ERG notes that an absence of evidence against the proportionality assumption is not the same as evidence in support of it, and that the analysis is based on very few patients and events (Figure 8). A consequence of making this assumption is to assume that the treatment effect is maintained for the lifetime of patients.

(vii) Treatment effect estimated only for PFS

The company's indirect comparison is limited to estimating an HR for PFS between Study 1118E and the European chart review cohort. However, as described in Section 5.2, the company's health economic model includes benefits of treatment both in terms of PFS and OS. It is unclear whether the company's matched indirect comparison approach could have been used to estimate the relative benefits of ibrutinib versus standard therapies on OS; given the limited number of events, it is likely

that external data (e.g. expert judgement) would also be required to estimate the relative survival benefits of ibrutinib versus standard therapies.

4.5 Safety evidence

Owing to the small number of patients (n=63) in the only relevant trial in WM (Study 1118E[11]), Appendix 3 of the CS also reports some results from the following studies of ibrutinib: RESONATE[16] (PCYC-1112), RESONATE-2[17] (PCYC-1115), PCYC-1102[18], PCYC-1103[19] and PCYC-1104[20] (see CS,[1] page 65). Further data from these studies were sourced by the ERG and are reported here. The details of the additional studies of ibrutinib in CLL, small lymphocytic lymphoma (SLL) and MCL populations are provided in Table 21. No AE data were available from the European chart review (clarification response,[14] question B35).

Table 21: Additional non-WM studies reporting safety data on ibrutinib

Study	Design	Patients	Number of patients	Ibrutinib dose
RESONATE (PCYC-1112)	Randomised, Phase 3 study comparing ibrutinib with ofatumumab	R/R CLL or SLL	195	420mg/day
RESONATE-2 (PCYC-1115)	Randomised, Phase 3 study comparing ibrutinib with chlorambucil	TN CLL or SLL	136	420mg/day
PCYC-1102	Non-randomised, open-label study	CLL or SLL	85	420mg or 840mg/day
PCYC-1103	Open-label, ongoing, extension study of PCYC-1103, with additional patients	TN and R/R CLL or SLL	132	420mg or 840mg/day
PCYC-1104	Phase 2, open-label single-arm study	R/R MCL	111	560mg/day

CLL - chronic lymphoid leukaemia; SLL - small lymphocytic lymphoma; MCL - mantle cell lymphoma; TN – treatment-naïve; RR - relapsed/refractory

The findings of these studies are presented below, together with the data from Study 1118E. However, it is not clear how these additional studies were identified or selected by the company, or whether further relevant studies have been excluded (one other study was included in the integrated dataset in the CHMP's consideration of safety [CS,[1] page 65]: 04753, a Phase 1, open-label, multicentre, dose-escalation study of ibrutinib in subjects with a variety of B-cell malignancies, including four subjects with previously treated WM). It is also unclear what processes were followed in the extraction and checking of data. Furthermore, no quality assessment of these studies is presented in the CS. In response to a request for clarification from the ERG (see clarification response,[14] question B31), the company reported that the identification and selection process for these additional studies was reported in the submissions for two other NICE appraisals (CLL - ID749 and MCL - ID753).

4.5.1.1 All adverse events

AEs of any grade were very frequent, with up to 100% of patients in any study experiencing at least one AE and between 37% and 57% experiencing the most frequent event, diarrhoea (see

Table 22). The CS did not report data for "any AE" for Study 1118E. In response to a request for clarification from the ERG (see clarification response,[14] question B32), the company stated that they could not provide these data from the 19th December 2014 DCO dataset. Instead they provided AE data for Study 1118E from an earlier analysis dated 28th February 2014. The ERG notes that the CSR reports that grade 1 AE data were collected retrospectively (CSR,[24] Section 3.12.2, page 30). Where specified, additional data on AEs of any grade were also provided by the company for the supplementary trials, otherwise these data were derived by the ERG from the relevant publications. The frequency of many AEs was consistently moderately high across four ibrutinib studies: between [redacted]% and [redacted]% of patients experienced fatigue; [redacted]% to [redacted]% experienced nausea, and up to more than [redacted]% in any study reported cough or pyrexia. A range of other AEs were reported for [redacted]% of patients in three studies, with higher frequencies reported for study PCYC-1104, which employed a higher dose of ibrutinib (560mg/day compared with 420mg/day).

Table 22: Any adverse event reported in at least 15% of patients in any trial: Study 1118E, RESONATE, RESONATE-2 and PCYC-1104 (all follow-up at least 6 months)

Adverse events (AEs)	Study 1118E* n=63	RESONATE n=195	RESONATE-2 n=135*	PCYC-1102 n=116*	PCYC-1104 n=111*
Any AE occurring during treatment	[redacted]	194 (99%)	[redacted]	[redacted]	[redacted]
Haematologic AEs					
Neutropenia	[redacted]	42 (22%)	21 (16%)	[redacted]	20 (18%)
Thrombocytopenia	[redacted]	33 (17%)	[redacted]	[redacted]	20 (18%)
Anaemia	[redacted]	44 (23%)	[redacted]	[redacted]	[redacted]
Non-haematologic AEs					
Diarrhoea	[redacted]	93 (48%)	57 (42%)	[redacted]	56 (50%)‡
Fatigue	[redacted]	54 (28%)	41 (30%)	[redacted]	46 (41%)
Nausea	[redacted]	51 (26%)	30 (22%)	[redacted]	34 (31%)
Pyrexia	[redacted]	46 (24%)	[redacted]	[redacted]	20 (18%)
Cough	[redacted]	38 (19%)	30 (22%)	[redacted]	20 (18%)
Arthralgia	[redacted]	34 (17%)	22 (16%)	[redacted]	[redacted]
Dry eye	[redacted]	NR	23 (17%)	[redacted]	NR
Decreased appetite	[redacted]	NR	[redacted]	[redacted]	23 (21%)
Upper respiratory tract infection	[redacted]	31 (16%)	[redacted]	[redacted]	26 (23%)
Constipation	[redacted]	30 (15%)	[redacted]	[redacted]	28 (25%)
Vomiting	[redacted]	28 (14%)	18 (13%)	[redacted]	25 (23%)
Muscle spasm	[redacted]	25 (13%)	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	23 (12%)	[redacted]	[redacted]	30 (27%)
Peripheral oedema	[redacted]	22 (11%)	NR	[redacted]	31 (28%)
Sinusitis	[redacted]	21 (11%)	NR	[redacted]	[redacted]
Contusion	[redacted]	21 (11%)	NR	[redacted]	19 (17%)
Abdominal pain	[redacted]	NR	[redacted]	[redacted]	19 (17%)
Rash	[redacted]	NR	NR	[redacted]	19 (17%)

AE- adverse event; NR – not reported;

* For Study 1118E, data were reproduced for the 28/2/2014 analysis from clarification response, question B32, Table A, which was also the source of CIC data for RESONATE-2, PCYC-1102 and PCYC-1104.

‡CS, Appendix 3, page 21 reports slightly higher figures for diarrhoea and other AEs based on longer-term follow-up, as reported in Wang 2015.

4.5.1.2 Adverse events of grades ≥2

The principal grade 3 and 4 AEs that occurred most often in Study 1118E were neutropenia (14% of patients) and thrombocytopenia (13%). Pneumonia (8%) and gastroesophageal reflux (5%) were the next most frequent AEs; however, the majority of events were grade 2 only (see

Table 23).

Table 23: Grades 2-4 adverse events associated with ibrutinib therapy in Study 1118E (reproduced from CS Table 26)

Event or abnormality	Grade 2	Grade 3	Grade 4	Grades 2-4 Total
	Number of patients (%)			
Blood and lymphatic system disorders				
Neutropenia	5 (8)	6 (10)	3 (5)	14 (22)
Thrombocytopenia	1 (2)	6 (10)	2 (3)	9 (14)
Anaemia	3 (5)	1 (2)	0 (0)	4 (6)
Febrile neutropenia	0 (0)	0 (0)	1 (2)	1 (2)
Cardiac disorders				
Atrial fibrillation	2 (3)	1 (2)	0 (0)	3 (5)
Sinus tachycardia	1 (2)	0 (0)	0 (0)	1 (2)
Gastrointestinal disorders				
Gastroesophageal reflux	3 (5)	0 (0)	0 (0)	3 (5)
Stomatitis	3 (5)	0 (0)	0 (0)	3 (5)
Constipation	2 (3)	0 (0)	0 (0)	2 (3)
Diarrhoea	2 (3)	0 (0)	0 (0)	2 (3)
Ulceration	2 (3)	0 (0)	0 (0)	2 (3)
Infections and infestations				
Pneumonia	4 (6)	1 (2)	0 (0)	5 (8)
Skin infection	3 (5)	0 (0)	0 (0)	3 (5)
Cellulitis	1 (2)	0 (0)	0 (0)	1 (2)
Herpes zoster	1 (2)	1 (2)	0 (0)	2 (3)
Sinusitis	1 (2)	0 (0)	0 (0)	1 (2)
Streptococcal endocarditis	0 (0)	1 (2)	0 (0)	1 (2)
Subcutaneous abscess	1 (2)	1 (2)	0 (0)	1 (2)
Urinary tract infection	1 (2)	1 (2)	0 (0)	1 (2)
Post-procedural complications				
Hematoma	0 (0)	1 (2)	0 (0)	1 (2)
Haemorrhage	1 (2)	0 (0)	0 (0)	1 (2)
Dehydration	2 (3)	0 (0)	0 (0)	2 (3)
Musculoskeletal and connective-tissue disorders				
Tendinitis	1 (2)	0 (0)	0 (0)	1 (2)
Tenosynovitis	1 (2)	0 (0)	0 (0)	1 (2)
Nervous system disorders				
Headache	1 (2)	0 (0)	0 (0)	1 (2)
Pre-syncope	1 (2)	0 (0)	0 (0)	1 (2)
Syncope	0 (0)	1 (2)	0 (0)	1 (2)
Respiratory, thoracic, and mediastinal disorders				
Epistaxis	2 (3)	0 (0)	0 (0)	2 (3)
Cough	1 (2)	0 (0)	0 (0)	1 (2)
Skin and subcutaneous tissue disorders				
Pruritus	1 (2)	0 (0)	0 (0)	1 (2)
Rash	1 (2)	0 (0)	0 (0)	1 (2)
Skin exfoliation	1 (2)	0 (0)	0 (0)	1 (2)
Vascular disorders				
Hypertension	3 (5)	0 (0)	0 (0)	3 (5)
Hypotension	1 (2)	0 (0)	0 (0)	1 (2)

The findings of the supplementary studies were generally similar to those of Study 1118E in terms of type and frequency of grade 3 and 4 AEs (≥2%). The most frequent grade 3 or 4 AE was neutropenia ([redacted]% in any study, see

Table 24). It should be noted that the data presented for Study 1118E in

Table 24 are from the 28th February 2014 DCO provided by the company (clarification response,[14] question B32, Table A) rather than the 19th December 2014 DCO because they were more extensive. However, there were some inconsistencies between studies: the frequency of grade 3 or 4 thrombocytopenia ranged from 2% in RESONATE-2 to [redacted]% in Study 1118E; grade 3 or 4 diarrhoea was reported in [redacted] patients ([redacted]%) in RESONATE, RESONATE-2 and PCYC-1104, but no case was reported at all for Study 1118E. The incidence of grade 3 or 4 anaemia was also relatively low within Study 1118E ([redacted] patient) compared with RESONATE and RESONATE-2 ([redacted] patients across the two trials, [redacted] %).

Table 24: Grade 3 and 4 adverse events reported in at least ≥2% of patients in any trial: Study 1118E, RESONATE, RESONATE-2 and PCYC-1104 (all follow-ups are at least 6 months) - data from publications, unless otherwise stated

Adverse events (AEs)	Study 1118E n=63*	RESONATE n=195	RESONATE-2 n=135	PCYC-1102 n=116*	PCYC-1104† n=111
Any Grade 3/4 AE occurring during treatment	[redacted]	57%**	NR	NR	NR
Haematologic AEs					
Neutropenia	[redacted]	32 (16%)	14 (10%)	[redacted]	18 (16%)
Thrombocytopenia	[redacted]	11 (6%)	3 (2%)	[redacted]	12 (11%)
Anaemia	[redacted]	9 (5%)	8 (6%)	[redacted]	(NR) 11%‡
Febrile neutropenia	[redacted]	NR	3 (2%)	[redacted]	3(3%)***
Atrial fibrillation	[redacted]	NR	NR	[redacted]	NR
Non-haematologic AEs					
Diarrhoea	[redacted]	8 (4%)	5 (4%)	[redacted]	7 (6%)†
Fatigue	[redacted]	4 (2%)	1 (1%)	[redacted]	5 (5%)
Nausea	[redacted]	3 (2%)	NR	[redacted]	0 (0%)
Pyrexia	[redacted]	3 (2%)	NR	[redacted]	NR
Dyspnoea	[redacted]	4 (2%)	NR	[redacted]	4 (4%)†
Pneumonia	[redacted]	13 (7%)	5 (4%)	[redacted]	NR
Urinary tract infection	[redacted]	7 (4%)	NR	[redacted]	NR
Peripheral oedema	[redacted]	NR	NR	[redacted]	2 (2%)
Decreased appetite	[redacted]	NR	NR	[redacted]	2 (2%)
Hypertension	[redacted]	NR	6 (4%)	[redacted]	NR
Upper respiratory tract infection	[redacted]	1 (1%)	3 (2%)	[redacted]	NR
Maculopapular rash	[redacted]	NR	4 (3%)	[redacted]	2 (2%)†
Decreased platelet count	[redacted]	NR	4 (3%)	[redacted]	NR
Abdominal pain	[redacted]	NR	4 (3%)	[redacted]	6 (5%)†
Hyponatremia	[redacted]	NR	4 (3%)	[redacted]	NR
Pleural effusion	[redacted]	NR	3 (2%)	[redacted]	NR
Cellulitis	[redacted]	NR	3 (2%)	[redacted]	NR

**The data for Study 1118E are from the 28/2/2014 analysis (reproduced from clarification response, question B32, Table A), rather than the publication, which reports lower rates of Grade 3/4 AEs, and the data from PCYC-1102 are reproduced from clarification response, question B33, Table B).*
† Wang 2013, median follow-up 15.3 months except where stated.
***Listed as 57% in Appendix 3 and Byrd 2013 text, but 51% in Byrd Table 2.*
****Wang 2015: 26.7 months follow-up data.*
‡In CS, Appendix 3, page 21.

Two studies provided long-term safety data on ibrutinib: 3-year data from PCYC-1103[18] (n=132), and PCYC-1104[20] (n=111), which provided data for 6-month intervals up to a median follow-up of 26.7 months. The PCYC-1103 trial reported that the most frequent AEs were non-haematologic ([redacted]% of patients affected), followed by infections ([redacted]%) and haematologic events ([redacted]%).[18] Hypertension, pneumonia and neutropenia were the most frequent grade 3 or 4 AEs in this study (see Table 25).

Table 25: Three-year safety data from PCYC-1103 in at least ≥5% of patients[18]

Adverse events (AEs)	Grade ≥3 n=132
Hypertension	27 (20%)
Pneumonia	27 (20%)
Neutropenia	19 (14%)
Thrombocytopenia	11 (8%)
Atrial fibrillation	8 (6%)
Diarrhoea	8 (6%)
Fatigue	7 (5%)
Sepsis	6 (5%)

It was reported in the PCYC-1104 study that, at a median follow-up of 26.7 months, "any bleeding" was the most frequent grade ≥3 AE: this was experienced by 6% of patients (Wang 2015[20]). It was also reported in this study that the rate of diarrhoea and infection at any level, at grade ≥3, or as a serious adverse event (SAE), decreased over time (estimated median follow-up of 26.7 months). However, this was based on decreasing numbers of patients (n=111 at 1-6 months and n=22 at >24 months). For example, the rate of any diarrhoea was 44% (49/111 patients) at 1-6 months, but 27% (6/22 patients) at >24 months, with the potential risk of bias introduced by missing data. This decrease in frequency was also the case for "any bleeding", but not for "major bleeding", which increased from 5% (6/111 patients) at 1-6 months, to 9% (2/22 patients) at >24 months.

4.5.1.3 Serious adverse events (SAEs)

The publications relating to Study 1118E did not report any SAEs, but at the request of the ERG, the company provided these data for the 28th February 2014 DCO (clarification response[14], question B32, Table B). These data are reported in

Table 26. RESONATE, RESONATE-2, PCYC-1102 and PCYC-1104 all reported SAEs. The most frequent SAEs were consistent across trials: pneumonia, pyrexia, atrial fibrillation, urinary tract infection and febrile neutropenia (see

Table 26). RESONATE-2[17] also reported basal-cell carcinoma ([redacted]% of patients) and PCYC-1102[19] reported bacteraemia, cellulitis and sinusitis that also affected [redacted]% of patients. PCYC-1104 reported three second primary malignancies in [redacted] patients: metastatic adenocarcinoma of the bladder and metastatic neoplasm ([redacted] patient), cutaneous squamous cell carcinoma ([redacted] patients) and basal cell carcinoma ([redacted] patient).

Table 26: Summary of SAEs (≥2% in any trial arm)

SAE	Study 1118E* n=63	RESONATE n=195	RESONATE-2 n=135	PCYC-1102* n=116	PCYC-1104† n=111
Number of patients reporting at least one SAE	[redacted]	81 (42%)	NR	NR	NR
Pneumonia	[redacted]	17 (9%)	5 (4%)	[redacted]	8 (7%)‡
Thrombocytopenia	[redacted]				
Atrial fibrillation	[redacted]	6 (3%)		[redacted]	7 (6%)
Bacteraemia				[redacted]	
Cellulitis	[redacted]			[redacted]	
Sinusitis				[redacted]	
Pyrexia	[redacted]	6 (3%)	1 (1%)		3 (3%)
Urinary tract infection		4 (2%)			4 (4%)
Febrile neutropenia	[redacted]	3 (2%)		[redacted]	3 (3%)
Abdominal pain					3 (3%)
Acute renal failure					3 (3%)‡
Subdural hematoma					3 (3%)
Basal cell carcinoma			5 (4%)		
Neoplasms (benign, malignant, unspecified)	[redacted]				
Hyponatremia			3 (2%)		
Lung infection		5 (3%)			
Lower respiratory tract infection		4 (2%)			
Confusional state					3 (3%)
Sepsis				[redacted]	

SAE – serious adverse event. Blank cells indicate that data are either not reported or <2% frequency.
*These data are from 28/2/2014 analysis of Study 1118E (reproduced from clarification response, question B32, Table B) and, for PCYC-1102, from question B33, Table D).
† Median follow-up of 26.7 months
‡1 patient had a grade 5 AE

4.5.1.4 Adverse events leading to discontinuation

In all of the studies, the principal reason for discontinuation was disease progression. Disease progression is not considered as an AE here. In Study 1118E, six out of 63 patients (10%) discontinued treatment due to AEs (see Table 27). Discontinuation for other studies is summarised in Table 28.

Table 27: AEs leading to discontinuation during treatment period in Study 1118E (reproduced from clarification response question B34)

Reason for discontinuation	Number of cases (n=6)
myelodysplastic syndrome	1
thrombocytopenia	1
post-procedural haematoma	1
pleural effusion	1
B-cell lymphoma	1
atrial fibrillation	1

Table 28: AEs leading to discontinuation (reproduced from clarification response question B33, Table E)

Trial	Discontinuation (%)
RESONATE (N=195)	4
RESONATE 2 (N=135)	[redacted]
PCYC 1102 (N=116)	[redacted]
PCYC 1104 (N=111)	[redacted]

There are some differences between the numbers of patients reported in the publications and those reported in the company's clarification response (question B33),[14] which are summarised in Table 28. The numbers were the same for the RESONATE trials: discontinuation of treatment owing to AEs occurred in 4% and [redacted]% of the ibrutinib groups in RESONATE and RESONATE-2, respectively. The figures are slightly different for PCYC-1102: at a median follow-up of 20.9 months, [redacted] patients ([redacted]%) had discontinued treatment due to AEs, including pneumonia, sepsis, staphylococcal bacteremia without physiological signs of sepsis, and gastrointestinal hemorrhage,[19] whilst at three-year follow-up (PCYC-1103), [redacted]/132 ([redacted]%) had discontinued due to AEs, but details were not reported.[18] In the publication for PCYC-1104, eight of the 111 MCL patients ([redacted]%), who received ibrutinib 560mg/day, discontinued the study due to AEs: the events were subdural hematomas, pneumonia, elevated bilirubin level, sepsis, metastatic adenocarcinoma, respiratory failure, and cardiac arrest.[31]

4.5.1.5 Mortality

The proportion of deaths within the ibrutinib arms of the included trials ranged from 2% to 11% but, according to the studies, none of the deaths were related to ibrutinib (see Table 29).

Table 29: Mortality within ibrutinib arms of included studies

Study	Reasons given	Median follow-up (months)	Total n (%)
Study 1118E	Not reported	19.1	3/63 (5%)
RESONATE	"These events were most commonly infectious in nature" (p.220)	9.4	8/195 (4%)
RESONATE-2	1 from klebsiella infection and 2 from unknown causes	17.2	3/135 (2%)
PCYC-1102[19]	1 died 292 days after ibrutinib discontinuation after gastrointestinal haemorrhage and 1 died from GVHD	20.9	2/85 (2%)
PCYC-1103[18]	Not reported	36	14/132 (11%)*
PCYC-1104[31]	12 due to "disease progression"; 2 due to pneumonia, 1 to sepsis, 1 to a cardiac event deemed to be "not drug related"	15.3	16/111 (7%)

**Within 30 days of last dose. GVHD - graft-versus-host-disease*

In summary, the CS refers to the EMA conclusion that *"in view of the safety profile, the benefits are considered to outweigh the combined risks and uncertainties"* (CS,[1] page 66).

4.5.2 Ongoing studies

As reported in the CS[1] (Section 4.14, pages 66-71), there is currently one ongoing study: PCYC-1127-CA (iNNOVATE) (NCT02165397). This is an international (including UK), multi-centre, Phase III trial evaluating the safety and efficacy of ibrutinib in combination with rituximab in patients with WM. Ibrutinib is not currently licensed as a combination therapy. This study includes a third arm of ibrutinib monotherapy, an open-label sub-study for patients who are refractory to rituximab (n=31). The study was initiated in July 2014 and the estimated completion date is January 2019. The CS states that interim results are expected in April 2017 at the earliest, but reports some early efficacy data from this study. However, as these data are derived from two published abstracts only, they would be excluded from the submission based on the company's own exclusion criteria (CS,[1] Section 4.1, page 38 and CS Appendix 2, Table 2, pages 5-6 and page 13). The company's clarification response[14] (questions B5 and B7) states that the study has been included because, despite being published as abstracts, more extensive data (including patient-level data) were available to the company from the protocols and CSRs.

In terms of safety, the CS states that, based on the posters/abstracts of iNNOVATE, no new or unexpected AEs were observed compared with previous ibrutinib trials. The frequency of any AE was high (94%) (CS,[1] page 71). AEs reported in >15% of patients included diarrhoea (39%), hypertension (23%), neutropenia and upper respiratory tract infection (19%) and thrombocytopenia and pyrexia. (16%).[25] Grade ≥3 AEs occurred in 52% of patients, the most frequently-reported events being neutropenia (13%), thrombocytopenia, anaemia, hypertension and diarrhoea (6%).[25] The CS[1] states that SAEs occurred in six patients (19%), but does not report any details of these events. It also states that all patients remained alive at the DCO, with no events of IgM flare, atrial fibrillation or major bleeding. By the DCO, two patients had discontinued: 1 patient due to early disease progression ($MYD88^{WT}$) and 1 patient after 8 days of treatment due to an AE of gastrointestinal amyloidosis unrelated to ibrutinib.

4.6 Conclusions of the clinical effectiveness section

The CS consists of a poorly-reported systematic review of the clinical efficacy evidence and a non-systematic review of selected safety evidence. There was no RCT or non-randomised controlled trial of ibrutinib in the relevant populations outlined in the final NICE scope,[7] i.e. adult patients with WM who have received at least one prior therapy or treatment-naïve adult patients with WM who are unsuitable for chemo-immunotherapy. The clinical evidence therefore consisted of one prospective, multi-centre, USA, Phase II, single-arm, open-label study of ibrutinib in 63 adult patients with WM who have received at least one prior therapy: Study 1118E[11] (PCYC-1118E). This was the principal

clinical evidence contained within the submission. No empirical clinical evidence was submitted on treatment-naïve patients with WM who were unsuitable for chemo-immunotherapy.

In Study 1118E, 63 previously-treated adult patients with WM from across three sites in the USA were allocated to receive the licensed 420mg/day dose of ibrutinib. Treatment was administered for a median of 19.1 months (range, 0.5 to 29.7 months) and 43/63 patients (68%) remained on treatment after the final DCO on 19th December 2014. The median age was 63.0 years (mean age = 64.5 years); the majority of patients were male (76.2%). The median time from diagnosis of WM to study entry was 76 months (range: 6 to 340 months). The median number of prior regimens was 2 (range: 1 to 9). Clinical advice received by the ERG suggests that this study population is relevant to clinical practice in England.

The principal efficacy outcomes were response and PFS. With the exception of CR, the definitions of minor response, PR and VGPR applied in Study 1118E, as reported in the CS and protocols, appear to differ from internationally recognised response criteria: in Study 1118E, they are limited to serum IgM level only, whilst international standards also require the presence or absence of clinically significant findings or symptoms.[2, 26, 28] The ERG notes that IgM response alone is insufficient as an outcome for WM because clinical benefit might be seen in patients without IgM response, or IgM reduction might not lead to an improvement in symptoms.[2, 25]

The reported ORR (any response) was 90.5% (95% CI 80.4% to 96.4%), which was achieved by 57/63 patients. Responders were categorised as follows: VGPR: n=10; PR: n=36; and minor response: n=11. The major response rate (defined as PR or better) was 73% (95% CI 60.3% to 83.4%). Based on data only available in the CSR, the Kaplan-Meier estimate for the event-free rate for all responders at 18 months was 80.9% (95% CI 64.9% to 90.2%), and the corresponding values for major responders were 86.7% (95% CI 67.9% to 94.9%). The CS presented subgroup analyses of ORR and major response rate and reported that response rates were "consistent across most subgroups" (e.g. by age, ECOG score at baseline, IPSSWM risk score). Whilst this generally appears to be the case for ORR, differences in major response are particularly apparent for patients with different levels of $ß_2$–microglobulin, haemoglobin, bone marrow disease involvement and genotype $MYD88^{L265P}$ and $CXCR4^{WT}$. The ERG would have preferred the use of a single model involving a covariate for each factor as this would allow mutual adjustment of covariates as well as the identification of confounding between factors.

Treatment with ibrutinib resulted in a significant decline in median percentage of bone marrow infiltration from 60% to 25% ($p<0.001$). There was no correlation between serum IgM levels and bone marrow involvement at 6 months ($r=0.03$, $p=0.83$), but there was at 12 months ($r=0.51$, $p<0.001$) and 24 months ($r=0.56$, $p<0.008$).[11] However, details of the assessment method are not

reported for Study 1118E, and it is not clear who conducted the assessment. The literature suggests that this assessment should be conducted by "central review" every 4-6 weeks in trials because the most appropriate time-point for assessment is unknown.[26] In Study 1118E, bone marrow biopsies were taken at cycles 6 (i.e. 24 weeks), 12 (48 weeks) and 24 (96 weeks) and annually thereafter.[11] At baseline, adenopathy and splenomegaly were identified by CT in 37/63 (59%) and 7/63 (11%) patients, respectively, and the number of patients with lymphadenopathy and splenomegaly were reduced after ibrutinib treatment.

The Kaplan-Meier curve estimates the rate of PFS at 24 months to be 69.1% (95% CI 53.2% to 80.5%). By the end of data collection (19th December 2014 DCO), 60 of the 63 patients were still alive and the estimated rate of OS was 95.2% (95% CI 86% to 98.4%).

The ERG considers that Study 1118E was a well-reported single-arm study, a study design of lower quality than a controlled trial. Patients were generally younger and had less severe disease than the R/R adults with WM who might routinely present in practice England. In terms of internal validity, the criteria relating to blinding were not relevant to this study design, but the statistical tests undertaken were appropriate, and analyses by subgroup were performed to evaluate the effect of potential confounders on two key outcomes (response and PFS). The outcome measures used were generally valid and reliable but the response criteria (the primary outcome) were "modified" from international standards.[2, 26, 28] There is a high risk of bias with studies of this single-arm design because of the absence of a control group; there is also a high risk of selection bias because of the absence of randomisation, and a high risk of performance and detection bias because of the absence of blinding. Inadequate reporting is also an issue because neither the CS nor the Study 1118E publication or its protocol[11] specified what methods were used to measure outcomes; different methods of assessment for response can produce different values and the assessments must be conducted in a single laboratory.[2, 26] None of this information was reported in the CS or publications relating to Study 1118E. The CS did acknowledge that, *"the phase 2 non-comparative nature of the study may not meet the rigour of evidence generally expected"* (CS,[1] Section 4.13, page 66).

Given the absence of randomised head-to-head studies comparing ibrutinib versus any other WM treatment, the CS presents an adjusted arm-based indirect comparison of PFS data from Study 1118E[11] and a matched cohort from a retrospective European chart review.[9] This indirect comparison estimates the HR for PFS for ibrutinib versus standard therapies using a multivariable Cox model. The company's multivariable Cox model produced an estimated HR for the effect of ibrutinib versus standard therapies on PFS of [redacted]. The use of alternative imputation methods produced more favourable HRs for PFS ranging from [redacted] to [redacted]. A repeated analysis using a different matched sample produced a higher HR for PFS of

[redacted]. With respect to the company's indirect comparison, the ERG has concerns regarding the reliability of the reported estimate of treatment effect, in particular: (i) the potential for unadjusted confounders; (ii) the lack of a unique matched sample from the chart review, and; (iii) the exclusion of patients who had received five or more prior lines of treatment. In addition, the ERG notes that the CS does not contain an analysis of the relative survival benefits of ibrutinib versus standard therapies.

On account of the small number of patients (n=63) in the only relevant study in WM (Study 1118E), the CS also reports some safety results from the following studies in which patients with CLL or MCL received ibrutinib: RESONATE[16] (PCYC-1112), RESONATE-2[17] (PCYC-1115), PCYC-1102[18], PCYC-1103[19] and PCYC-1104.[20] Following clarification, the company also provided additional data, and the ERG also sourced additional data from study publications. AEs of any grade were very frequent in all trials, with up to 100% of patients in any study experiencing at least one AE and between 42% and 57% experiencing the most frequent event, diarrhoea. The principal grade 3 and 4 events that occurred most often in Study 1118E were: neutropenia (14% of patients); thrombocytopenia (13%); pneumonia (8%), and; gastroesophageal reflux (5%). The findings of the supplementary studies were generally consistent with those of Study 1118E in terms of type and frequency of grade 3 and 4 AEs ($\geq$2%). The most frequent grade 3 or 4 AEs were: neutropenia (up to 16% in any study); thrombocytopenia and anaemia (up to 11%), and; pneumonia (up to 7%).

In Study 1118E, 6 out of 63 patients (10%) discontinued treatment due to AEs (not including disease progression): possible treatment-related disease transformation; treatment-aggravated thrombocytopenia; infection unrelated to ibrutinib; haematoma post bone marrow biopsy and myelodysplasia and acute myeloid leukaemia related to prior treatments. The other ibrutinib studies reported a rate of between 4% and 11% discontinuation due to such AEs. The number of deaths within the ibrutinib arms of the included studies ranged from 2% to 11% but, according to the studies, none of the deaths were related to ibrutinib.

There is one single ongoing study: PCYC-1127-CA (iNNOVATE) (NCT02165397). This is an international (including UK), multi-centre, Phase III trial evaluating the safety and efficacy of ibrutinib in combination with rituximab in patients with WM. Ibrutinib is not currently licensed as a combination therapy.[10] This study includes a third arm of ibrutinib monotherapy, an open-label sub-study for patients who are refractory to rituximab (n=31). The study was initiated in July 2014 and the estimated completion date is January 2019. The CS states that interim results are expected in April 2017 at the earliest.

Limitations

The ERG notes that the main limitations of the company's evidence relate to the following:

- The absence of any RCT or non-randomised controlled trial in the previously-treated WM population
- The absence of any evidence for ibrutinib treatment in the treatment-naïve WM population defined in the final NICE scope
- The principal evidence consists of one single–arm, open-label study of 63 patients, which. on account of its design, is at high risk of selection, performance and other bias
- Uncertainty surrounding the extent to which the population in Study 1118E represents the population likely to present in clinical practice in England
- The response measure in Study 1118E used different criteria from accepted international standards and other details of the assessment were unclear
- An indirect estimate of the effect of ibrutinib versus rituximab/chemotherapy on PFS was based on an adjusted arm-based comparison against a mixed comparator and excluded patients who had previously received at five or more prior lines of treatment
- AEs of any grade were very frequent but were generally mild; SAEs and grade 3 and 4 AEs are only reported to affect up to 14% of patients in any trial, although approximately 50% of patients in two studies have reported grade 3 or 4 AEs.

5. COST EFFECTIVENESS

This chapter presents a summary and critical appraisal of the methods and results of the company's review of published economic evaluations and the *de novo* health economic analysis presented within the CS.[1]

5.1 ERG comment on the company's systematic review of cost-effectiveness evidence

5.1.1 Description of company's systematic review of cost-effectiveness evidence

The company undertook a systematic review to identify economic models and studies reporting economic outcomes and data relating to the treatment of WM patients with any chemotherapeutic, biologic or investigational pharmaceutical agent. The company's review methods are presented in CS Section 5.1 (pages 72-74) and CS Appendix 5.

The company performed a search of the literature to identify health economic analyses and HRQoL studies. The strategies of the initial search (6th February 2015) and the updated searches (3rd May 2016) were fully reported in Appendices 5 and 6 of the CS. Searches were undertaken in the following databases:

- MEDLINE (via PubMed) and MEDLINE (R) In-process (via PubMed)
- Embase, and Embase In-process
- CENTRAL
- Database of Abstracts of Reviews of Effects (DARE)
- National Health Service Economic Evaluation Database (NHS EED)
- National Health Service Health Technology Assessment (HTA) database
- EconLit.

The electronic database searches were supplemented with other sources including conference abstracts. The proceedings from the past three years (as available) for the following conferences were reviewed:

- ASCO 2013–2015 (via Embase)
- ASH 2013–2015 (via Embase)
- EHA 2013–2015 (via Embase)
- ISPOR 2013–2015 international and European meetings (http://www.ispor.org/)
- IWWM 2013 and 2015 (http://www.wmworkshop.org/).

The company's inclusion and exclusion criteria for the review of existing economic analyses are summarised in

Table 30. Study selection was performed across two stages. The first stage involved reviewing titles and abstracts of all unique records against the inclusion and exclusion criteria for the review. The second stage involved reviewing potentially includable studies based on full-text publications. Both rounds were undertaken by two reviewers; discrepancies were resolved through the inclusion of a third reviewer. Data were extracted by a single reviewer and validated by a second reviewer, with discrepancies resolved through the use of a third reviewer.

The search identified a total of 395 records. Following de-duplication and sifting according to titles and abstracts, 391 records were excluded. Following the full text review of the remaining four studies, two further studies were excluded, hence a total of two studies were included.[32, 33] Both of the included studies were cost analyses; neither study included a full economic evaluation of treatments for WM.

Table 30: Inclusion and exclusion criteria for review of existing economic analyses

	Inclusion criteria	Other delimiters and exclusion criteria
Population	• WM*	• Patients without WM or LPL (LPL alone was rejected at full-text screening)
Intervention(s) **	• Ibrutinib monotherapy • Ibrutinib combination therapy	• No treatment of interest (e.g. radioimmunotherapy alone)
Comparator(s)	• Alemtuzumab monotherapy • Allogeneic stem cell transplant (ASCT) • Bendamustine ± rituximab (BR) • Bortezomib + dexamethasone • Bortezomib + dexamethasone + rituximab • Bortezomib ± rituximab • Carfilzomib + rituximab + dexamethasone • Chlorambucil + ofatumumab • Chlorambucil ± rituximab • Cladribine ± rituximab (Clad-R) • Cyclophosphamide + doxorubicin[hydroxydaunomycin] + vincristine + prednisone ± rituximab (CHOP/R-CHOP) • Dexamethasone + rituximab + cyclophosphamide (DRC) • DRC+ bortezomib • Everolimus • Enzastaurin • Fludarabine + cyclophosphamide + rituximab (FCR) • Fludarabine ± rituximab • Idelalisib • Lenalidomide • Obinutuzumab • Ofatumumab • Perifosine • Rituximab + cyclophosphamide + vincristine + prednisone (RCVP) • Rituximab + cyclophosphamide + prednisone • Rituximab + high-dose methyl prednisone/steroids (R+HDMP) • Rituximab monotherapy • Thalidomide ± rituximab • "Watchful waiting"/no treatment/prophylactic therapy/palliative care	• Non-randomised, comparative clinical efficacy and safety studies reporting on only one treatment of interest
Outcome(s)	<u>PRO or HRQoL outcomes</u> • Measure of outcome used • Value or change in value of PRO/HRQoL scores <u>Economic and healthcare resource use (HCRU)</u> • Cost-effectiveness estimates • Quality-adjusted life-years (QALYs) • Medical resource use • Cost data • Disease progression costs • Utility or utility input values • Disutilities	• Publications that do not report economic outcomes, PROs, or HRQoL outcomes for WM specifically
Study design	<u>Economic</u> • Economic evaluations conducted either as part of a prospective interventional trial/observational study or as a standalone model <u>Observational studies</u> • Retrospective analyses • QoL • Prospective interventional trials • Observational studies • Retrospective analyses	• Narrative publications, non-systematic reviews, case studies, case reports, and editorials • Non-English, full-text articles or articles without an English abstract • Comparative studies with fewer than 10 patients with WM per treatment group in at least two treatment arms or single-arm studies with fewer than 10 patients.

*** LPL disease designation was accepted at the abstract screening level; outcomes had to be reported separately for WM patients within the full text.*

**Interventions were considered as inclusion criteria for data extraction and summarization only. Studies were not excluded based on interventions (any specific chemotherapeutic agent) until after full-text screening was complete.*

5.1.2 ERG critique of company's systematic review of cost-effectiveness evidence

The ERG notes that the NHS EED and DARE coverage is until 2015 and that these databases are no longer updated. The ERG concurs with the company's approach to search the WM population combined with the economic or HRQoL terms without named interventions and comparators. Whilst the collective economic terms in the strategy were not the same as a published economics filter (as listed in the ISSG filter resource [https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/filters-to-find-i]), the ERG re-ran the company's PubMed searches and the terms alone retrieved a high number of records: this suggests that the company's search was sensitive. The ERG is therefore satisfied that the company's searches will not have missed relevant economic or HRQoL studies.

The ERG agrees that neither of the studies included in the company's review is relevant to the evaluation of the cost-effectiveness of ibrutinib for treating WM.

5.2 Description of the company's model

5.2.1 Health economic evaluation scope

As part of their submission to NICE, the company submitted a fully executable health economic model programmed in Microsoft Excel®. The scope of the company's economic analysis is summarised in

Table 31. The company's model assesses the cost-effectiveness of second-line ibrutinib versus a blend of second-line rituximab/chemotherapy options (referred to as "physician's choice" in the CS[1]) for the treatment of patients with R/R WM. Following disease progression on second-line treatment, subsequent treatment (for a proportion of patients) in both groups is assumed to include third- and fourth-line rituximab/chemotherapy regimens and BSC. The incremental health gains, costs and cost-effectiveness of ibrutinib are evaluated over a lifetime horizon from the perspective of the UK NHS and PSS (although the ERG notes that no PSS costs are actually included in the company's model). All costs and health outcomes are discounted at a rate of 3.5% per annum. Unit costs are valued at 2014/15 prices.

Table 31: Company's health economic model scope

Population	Patients with R/R WM
Intervention	Ibrutinib 3 x 140mg capsules (420mg) o.d.
Comparator	A blend of chemotherapy and/or rituximab options including: • rituximab and bendamustine (BR) • rituximab, dexamethasone and cyclophosphamide (DRC) • rituximab and fludarabine and cyclophosphamide (FCR) • cladribine plus rituximab • chlorambucil plus rituximab • cladribine monotherapy • rituximab monotherapy • chlorambucil monotherapy
Primary health economic outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Time horizon	Lifetime (30 years)
Discount rate	3.5% per year
Price year	2014/2015

QALY – quality-adjusted life year; NHS – National Health Service; PSS – Personal Social Services; o.d. – once daily

Population

The population considered within the company's model relates to patients with R/R WM who have received one prior therapy. This is largely inconsistent with the population recruited into Study 1118E,[11] whereby 71.4% of the overall study population had received more than one prior therapy. Given the matching process used to underpin the company's adjusted indirect comparison of ibrutinib versus standard therapies, this is therefore also inconsistent with the evidence used from the European chart review,[9] whereby [redacted] of patients in both groups had previously received more than one prior line of therapy; this issue is discussed in further detail in Section 5.3. At model entry, the population is assumed to be 64.5 years of age and 76.2% of patients are assumed to be male. The mean body mass of the population is assumed to be 79.30kg with a mean body surface area (BSA) of 1.96m^2.

The CS does not include any economic analyses relating to the treatment-naïve population for whom chemo-immunotherapy is unsuitable.

Intervention

The intervention under consideration within the company's health economic analysis is ibrutinib. Ibrutinib is assumed to be administered orally at a fixed dose of 420mg o.d. (three capsules). The SmPC for ibrutinib states that treatment with ibrutinib should continue until disease progression or until the treatment is no longer tolerated by the patient.[10] The company's model is in line with this continuation rule.

Comparators

Within the company's base case analysis, the comparator is assumed to reflect a blend of second-line rituximab/chemotherapy regimens including: (i) rituximab and bendamustine (BR); (ii) rituximab, dexamethasone and cyclophosphamide (DRC); (iii) rituximab and fludarabine with cyclophosphamide (FCR); (iv) cladribine with rituximab; (v) cladribine monotherapy; (vi) rituximab monotherapy; (vii) chlorambucil monotherapy, and; (viii) chlorambucil with rituximab. The dosing schedule for each regimen included in the model is summarised in

Table 32, based on information provided in the CS[1] and the company's clarification response[14] (question C3). It should be noted that there are discrepancies between the CS, the clarification response and the company's model with respect to the comparator regimens evaluated (see Section 5.3.3). The benefits of these rituximab/chemotherapy regimens and the usage of each regimen were taken from separate sources: the proportionate use of each regimen was based on the average of all responses from a survey of five clinical experts undertaken by the company together with additional assumptions (see CS,[1] Appendix 4), whilst the clinical effectiveness of the regimens (as a whole) was based on the company's European chart review.[9] Thus, whilst each regimen is costed individually and weighted according to its proportionate use, treatment effects are not differentiated by regimen.

Table 32: Comparator regimens included in the company's model

Regimen	Assumed dosing and frequency (from CS[1] and clarification response[14])	Usage second-line	Usage third-/fourth-line
FCR*	Fludarabine: 25 mg/m^2 on days 2–4 every 28 days for six cycles Cyclophosphamide: 250 mg/m^2 on days 2–4 every 28 days for six cycles Rituximab: 375 mg/m^2 on day 1 of first cycle every 28 days for six cycles	11%	9%
DRC	Dexamethasone: 20 mg IV on day 1 every 21 days for six cycles Rituximab: 375 mg/m^2 IV on day 1 every 21 days for six cycles Cyclophosphamide:100mg/m^2 orally on days 1–5 every 21 days for six cycles	31%	15%
BR	Bendamustine: 90 mg/m^2 every 28 days for 6 cycles Rituximab: 375 mg/m^2 every 28 days for six cycles	47%	43%
Cladribine + rituximab	Cladribine: 0.14 mg/kg every 28 days for 4 cycles Rituximab: 375 mg/m^2 every 28 days for 4 cycles	0%	30%
Cladribine	Not stated in CS. Clarification response states: 0.14 mg/kg every 28 days for 4 cycles	2.75%	0%
Chlorambucil	Not stated in CS. Clarification response states: 0.2 mg/kg/day for 8 weeks	2.75%	1%
Rituximab	Not stated in CS. Clarification response states: 375 mg/m2 every 28 days for 6 cycles	2.75%	1%
Chlorambucil + rituximab	Not stated in CS or clarification response.	2.75%	1%

IV - intravenous; CS - company's submission

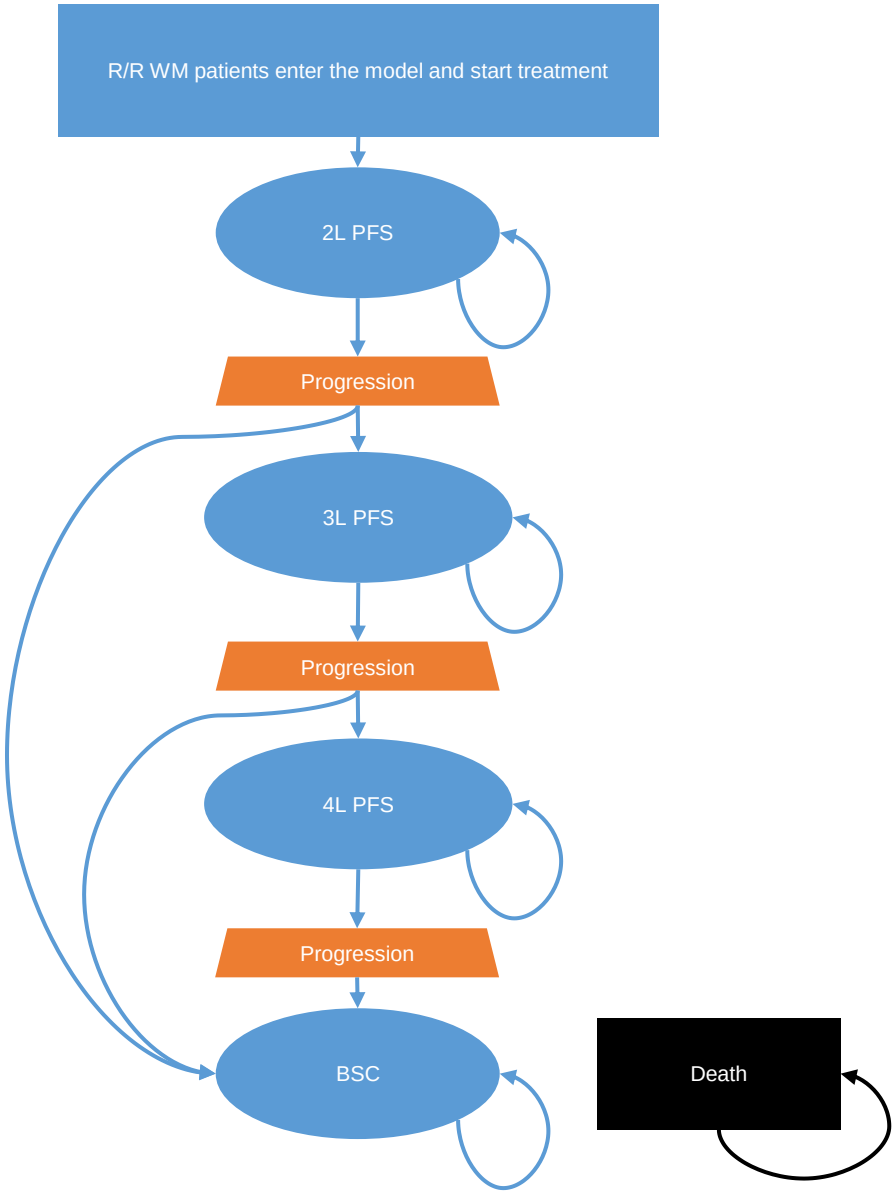
Following disease progression on second-line therapy (ibrutinib or rituximab/chemotherapy), the model assumes that a proportion of patients will go on to receive third-line treatment using rituximab/chemotherapy regimens. The remainder are assumed to receive best supportive care (BSC). Similarly, following progression on third-line therapy, the model assumes that a proportion of patients will go on to receive fourth-line rituximab/chemotherapy, whilst the remainder receive BSC. The rituximab/chemotherapy regimens included at the third- and fourth-lines are assumed to be the same as those included in the comparator group at second-line, with the exceptions of cladribine monotherapy (second-line usage – 2.75%; third-/fourth-line usage – 0%) and cladribine in combination with rituximab (second-line usage – 0%; third-/fourth-line usage – 30%).

5.2.2 Description of the company's health economic model structure and logic

The general structure of the company's model is presented diagrammatically in

Figure 9. The model adopts a Markov approach based on five health states: (1) second-line progression-free; (2) third-line progression-free; (3) fourth-line progression-free; (4) BSC, and; (5) dead. The model uses parametric survival models fitted to data on PFS, time to progression, pre-progression mortality and post-progression survival to inform transition rates between the health states. The model adopts a 28-day cycle duration. Costs and health outcomes for competing treatment options are evaluated over a total of 392 cycles (until the surviving patient cohort is approximately 95 years of age); at this point more than 99.6% of patients in both treatment groups have died. A half-cycle correction is applied to account for the timing of events.

Figure 9: Company's model structure (reproduced from CS Figure 19)



R/R WM – relapsed/refractory Waldenström's macroglobulinemia; 2L – second-line; 3L – third-line; 4L – fourth-line; PFS – progression-free survival; BSC – best supportive care

Model logic

Patients enter the model in the second-line progression-free state and receive treatment with ibrutinib or rituximab/chemotherapy. Within the ibrutinib group, the probability of being progression-free at any time *t* is modelled using a parametric (Weibull) survivor function fitted to the empirical PFS time-to-event data from Study 1118E.[11] Patients are assumed to remain on ibrutinib treatment until disease progression or death, whichever occurs first. Within the ibrutinib group, the probability that a patient leaving the second-line progression-free state dies during a given interval is modelled using age- and sex-adjusted general population mortality hazards derived from life tables.[34] Within the rituximab/chemotherapy group, PFS in second-line is modelled using the inverse of the HR derived

from the multivariable Cox model applied to the ibrutinib PFS curve (see Sections 4.3 and 4.4), whilst the probability that a patient leaving the second-line progression-free state dies is modelled using data derived from the European chart review cohort (1-4 prior lines of therapy).[9] The duration of treatment using second-line rituximab/chemotherapy is up to a maximum of 6 cycles (depending on the regimen assumed); hence, the second-line progression-free interval for the comparator includes a period in which patients are receiving treatment followed by a period in which patients have discontinued treatment but remain progression-free.

Within both treatment groups, patients who do not die prior to progression from the second-line progression-free state are assumed to transit either to the third-line progression-free state or subsequently receive BSC. The probability of being in the third-line progression-free state at any time *t* is given by the proportion of patients who were in the third-line progression-free state at time *t*-1 plus any new patients progressing to the third-line progression-free state at time *t*, less any patients on third-line therapy dying during the interval *t*-1 and *t* and any patients on third-line therapy progressing to the fourth-line progression-free or BSC states at time *t*. Similarly, a proportion of surviving patients progressing from third-line therapy are assumed to go on to receive fourth-line therapy, whilst the remainder receive BSC. The probability of being in the fourth-line progression-free state at any time *t* is given by the proportion of patients who were in the fourth-line progression-free state at time *t*-1 plus any new patients progressing to the fourth-line progression-free state at time *t*, less any patients on fourth-line therapy dying during the interval *t*-1 and *t* and any patients on fourth-line therapy progressing to BSC at time *t*. Surviving patients progressing from the fourth-line progression-free state are assumed to transit to the BSC state. The probability of being in the BSC state at time *t* is given by the proportion of patients who were on BSC at time *t*-1 plus any new patients who progress to BSC from the second-, third- or fourth-line progression-free states less any patients on BSC dying during the interval *t*-1 and *t*. Following entry into the third-line progression-free state, all transitions assume a constant underlying hazard rate modelled using exponential distributions; these same transition rates are applied to both treatment groups. The treatment duration for rituximab/chemotherapy within these states is again up to a maximum of 6 cycles (depending on the regimen assumed), hence these states include a period in which patients are receiving treatment followed by a period in which patients have discontinued treatment but remain progression-free.

Health utility is differentiated according to the presence/absence of disease progression, with the same higher baseline value applied to each of the progression-free states compared with the BSC state. Disutilities associated with AEs are included only for second-line treatment; AEs associated with active subsequent-line treatment are not included in the model.

The company's model includes costs associated with: (i) drug acquisition; (ii) drug administration (for rituximab/chemotherapy regimens only); (iii) routine follow-up; (iv) the management of AEs; (v) BSC, and; (vi) terminal care. The base case version of the company's model assumes that vial sharing for the rituximab/chemotherapy regimens is not permitted. Treatment costs for all regimens are adjusted according to relative dose intensity (RDI).

The application of different PFS and pre-progression mortality curves during the second-line progression-free period leads to different trajectories through the remainder of the model and hence produces different profiles of costs and health outcomes for the two treatment groups. Incremental cost-effectiveness is calculated in a pairwise fashion as the difference in costs divided by the difference in QALYs for ibrutinib and rituximab/chemotherapy.

Key structural assumptions employed within the company's model

The company's model employs the following structural assumptions:

- All patients enter the model in the second-line progression-free health state.
- Following model entry, patients may receive up to three lines of active therapy followed by BSC. Following progression from the second-line and third-line progression-free states, a proportion of patients will not receive further active therapy. Following progression from the fourth-line progression-free state, all patients are assumed to subsequently receive BSC.
- Within the second-line progression-free state, PFS is assumed to follow a Weibull distribution.
- The treatment effect for PFS for rituximab/chemotherapy is assumed to be proportional to that for ibrutinib and the same HR is assumed to apply indefinitely within the second-line progression-free state. The modelled benefits of rituximab/chemotherapy are not directly related to the proportionate use of the specific regimens received.
- Pre-progression mortality in the rituximab/chemotherapy group is assumed to follow a lognormal distribution.
- Pre-progression mortality in the ibrutinib group is assumed to reflect age- and sex-adjusted general population life tables.
- Within both treatment groups, the probability of pre-progression death is modelled conditional on the probability of being alive and progression-free (applied to patients leaving the progression-free states).
- The probabilities of progression and death during the third- and fourth-line progression-free intervals are assumed to follow an exponential distribution. The probability of death for patients receiving BSC is also assumed to follow an exponential distribution, with the same death rate as the third- and fourth-line progression-free states. Beyond progression from the

second-line progression-free state, the probabilities of these events are assumed to be the same for both treatment groups.

- Ibrutinib is assumed to be given until disease progression.
- Rituximab/chemotherapy is assumed to be given for a fixed duration of between 4 and 21 weeks, depending on the regimen received (see
- Table 32).
- Health utility is determined by the presence/absence of disease progression with a lower utility value assumed for patients receiving BSC. Health utilities are age-adjusted.
- The health gains associated with treatment are assumed to be reduced by the incidence of AEs; treatment-specific QALY losses for AEs are applied in the first model cycle only. HRQoL decrements associated with AEs resulting from the use of third- and fourth-line treatments are not included in the model.
- Rituximab/chemotherapy dosing is based on mean body mass and mean height rather than the distributions for the patient population.

5.2.3 Evidence used to inform the company's model parameters

Table 33 summarises the evidence sources used to inform the parameters of the company's model. The derivation of the model parameter values using these sources is described in further detail in the following sections.

Table 33: Summary of evidence sources used to inform the model parameters

Parameter type	Parameter	Source(s)
Patient characteristics	Age	Study 1118E[11]
	Body surface area	
	Percent male	
Transition probabilities	HR for PFS ibrutinib versus rituximab/chemotherapy	Regression adjusted arm-based indirect comparison using Study 1118E[11] and the European chart review[9] (multivariable Cox model, patients who had received ≤4 prior lines of therapy)
	PFS (second-line) - ibrutinib	Study 1118E[11] (full study population)
	Pre-progression mortality - ibrutinib	Age- and sex-adjusted general population life tables[34]
	Pre-progression mortality – rituximab/chemotherapy	Derived from the European chart review[9] (various subgroups with differing numbers of prior therapies, see Section 5.3.3)
	Probability of progression - third-line treatment	
	Pre-progression mortality – third-line treatment	
	Probability of progression - fourth-line treatment	
	Pre-progression mortality – fourth-line treatment	
	Post-progression survival – BSC	
	Probability patient progressing from second-line treatment receives third-line treatment	Expert opinion plus assumption[1]
	Probability patient progressing from third-line treatment receives fourth-line treatment	
AE frequency	Incidence of AEs due to second-line treatment	Treon *et al*,[11] Tedeschi *et al*,[35] Tedeschi *et al*,[36] Dimopoulos *et al*,[15] Treon *et al*,[37] Electronic Medicines Compendium (eMC)[38]
Health-related quality of life	Utility - progression-free states	RESONATE trial[16]
	Utility - BSC	RESONATE trial,[16] Beusterien *et al.*[39]
	AE disutilities	Beusterien *et al*,[39] Tolley *et al.*[40] and assumptions
Resource use	Dosing regimen for ibrutinib	Ibrutinib SmPC[10]
	Dosing intensity for ibrutinib	Study 1118E CSR[24]
	Dosing intensity for rituximab/chemotherapy	Assumed to be the same as ibrutinib
	Dose and frequency of second-line rituximab/chemotherapy regimens	Expert opinion plus assumption[1]
	Dose and frequency of third- and fourth-line treatments	Expert opinion plus assumption[1]
	IV administration	Based on assumed dosing schedules
	Follow up resource use	Expert opinion[1]
	Hyperviscosity-related resource use	Expert opinion[1]
Unit Costs	Drug acquisition	British National Formulary 2016[12]
	Drug administration	NHS Reference Costs 2014/2015[41]
	Follow up	NHS Reference Costs 2014/2015[41]
	Hyperviscosity	NHS Reference Costs 2014/2015[41]
	Management of AEs	NHS Reference Costs 2014/2015[41]
	Terminal care	Round *et al*[42]

BSC – best supportive care; AE – adverse events; IV – intravenous; SmPC – Summary of Product Characteristics

Patient characteristics

The model includes parameters describing patient characteristics relating to age, patient height and weight. The model assumes that patients enter the model aged 64.5 years and patients have a mean height of 174.7cm and a mean weight of 79.3kg (corresponding to a mean BSA of 1.96m^2); these parameters were derived from Study 1118E.[11]

Transition probabilities

Transitions between the model health states were derived from PFS data from Study 1118E,[11] the company's indirect comparison, the European chart review[9] and general population life tables.[34] The evidence used to inform transition probabilities is summarised in Table 34.

Table 34: Evidence used to inform 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[34]	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		

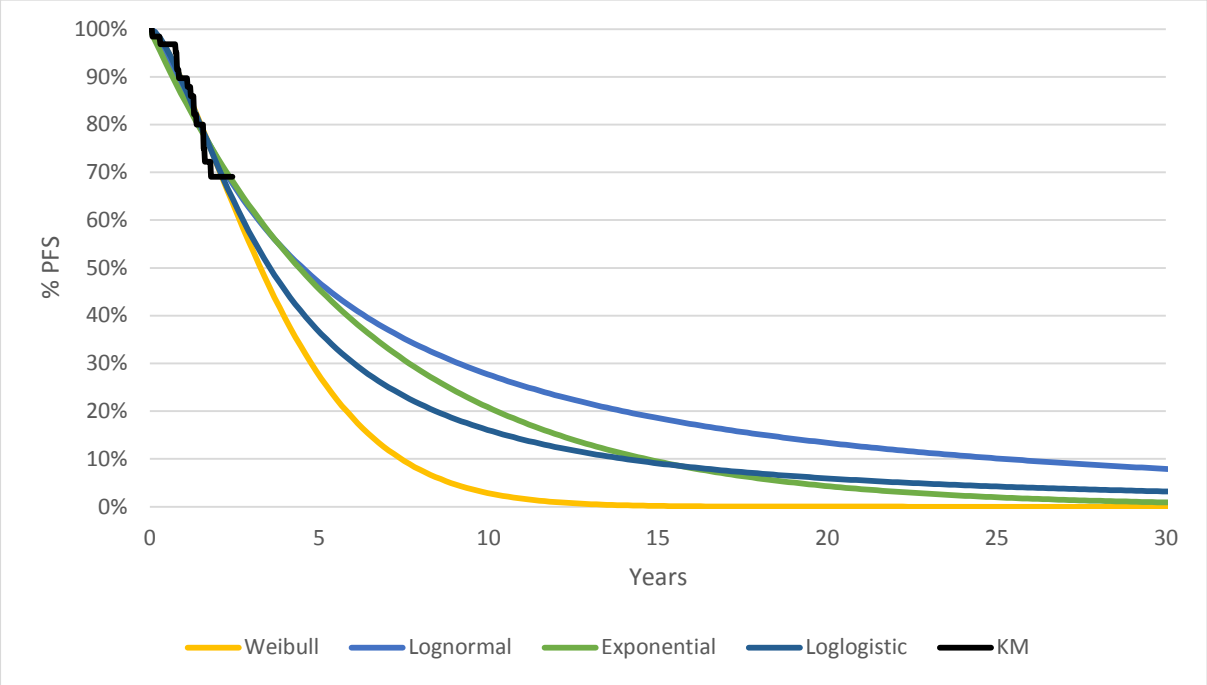
PFS – progression-free survival; HR – hazard ratio; ONS – Office for National Statistics; BSC – best supportive care

Progression-free survival – second-line ibrutinib

Within the ibrutinib group, the probability of remaining alive and progression-free in the second-line progression-free state during each model cycle was estimated by fitting parametric survivor functions to the PFS data from Study 1118E (n=63).[11] Exponential, Weibull, log normal, and log logistic models were fitted to the available PFS time-to-event data. Model discrimination was undertaken through examination of goodness-of-fit statistics (the Akaike Information Criterion [AIC] and the Bayesian Information Criterion [BIC]), visual inspection and plausibility of the extrapolated portion of the curves. Figure 10 presents a comparison of the fitted parametric models and the observed

Kaplan-Meier PFS curve. The AIC and BIC statistics for each candidate survivor function are summarised in Table 35; the lowest AIC and BIC values are highlighted in bold.

Figure 10: Parametric curve fitting – ibrutinib PFS (reproduced from CS Figure 20)



PFS: Progression-free survival; KM – Kaplan-Meier

Table 35: Goodness-of-fit statistics – ibrutinib PFS (adapted from CS Table 35)

Survivor function	AIC	BIC
Weibull	89.266	93.552
Log normal	90.220	94.506
Log logistic	**89.138**	93.424
Exponential	89.930	**92.073**

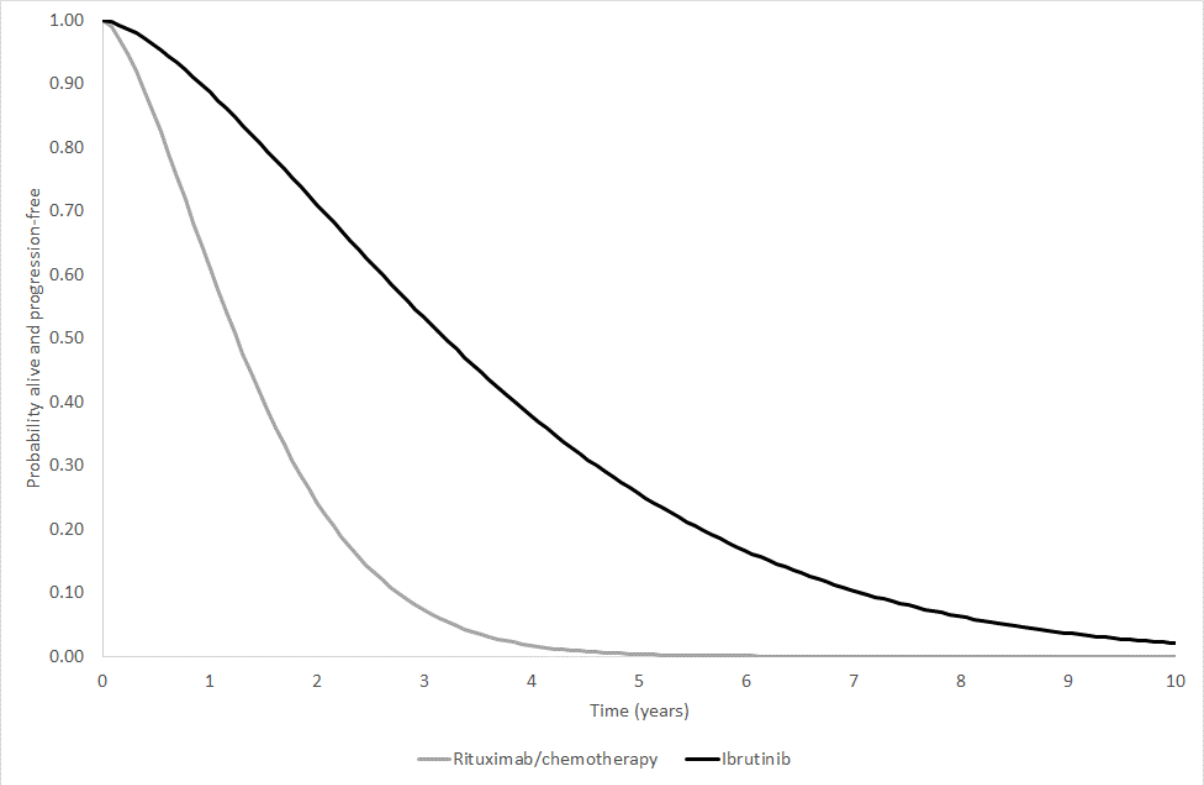
AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

As shown in Figure 10, there is a high level of censoring in the available data from Study 1118E; at the last available observation, the probability of PFS is around 0.69. Based on the company's curve-fitting exercise, the AIC was lowest for the log logistic function, whilst the BIC was lowest for the exponential function. The CS[1] (page 84) notes that there is little difference between the AIC and BIC statistics or the visual fit of each curve to the observed data. On the basis of the plausibility of the long-term extrapolation, the Weibull function was selected for use in the company's base case, whilst the log logistic model was included in the company's scenario analysis. The ERG notes that the Weibull model has the lowest mean PFS duration; however, given that treatment is assumed to be continued until progression, this is the most favourable function to use in terms of incremental costs for ibrutinib versus rituximab/chemotherapy.

Progression-free survival – second-line rituximab/chemotherapy

PFS outcomes for the rituximab/chemotherapy group were estimated by applying the inverse of the HR derived from the company's indirect comparison (see Section 4.4) to the baseline ibrutinib PFS curve described above. An HR for PFS of [redacted] (ibrutinib versus rituximab/chemotherapy) was used in the company's base case (see Figure 11). Alternative HRs were used in the company's sensitivity analyses ([i] Cox model based on the cohort with complete characteristics data [n=89], HR=[redacted] and; [ii] Cox model based on the full cohort [n = 175] but using risk categories only for the imputation of missing data, HR=[redacted]).

Figure 11: Modelled PFS curves for ibrutinib and rituximab/chemotherapy



Pre-progression mortality – second-line ibrutinib

The company's model assumes that the risk of death for patients who are receiving ibrutinib is the same as that for the age- and sex-adjusted general population (based on life tables for England published by the Office for National Statistics[34]). The CS states that three deaths were observed in Study 1118E during the study follow-up (24 months), all of which occurred prior to disease progression (see Figure 7). Based on an estimated 122 years of total treatment exposure, this equates to an estimated 1-year probability of 0.025 (see equation [i]).

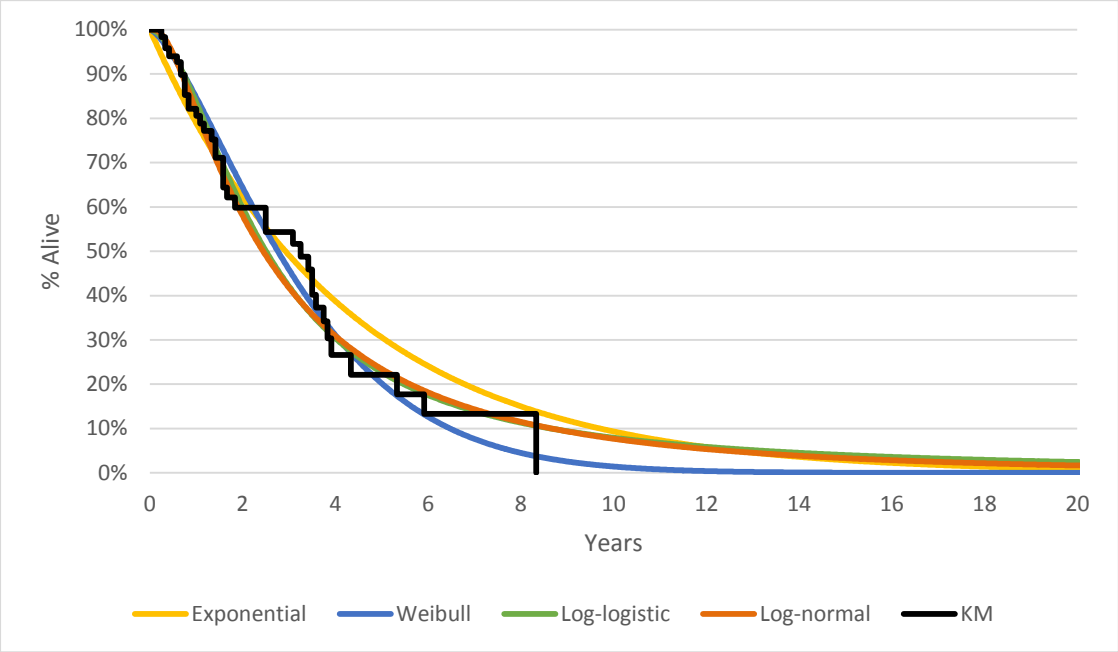
1-year probability of death = No. deaths / (no. patients x mean follow-up duration in years) [i]

The CS states that the company compared this probability of 0.025 to the general population mortality risks and that: *"As the data matched well, the general population mortality was used"* (CS,[1] page 85). The credibility of this assumption is discussed in detail in Section 5.3.

Pre-progression mortality – second-line rituximab/chemotherapy

According to the CS, the probability of pre-progression death for rituximab/chemotherapy was based on data from patients receiving second-, third- or fourth-line treatment within the European chart review (n=175).[9] The ERG notes some discrepancy with respect to the actual data used to inform this event risk: whilst the CS refers to these data as "time to death" (i.e. overall survival), the company's clarification response (question C9) states that the text of the CS was *"inaccurate"* and that the curve actually reflects pre-progression-mortality (time to death, censoring for progression). Despite this clarification, the ERG remains unclear regarding whether these data reflect pre-progression deaths or all deaths (see Section 5.3). The company fitted log logistic, log normal, exponential and Weibull survivor functions to the available data. Model discrimination was undertaken through examination of goodness-of-fit statistics (AIC and BIC), visual inspection and clinical plausibility of the long-term extrapolation. Figure 12 presents a comparison of the fitted parametric models and the observed Kaplan-Meier survival curve. The AIC and BIC statistics for each candidate survivor function are summarised in Table 36; the lowest AIC and BIC values are highlighted in bold.

Figure 12: Parametric curve-fitting – pre-progression mortality applied to second-line rituximab/chemotherapy (from European chart review, reproduced from CS Figure 21)



KM – Kaplan-Meier

Table 36: Goodness-of-fit statistics – pre-progression mortality applied to second-line rituximab/chemotherapy (from European chart review, adapted from CS Table 36)

Survivor function	AIC	BIC
Weibull	167.121	173.451
Log normal	**165.151**	**171.480**
Log logistic	167.382	173.712
Exponential	174.989	178.154

AIC – Akaike information criterion; BIC – Bayesian information criterion

The CS states that the log normal distribution was selected for use in the base case analysis as this function provided the best fit according to AIC and BIC statistics and visual inspection as well as the clinical plausibility of the long-term extrapolation. The Weibull distribution was considered in the company's scenario analyses.

Time to progression – third- and fourth-line treatment (both groups)

Time to progression in the third- and fourth-line progression-free states (censoring for death) was informed by data from patients starting fourth-line treatment within the European chart review (n=52).[9] The CS does not include a graphical comparison of the alternative candidate survivor functions against the observed Kaplan-Meier survival curve or the AIC/BIC statistics for the alternative parametric models. The CS states that the curve-fitting exercise for time to progression found that the exponential model provided the best fit, indicating a constant probability of progression (4-week probability=[redacted]). Based on additional information provided following the clarification process, the ERG considers this judgement to be inaccurate (see Section 5.3).

Pre-progression mortality for third- and fourth-line treatment and post-progression survival for BSC

The company's model assumes the same constant rate of death within the third- and fourth-line progression-free and BSC states, regardless of prior treatment. The CS presents AIC and BIC statistics (see Table 37) for the candidate survivor functions fitted to mortality data from the European chart review,[9] based on patients who had progressed from third-line treatment (n=60). Page 87 of the CS states that *"Survival was determined by the probability of death, and was not influenced by the probability of progression."* This appears to indicate that progression events were not censored, hence the curve reflects overall mortality rather than mortality in the third- or fourth-line progression-free states. The CS states that an exponential function was found to be the best fit; however, the CS does not present a graphical comparison of the alternative candidate survivor functions against the observed Kaplan-Meier survival curve to allow for a visual assessment.

Table 37: Goodness-of-fit statistics - pre-progression mortality for third- and fourth-line treatment and post-progression survival for BSC (from European chart review, adapted from CS Table 38)

Survivor function	AIC	BIC
Weibull	109.395	113.584
Log-normal	**107.046**	111.234
Log-logistic	108.204	112.392
Exponential	107.813	**109.907**
Generalised gamma	109.000	115.283
Gompertz	109.811	114.000

AIC – Akaike information criterion; BIC – Bayesian information criterion

Probability of receiving subsequent treatment

The company's model assumes that the probability of receiving subsequent active treatment (i.e. progressing from second-line to third-line and from third-line to fourth-line treatment) was based on data from the European chart review and UK clinical opinion. The company's model assumes that 86% of patients progressing from second-line treatment will receive third-line treatment and 70% of patients progressing from third-line treatment will receive fourth-line treatment; the remainder are assumed to receive BSC. The ERG notes that the European chart review indicated a higher probability of receiving fourth-line treatment compared with that used in the company's model; this estimate was deflated based on subjective clinical opinion obtained by the company (70% rather than [redacted], see CS Appendix 4).

Adverse event rates

The company's model includes common grade 3/4 AEs which occurred in ≥5% of patients. AEs are included for all second-line treatments and are assumed to impact both on HRQoL and costs during the first model cycle. AE rates for each product were derived from clinical studies[11, 15, 35-37] and the Electronic Medicines Compendium (eMC).[38] The CS notes that AEs that were not reported in some of the studies (denoted "NR" in Table 38) were assumed to be 0% in the model and that this is a "conservative" assumption. The CS does not include any justification for the selection and use of these sources to inform AE rates.

Table 38: Adverse event frequencies for second-line treatment regimens included in the company's model

AE	Ibrutinib[11]	FCR[35, 36]	DRC[15]	BR[37]	Cladribine + R[38]	Other treatment[38]
Anaemia	1.59%	2.30%	NR	4.00%	1.00%	1.00%
Leukopenia	NR	NR	NR	NR	10.00%	10.00%
Neutropenia	14.29%	87.72%	9.00%	19.33%	10.00%	10.00%
Thrombocytopenia	12.70%	4.60%	0.00%	6.12%	10.00%	10.00%
Lymphocytopenia	NR	NR	NR	NR	NR	NR
Infection (non-pneumonia)	6.35%	NR	NR	6.16%	10.00%	10.00%
Neuropathy	NR	NR	NR	13.45%	NR	NR
Lung toxicity	NR	NR	NR	5.00%	NR	NR
Diarrhoea	0.00%	NR	NR	3.00%	1.00%	1.00%
Constipation	NR	NR	NR	3.00%	1.00%	1.00%

NR – not reported

Health-related quality of life

Health state utilities

The model includes health utility scores associated with the four living health states (second-, third-, and fourth-line progression-free and BSC). Study 1118E did not include a preference-based measure of HRQoL, or indeed any measure of HRQoL, and no studies were identified in the company's systematic review of HRQoL evidence. Utility estimates used in the model were instead derived from EQ-5D-5L data collected within the RESONATE study of ibrutinib in R/R CLL.[16] The CS does not report the original EQ-5D values by timepoint and these data are redacted within the company's CLL submission.[43]

Health utilities applied in the company's model are presented in Table 39. Utilities for the progression-free states were assigned a utility value of 0.799, based on the weighted average of EQ-5D-5L scores over time for patients who remained progression-free from weeks 4 to 60 in the RESONATE CLL trial.[16] Patients in the BSC state were assigned a utility value of 0.665; this was obtained by applying a utility decrement of 12.8% (taken from a UK CLL standard gamble valuation study reported by Beusterien *et al.*[39]) to the baseline utility value of 0.763 from the RESONATE trial. Utility estimates were age-adjusted in the model by applying the formula reported by Ara and Brazier.[44]

Table 39: Utility values employed within the company's model (excluding age-adjustment, adapted from CS Table 43)

Health State	Mean	SE	Source
Second-line	0.799	0.080	RESONATE CLL trial[1]
Third-line	0.799	0.080	
Fourth-line	0.799	0.080	
BSC	0.665	0.067	Disutility from Beusterien *et al.*[39] applied to RESONATE CLL trial baseline score[1]

BSC – best supportive care; SE – standard error; CLL - chronic lymphocytic leukaemia

Disutilities due to AEs

According to the CS, disutilities for neutropenia, thrombocytopenia and infection (non-pneumonia) were taken from Tolley *et al.*[40] (time-trade-off, general public valuation of seven CLL states) whilst the disutility for anaemia was taken from Beusterien *et al*[39] (standard gamble, general population valuation of CLL states). The CS does not report any details regarding the derivation of these disutilities and the ERG was unable to reproduce these using the utility valuations reported in the original papers. The remaining AEs are assumed to incur a disutility of -0.185 or -0.195, based on assumptions; these are not explained or justified in the CS. Disutilities due to AEs are applied as a once-only decrement in the first model cycle (i.e. at the initiation of second-line treatment for R/R disease). The model assumes a QALY loss of -0.0021 for ibrutinib and a QALY loss of -0.0031 for

rituximab/chemotherapy. These QALY losses were derived by multiplying the frequency of each AE for each treatment (Table 37) by their respective disutilities (Table 40), assuming that each AE has a duration of 14 days. The QALY loss applied to the rituximab/chemotherapy group was based on the proportionate use of each second-line regimen (see Table 32).

Table 40: Disutilities associated with adverse events

AE	Utility decrement	Source
Anaemia	-0.088	Beusterien *et al.*[39] (standard gamble, 89 members of the general public, 12 CLL states)
Neutropenia	-0.185	Tolley *et al.*[40] (time trade-off, 110 members of the general public, 7 CLL states)
Thrombocytopenia	-0.123	
Infection (non-pneumonia)	-0.195	
Leukopenia	-0.185	Assumption
Lymphocytopenia	-0.185	
Neuropathy	-0.195	
Renal toxicity	-0.195	
Lung toxicity	-0.195	
Diarrhoea	-0.195	
Constipation	-0.195	

AE – adverse event; CLL - chronic lymphocytic leukaemia

QALY losses and costs associated with AEs during third- and fourth-line treatment are not included in the company's model.

Resource use and costs

The company's model includes the following resource costs:

- Drug acquisition
- Drug administration
- Routine follow-up
- Management of AEs
- BSC
- Terminal care.

Drug acquisition

Drug acquisition costs were taken from the British National Formulary (BNF, accessed May 2016). The company's model includes a PAS for ibrutinib based on a simple [redacted] price discount. Drug costs for ibrutinib were modelled assuming a fixed dose of 420mg o.d., adjusted according to the RDI observed within Study 1118E[14] (93%). The RDI for the rituximab/chemotherapy options was assumed to be the same as that for ibrutinib. The unit costs for each regimen component, as reported in the CS,[1] are summarised in Table 41.

Table 41: Drug acquisition costs applied in the company's model (adapted from CS Table 47)

Treatment	Unit size	Tablet / vial	Administration route	Unit cost
Ibrutinib	140mg	1	oral	£38.33
Bendamustine	10.0mg/ml	10ml	IV	£275.81
Chlorambucil	2.0 mg	25	oral	£40.51
Cyclophosphamide	500mg	1	IV	£9.20
Dexamethasone	3.8mg	1	IV	£1.99
Fludarabine	50mg	1	IV	£147.07
Rituximab	10mg	50	IV	£873.15
Cladribine	2.0mg/ml	5ml	IV	£165.00

Drug administration costs

The model includes administration costs for infusional rituximab/chemotherapy options used in the second-, third- and fourth-lines of treatment. The model assumes a cost of £239.12 per visit based on NHS Reference Costs 2014/15[41] (code SB12Z).

Table 42 summarises the acquisition and administration costs applied during each cycle. Within the model, the costs of third- and fourth-line rituximab/chemotherapy options are weighted according to the cumulative survival probabilities for PFS applied to each state and are discounted according to time since model entry. The full cost of the whole third-/fourth-line chemotherapy course is then applied at the point of entry into the third-/fourth-line progression-free state. It should be noted that the company's cost estimates includes some errors and discrepancies which have not been corrected in Table 42; these are discussed in Section 5.3.3.

Table 42: Drug acquisition and administration costs applied during each cycle

Cycle	Second-line ibrutinib (drug acquisition only)	Second-line rituximab/ chemotherapy acquisition and administration	Third-line rituximab/ chemotherapy acquisition and administration	Fourth-line rituximab/ chemotherapy acquisition and administration
1	[redacted]	£3,706.45	£5,807.25	£5,807.25
2	[redacted]	£2,673.67	£4,871.92	£4,871.92
3	[redacted]	£2,644.66	£4,525.11	£4,525.11
4	[redacted]	£3,463.73	£4,609.07	£4,609.07
5	[redacted]	£1,825.60	£2,127.67	£2,127.67
6	[redacted]	£1,825.60	£1,729.75	£1,729.75
7+	[redacted]	£0.00	£0.00	£0.00

Routine follow-up costs

Table 43 summarises the routine follow-up costs assumed in both groups of the company's model. The frequency of follow-up visits was based on expert opinion. Unit costs associated with each

resource use component were taken from NHS Reference Costs 2014/2015.[41] These costs are applied to the second-line progression-free state.

Table 43: Routine follow-up costs applied in the company's model

Component	Annual resource use			Unit cost	NHS reference costs 2014/2015 code
	Years 1-2	Years 3-5	Year 6+		
Full blood count	5	4	3	£3.01	DAPS 05 Haematology
IgM	5	4	3	£5.49	DAPS 06 Immunology
Chemistry	5	4	3	£1.19	DAPS 04 Clinical biochemistry
Plasma viscosity	5	4	3	£5.49	DAPS 06 Immunology
Paraprotein	5	4	3	£1.19	DAPS 04 Clinical biochemistry
Haematologist	5	4	3	£150.38	WF01A Clinical haematology, consultant-led, non-admitted face to face follow-up
Annual total cost	£833.75	£667.00	£500.25	-	-
Cost per cycle	**£63.92**	**£51.13**	**£38.35**	-	-

IgM – immunoglobulin M

With respect to the third- and fourth-line progression-free states, the model assumes lower costs for years 1-2 and years 3-5; these are calculated by subtracting the year 6+ follow-up cost estimates from those for years 1-2 and years 3-4, respectively. These calculations are not explained in the CS, nor do they follow any obvious logic.

Within the BSC state, the model includes a cost associated with planned medical resource use of £46.11 per 28-day cycle, based on an assumption of four haematologist appointments per year.

Costs associated with unplanned medical resource use

The model includes costs associated with unplanned medical resource use which was assumed to be based on the management of hyperviscosity via plasmapheresis. The incidence of hyperviscosity was stratified by health state based on expert opinion. The management of hyperviscosity was assumed to incur a cost of £2,493.75. This cost is applied to the incident number of patients entering each progressive health state, weighted according to the estimated incidence of hyperviscosity (9% in second-/third-line progression-free states, 11% in fourth-line progression-free and BSC states).

Costs associated with the management of AEs

The model includes costs associated with the management of AEs experienced during second-line treatment. The cost of managing AEs for each treatment regimen was estimated as the sum of the product of the frequency of each AE type (see Table 38) and their associated unit costs. AE costs are applied as a once-only cost during the first model cycle. The model applies a cost of £563.03 for management of infection based on NHS Reference Costs 2014/15[41] (infections or other complications

of procedures, without interventions, with CC Score 0-4 [WH07F –WH07G, costed as a weighted average of elective inpatient, non-elective inpatient (long and short stay) and day case attendances]). A cost of £162.02 is applied to all other AEs, again based on NHS Reference Costs 2014/15[41] (estimated as a weighted average of non-admitted clinical haematology visit codes: WF01A, WF01B, WF01C, WF01D, WF02A, WF02B, WF02C, WF02D).

Terminal care costs

The model includes a once-only cost of terminal care applied to all patients at the point of death (irrespective of cause). This was estimated to be £7,287 per cancer related death in 2014 (inflated to £7,352) based on Round *et al*.[42]

5.2.4 Methods for model evaluation

The CS presents the results of the economic evaluation in terms of the incremental cost per QALY gained for second-line ibrutinib versus a blend of second-line rituximab/chemotherapy options. The base case results are presented deterministically based on point estimates of parameters. The CS also includes the results of probabilistic sensitivity analysis (PSA), deterministic sensitivity analyses (DSA) and scenario analyses. The results of the PSA are presented in the form of cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs), based on 1,000 Monte Carlo simulations. The results of the DSAs are presented in the form of a tornado diagram (reported in terms of ICERs for ibrutinib versus rituximab/chemotherapy). The distributions applied in the company's PSA are summarised in Table 44; the ERG's comments regarding the implementation of the PSA is presented in the right-hand column of the table.

Table 44: Summary of distributions used in company's PSA

Parameter group	Parameters	Distribution	ERG comments
Patient characteristics	Age, body surface area, probability patient is male	Fixed	Not included in the PSA
Transition probabilities and treatment effects	PFS HR ibrutinib versus rituximab/ chemotherapy	Fixed	Not included in the PSA
	Ibrutinib PFS survivor function	Bivariate normal with Cholesky decomposition	Only the Weibull distribution is included in the PSA (base case).
	Ibrutinib pre-progression mortality	Fixed	Not included in the PSA
	Rituximab/chemotherapy pre-progression mortality	Bivariate normal with Cholesky decomposition	Only the Weibull distribution is included in the PSA. No uncertainty is included for the log normal distribution used in the base case.
	Other transition probabilities (probabilities of progression and death in subsequent treatment lines, probability of receiving subsequent-line treatment).	Beta	The parameters of the beta distribution are estimated from the mean and standard error of each parameter. Probabilities of progression/death are sampled independent of treatment line but based on the same inputs.
AE frequency	AE incidence rates	Fixed	Not included in the PSA
Health-related quality of life	Health state utilities (second-, third- and fourth-line, BSC)	Beta	Utilities for second-, third- and fourth-line progression-free states sampled from independent distributions leading to problems of monotonicity being violated. Consequently, sampled utility values applied to more advanced states are commonly better than those for less advanced states.
	Adverse event disutilities	Uniform	Derivation of 10% range around mean unclear
Resource use	Proportionate use of rituximab/chemotherapy in second-, third-, and fourth-line progression-free states	Fixed	Not included in the PSA
	Dosing regimens and treatment frequencies	Fixed	Not included in the PSA

Parameter group	Parameters	Distribution	ERG comments
	Drug administration frequency	Fixed	Not included in the PSA
	Medical resource use for progression-free states and BSC	Fixed	Not included in the PSA
	Percentage of patients with hyperviscosity	Beta	Standard error assumed to be 10% of mean
Costs	Drug acquisition costs	Fixed	Not included in the PSA
	Drug administration costs	Fixed	Not included in the PSA
	Routine follow-up costs for progression-free states and BSC	Gamma	The standard error is incorrectly specified as the number of visits per year
	AE costs	Gamma	AE costs incorrectly specified resulting in these parameters being fixed at their mean values
	Unplanned resource use costs	Gamma	Standard error assumed to be 10% of mean
	Terminal care costs	Fixed	Not included in the PSA

PSA – probabilistic sensitivity analysis; PFS – progression-free survival; HR – hazard ratio; BSC – best supportive care; AE – adverse event

As shown in Table 44, many of the model parameters are held fixed within the PSA. The ERG's concerns regarding the company's characterisation of the uncertainty surrounding the decision problem is discussed further in Section 5.3.

5.2.5 Cost-effectiveness results presented within the CS

This section presents the results of the company's health economic analysis. All results presented in this section include the company's agreed PAS ([redacted] simple price discount). The results of the company's analyses based on the list price for ibrutinib are presented in Appendix 1.

Base case cost-effectiveness results

Table 45 presents the company's base case cost-effectiveness results. Based on a re-run of the probabilistic version of the company's base case model by the ERG, ibrutinib is expected to produce an additional [redacted] QALYs at an additional cost of [redacted] compared with rituximab/chemotherapy; the ICER for ibrutinib versus rituximab/chemotherapy is expected to be £58,905 per QALY gained. The results of the deterministic model are similar, with ibrutinib yielding an ICER of £58,630 per QALY gained compared with rituximab/chemotherapy.

Table 45: Central estimates of cost-effectiveness

Probabilistic model*					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£58,905**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-
Deterministic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£58,630**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

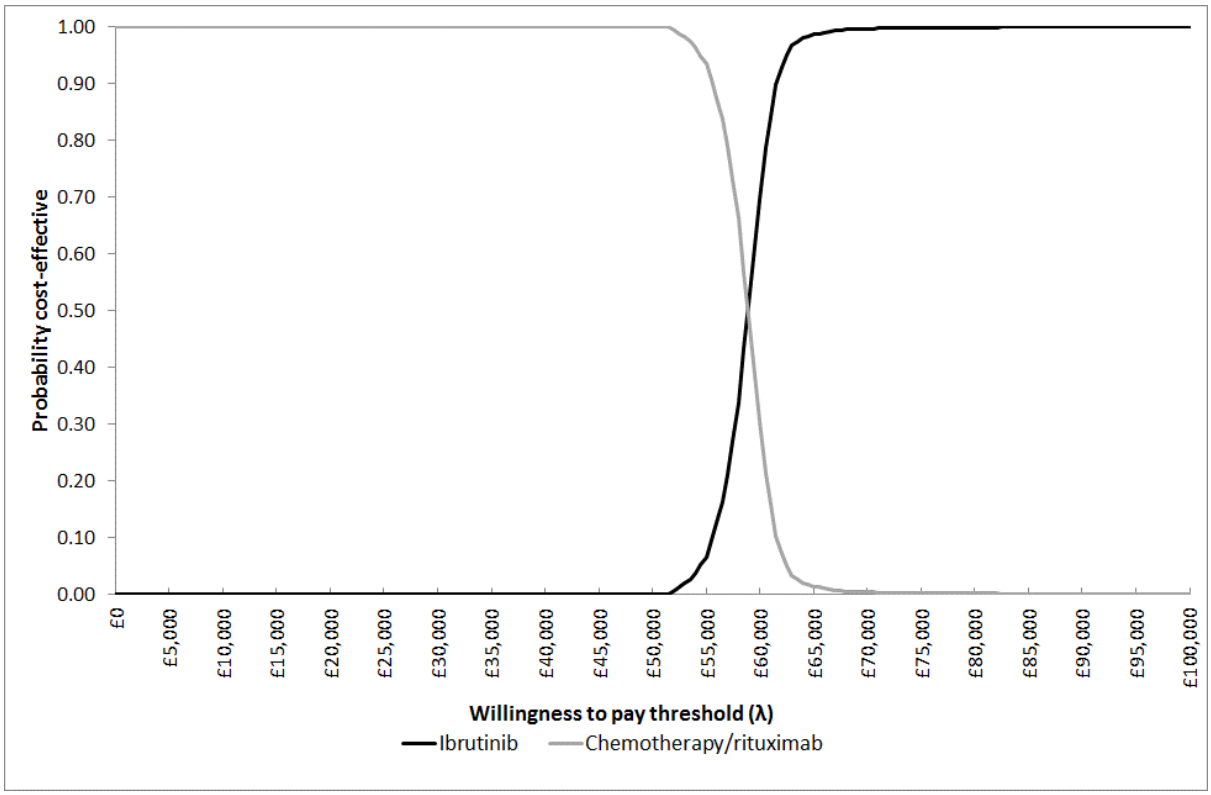
QALY – quality-adjusted life year
** Produced from a re-run of the company's model by the ERG*

Probabilistic sensitivity analysis results

Figure 13 and Figure 14 present the cost-effectiveness plane and CEACs for ibrutinib versus rituximab/chemotherapy, respectively; each figure is based on a re-run of the company's PSA by the ERG. Assuming a willingness-to-pay (WTP) threshold of £30,000 per QALY gained, the company's base case model suggests that the probability that ibrutinib produces more net benefit than rituximab/chemotherapy is approximately zero.

Figure 13: Cost-effectiveness plane – ibrutinib versus rituximab/chemotherapy

Figure 14: Cost-effectiveness acceptability curves – ibrutinib versus rituximab/chemotherapy



Deterministic sensitivity analysis results

Figure 15 and Table 46 present the results of the company's one-way DSA, reported in terms of the ICER for ibrutinib versus rituximab/chemotherapy. The results of the DSA suggest that the discount rate for health benefits and costs, the utility value associated with PFS in the second-line progression-free state, the hazard of death during BSC and the RDI for ibrutinib are the five most influential parameters. Importantly, the model is not sensitive to the HR for PFS; this is discussed in further detail in Section 5.3. The ICER for ibrutinib versus rituximab/chemotherapy is estimated to be greater than £47,000 per QALY gained across all analyses. It should be noted that for several of the analyses, the results presented in Appendix 9 of the CS are incorrect (see footnotes to Table 46); whilst the ERG has corrected the values in the table by re-running all the DSAs, the values shown in Figure 15 still include the company's errors and should therefore be interpreted with some caution.

Figure 15: Deterministic sensitivity analysis tornado diagram (amended from company's model, not corrected by the ERG)

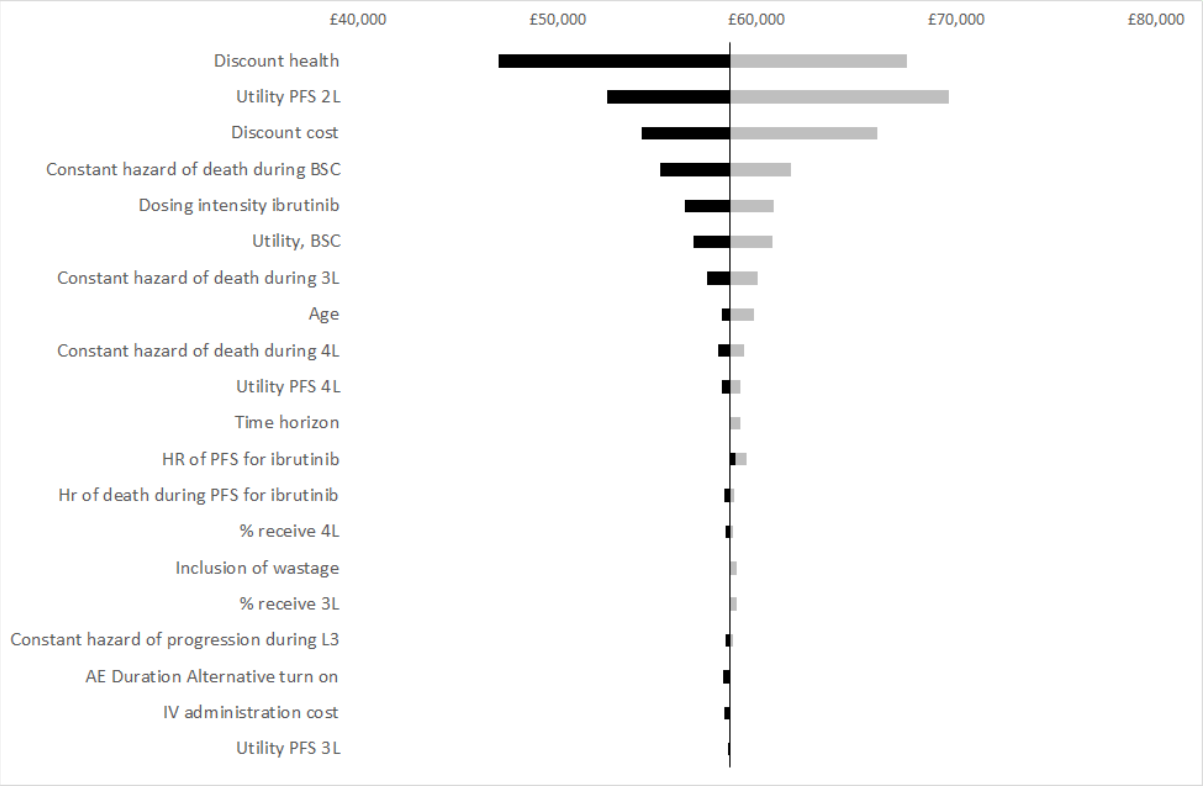


Table 46: Deterministic sensitivity analysis results (corrected by ERG)

Scenario	Base case value	Sensitivity analysis value	Incremental – ibrutinib versus rituximab/chemotherapy		
			Inc. QALYs	Inc. costs	ICER (per QALY gained)
Base case			[redacted]	[redacted]	£58,630
Discount health	3.5%	0%	[redacted]	[redacted]	£47,050
		6%	[redacted]	[redacted]	£67,489
Utility PFS 2L	0.799	0.62	[redacted]	[redacted]	£69,607*
		0.93	[redacted]	[redacted]	£52,523*
Discount cost	3.5%	0%	[redacted]	[redacted]	£66,040*
		6%	[redacted]	[redacted]	£54,231*
Constant hazard of death during BSC	[redacted]	[redacted]	[redacted]	[redacted]	£55,176
		[redacted]	[redacted]	[redacted]	£61,704
Dosing intensity ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	£56,115
		[redacted]	[redacted]	[redacted]	£61,145
Utility BSC	0.67	0.53	[redacted]	[redacted]	£60,732*
		0.79	[redacted]	[redacted]	£56,833*
HR of PFS for ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	£58,949
		[redacted]	[redacted]	[redacted]	£59,460
Constant hazard of death during 3L	[redacted]	[redacted]	[redacted]	[redacted]	£57,527
		[redacted]	[redacted]	[redacted]	£60,066
Utility PFS 3L	0.799	0.62	[redacted]	[redacted]	£59,672*
		0.93	[redacted]	[redacted]	£57,885*
Age	64.5	61.9†	[redacted]	[redacted]	£58,291
		67.1†	[redacted]	[redacted]	£59,796
Constant hazard of death during 4L	[redacted]	[redacted]	[redacted]	[redacted]	£58,037
		[redacted]	[redacted]	[redacted]	£59,383
Utility PFS 4L	0.799	0.62	[redacted]	[redacted]	£59,149*
		0.93	[redacted]	[redacted]	£58,253*
Time horizon	30 years	20	[redacted]	[redacted]	£59,190*
		30	[redacted]	[redacted]	£58,630*
Inclusion of wastage	Yes	No	[redacted]	[redacted]	£59,016*
		Yes	[redacted]	[redacted]	£58,630*
HR of death during PFS for ibrutinib	1	0.90	[redacted]	[redacted]	£58,395
		1.10	[redacted]	[redacted]	£58,867
Constant hazard of progression during 3L	[redacted]	[redacted]	[redacted]	[redacted]	£58,415
		[redacted]	[redacted]	[redacted]	£58,781
Duration of AE disutility	14	180	[redacted]	[redacted]	£58,312
		14	[redacted]	[redacted]	£58,630
IV administration cost	239	239	[redacted]	[redacted]	£58,630*
		389	[redacted]	[redacted]	£58,346
Constant hazard of progression during 4L	[redacted]	[redacted]	[redacted]	[redacted]	£58,561
		[redacted]	[redacted]	[redacted]	£58,672*
% receive 4L	70%	50%	[redacted]	[redacted]	£58,411
		86%	[redacted]	[redacted]	£58,804*

2L – second-line; 3L – third-line; 4L – fourth-line; BSC – best supportive care; PFS – progression-free survival; HR – hazard ratio; AE – adverse event; IV – intravenous; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; inc. - incremental

** value reported in CS Appendix 9 incorrect – corrected values produced by ERG*

† ranges reported in CS Appendix 9 incorrect – corrected values applied to generate results

Scenario analysis results

Table 47 presents the results of the company's scenario analyses. The ICER for ibrutinib versus rituximab/chemotherapy remains greater than £56,000 per QALY gained across all four scenarios.

Table 47: Scenario analysis results (generated using the company's model)

Scenario	Base case	Scenario analysis	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Base case			[redacted]	[redacted]	£58,630
Age adjustment for utilities	Yes	No	[redacted]	[redacted]	£56,646
Distribution for PFS of ibrutinib	Weibull	Log-logistic	[redacted]	[redacted]	£61,303
HR PFS Scenario 1. Imputed patient characteristics. No individual clinical measurement (risk category only)*	[redacted]	[redacted]	[redacted]	[redacted]	£58,669
HR PFS Scenario 2. Sample with complete patient characteristics, no imputation. All variables (individual clinical measurements & risk category)*	[redacted]	[redacted]	[redacted]	[redacted]	£58,729

PFS – progression-free survival; HR – hazard ratio; 2L – second-line; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; inc. – incremental
** Reproduced by ERG. Results differ slightly from those reported within the CS Appendix 9 due to a rounding errors*

5.3 Critical appraisal of the company's health economic analysis

This section presents a critical appraisal of the health economic analysis presented within the CS.[1] Section 5.3.1 details the methods used by the ERG to interrogate and critically appraise the company's submitted health economic analysis. Section 5.3.2 summarises of the extent to which the company's analysis adheres to the NICE Reference Case.[45] Section 5.3.3 summarises the ERG's verification of the company's implemented model and highlights inconsistencies between the model, the CS,[1] and the evidence sources used to inform the model parameter values. Section 5.3.4 presents a detailed critique of the ERG's main concerns surrounding the company's analysis.

5.3.1 Methods for reviewing the company's health economic evaluation and model

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted health economic evaluation and the underlying model upon which this was based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists[46, 47] to critically appraise the company's model and analysis.
- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the ERG.
- Partial double-programming of the deterministic version of the company's model to assess the logic of the company's model structure, to draw out any unwritten assumptions and to identify any apparent errors in the implementation of the model.

- Examination of the correspondence between the description of the model reported within the CS[1] and the company's executable model.
- Replication of the base case results, PSA, one-way sensitivity analysis and scenario analysis presented within the CS.[1]
- Where possible, checking of parameter values used in the company's model against the original data sources.
- The use of expert clinical input to judge the clinical credibility of the company's model.

5.3.2 Adherence of the company's economic analysis to the NICE Reference Case

Table 48 summarises the extent to which the company's economic analysis adheres to the NICE Reference Case.

Table 48: Adherence to the NICE Reference Case

Element of HTA	Reference Case	ERG comments
Defining the decision problem	The scope developed by NICE	Whilst the company's decision problem statement (see CS[1] Table 1) states that the CS is in line with the final NICE scope,[7] no clinical or economic evidence is presented for ibrutinib for the subgroup of adults with WM who have not received prior therapy and for whom chemo-immunotherapy is unsuitable. For the population of adults with WM who have received at least one prior therapy, the company's economic analysis is partially in line with the final NICE scope.[7] However, the ERG notes that the company's model is structured according to a sequence of treatment lines whereby upon model entry all patients have received exactly one prior therapy; this was not requested in the final NICE scope[7] and is not consistent with the evidence from Study 1118E.[11]
Comparator(s)	As listed in the scope developed by NICE	The comparator involves a blend of second-line rituximab/chemotherapy options.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The base case analysis includes direct health effects on patients.
Perspective on costs	NHS and PSS	The CS states that the economic analysis adopts an NHS and PSS perspective. Whilst this description is accurate, no PSS costs are included in the model.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The company's economic evaluation takes the form of a cost-utility analysis. Model results are presented in terms of the incremental cost per QALY gained.
Time horizon	Long enough to reflect all important differences between the technologies being compared	A 30-year time horizon is assumed, which is intended to reflect patients' remaining lifetimes.
Synthesis of evidence on health effects	Based on systematic review	The CS states that there are no head-to-head RCTs. An HR for PFS was derived from the company's adjusted arm-based indirect comparison of Study 1118E[11] and the European chart review.[9] The mortality hazard whilst patients are progression-free on ibrutinib is assumed to reflect that of the age- and sex-adjusted general population.

Element of HTA	Reference Case	ERG comments
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	Health outcomes are measured and valued in terms of QALYs. Neither Study 1118E[11] nor the European chart review[9] included the use of a preference-based measure of HRQoL. Health state utilities were instead derived from the RESONATE R/R CLL trial[16] and Beusterien *et al*.[39] Disutilities for AEs were taken from Beusterien *et al*,[39] Tolley *et al*[40] and assumptions.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No equity weighting is applied.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource costs reflect those relevant to the NHS. Unit costs were valued at 2014/15 prices.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Health outcomes and costs are discounted at a rate of 3.5% per annum.

The company's economic analysis is partially in line with the final NICE scope[7] and the NICE Reference Case.[45] The two most notable issues are: (i) the CS does not present any clinical or economic evidence for ibrutinib for the subgroup of adults with WM who have not received prior therapy and for whom chemo-immunotherapy is unsuitable, and; (ii) the R/R model structure is inconsistent with the evidence available to populate it. These issues are discussed in detail in Section 5.3.3.

5.3.3 Summary of main issues identified within the critical appraisal

Box 1 summarises the main issues identified within the ERG's critical appraisal of the company's health economic analysis.

Box 1: Main issues identified within the critical appraisal of the company's model

(1) Absence of any economic analysis of ibrutinib in the first-line (treatment-naïve) setting for patients in whom chemo-immunotherapy is unsuitable
(2) Model implementation and reporting errors
(3) Concerns regarding the company's modelling approach
(4) Potentially inappropriate data used to inform pre-progression mortality for rituximab/chemotherapy
(5) Questionable assumption of general population mortality rates for ibrutinib patients in the second-line progression-free state
(6) Limited clinical evidence available for ibrutinib versus rituximab/chemotherapy
(7) Concerns regarding company's estimation of time-to-event parameters
(8) Disconnect between sources used to estimate health gains and costs for rituximab/ chemotherapy
(9) Use of a blended comparator
(10) Concerns regarding health utilities assumed in the model
(11) Errors and discrepancies relating to drug acquisition costs for rituximab/chemotherapy
(12) Incomplete characterisation of uncertainty

(1) Absence of any economic analysis of ibrutinib in the first-line (treatment-naïve) setting for patients in whom chemo-immunotherapy is unsuitable

As noted above, the CS does not contain any evidence relating to the clinical effectiveness or cost-effectiveness of ibrutinib in treatment-naïve patients for whom chemo-immunotherapy is unsuitable. As such, the evidence contained within the CS is narrower than the populations defined by the marketing authorisation for ibrutinib in the WM indication.[10] In response to a request for clarification from the ERG (see clarification response,[14] question C2), the company stated:

"Given the general clinical view in oncology that treatment options perform better the earlier they are prescribed within the treatment pathway, it is not clinically implausible that ibrutinib will perform even better when given in the treatment-naive setting relative to the results observed in the R/R setting… The MEA will provide the opportunity to collect data to support the assertion that ibrutinib will be equally effective, if not more effective, in the treatment-naive setting relative to the R/R setting. These data would also allow for an understanding of where clinicians believe ibrutinib is best used in the treatment pathway. Janssen believe that inclusion of the additional data from the UK WM Registry will support that ibrutinib is a cost-effective treatment option in WM." (Clarification response,[14] question C2).

The ERG notes that whilst future data collection is essential to inform questions regarding the clinical and cost-effectiveness of ibrutinib in the first-line setting, patients enter the company's model in the second-line progression-free state, thus treatment-naïve patients are specifically excluded from the company's model structure. Should future data be collected on clinical outcomes for the treatment-naïve population, either as part of the company's proposed MEA or through some other mechanism, the economic evaluation of first-line ibrutinib will require a different model to that submitted by the company to inform this appraisal.

All subsequent discussion within this critical appraisal relates to the R/R WM population considered in the company's submitted model.

(2) Model implementation and reporting errors

The ERG partially rebuilt the deterministic version of the company's base case model for patients with R/R WM in order to verify its implementation. Given the complexity of the calculations used to generate drug acquisition costs within the company's model, the ERG's double-programming exercise was limited to reproducing the company's Markov trace and the estimated survival and QALY gains accrued in each treatment group. This process did not identify any major programming errors in the implementation of this portion of the model (see Table 49).

Table 49: Comparison of company's base case model and ERG's rebuilt model

Treatment option	Company's model		ERG's rebuilt model	
	LYGs	QALYs	LYGs	QALYs
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Rituximab/chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]

LYG – life years gained; QALY – quality-adjusted life year

The ERG also scrutinised the formulae and coding throughout the company's model and reproduced the base case analyses and DSAs reported in the CS.[1] In addition, the ERG compared the model inputs

against those described in the CS.[1] Excluding broader concerns regarding model validity, this verification process identified five issues:

(i) The company's 1-way SA tornado diagram (see Figure 15) and table of DSA results (CS Appendix 9 Table 52) include multiple transcription errors. The numerical values of the DSAs have been corrected in the results previously presented in Table 46.

(ii) The disutility associated with AEs for second-line rituximab/chemotherapy used in the model is not in line with the value reported in the CS (CS reported disutility = 0.0045; model disutility = 0.0031). Following clarification, the company confirmed that the correct value is used in the model (see clarification response,[14] question C14).

(iii) The company's implemented cost calculations include multiple programming errors. There are also several discrepancies between the model and the CS with respect to the derivation of these estimates. These issues are discussed in further detail in critical appraisal point 11.

(iv) The costs of third- and fourth-line rituximab/chemotherapy treatment are discounted twice. This issue is discussed in further detail in Section 5.3.3, critical appraisal point 11.

(v) As discussed in Section 5.2.3, the calculation of lower follow-up costs in the third- and fourth-line progression-free states are not explained in the CS, nor do they follow any obvious logic. Clinical advisors to the ERG suggested that follow-up costs would remain constant or increase with each consecutive line of therapy.

The latter three issues are minor, but do have some impact upon the ICER for ibrutinib versus rituximab/chemotherapy (see Section 5.4).

(3) Concerns regarding the company's modelling approach

The ERG has concerns regarding the structure and logic of the company's model as well as the use of evidence therein. These concerns relate to three main issues: (i) the company's model imposes a sequence of treatments which is not consistent with the data from Study 1118E;[11] (ii) the model imposes potentially inappropriate structural relationships between progression and death; and; (iii) the model includes a structural assumption whereby survival following progression from second-line therapy must follow an exponential distribution.

(i) Model structure inconsistent with data from Study 1118E

The company's model structure includes three progression-free health states in which active treatment is assumed (second-, third- and fourth-line therapy). All patients enter the model in the second-line progression-free state. This is, however, inconsistent with the evidence which has been used to inform the baseline PFS curve for ibrutinib and the evidence used to inform the indirect comparison. Within the subset of patients from Study 1118E who were included in the company's matching exercise used to generate the treatment effect for ibrutinib (n=47), only [redacted] of patients had received one prior

line of therapy, whilst the remaining [redacted] of patients had received two or more prior lines of therapy (up to a maximum of four prior lines). Similarly, the matched cohort from the European chart review (n=175) had received a median of two prior lines of therapy (range 1-4). Consequently, the baseline risk of PFS and the treatment effects estimated from the multivariable Cox model do not correspond to the second-line progression-free health state defined in the model. The ERG also notes that the full cohort of patients from Study 1118E was used to inform the company's curve-fitting for PFS, whilst the HR for PFS was estimated only from a subset of this cohort (≤4 prior lines of therapy); this is again inconsistent.

Given that the company's HR for PFS has been estimated using outcomes for patients who have received multiple prior lines of therapy, but is applied only in the second-line progression-free state, this seems to imply an underlying assumption that the number of prior lines of therapy received is not a treatment effect modifier. This assumption is however inconsistent with the evidence used to populate the transition probabilities for the third- and fourth-line progression-free health states whereby different progression rates and distributions are employed compared with the second-line progression-free health state (see Table 34).

The ERG also notes that the evidence used to inform progression and death event rates throughout the subsequent states of the model is inconsistent with the definition of health states within the model (see Table 50). For example, time to progression in the third-line progression-free state is based on data from patients who were starting fourth-line treatment in the European chart review, whilst post-progression survival outcomes in BSC were estimated from patients who were receiving fourth-line active therapy.

Consequently, the ERG does not consider that the evidence available justifies the sequence-based model structure developed by the company.

Table 50: Summary of evidence used to inform progression and death event rates by line of therapy

Model health state	Progression		Death	
	Ibrutinib	**Rituximab/chemotherapy**	**Ibrutinib**	**Rituximab/chemotherapy**
Second-line progression-free	Full population from Study 1118E (1-9 prior treatments). *ERG comment:* *Patients in the model by definition have only received one prior line of therapy on entry*	Patients who had received between 1 and 4 prior lines of therapy in the European chart review. *ERG comment:* *Patients in the model by definition have only received one prior line of therapy on entry*	Based on life tables.	Patients receiving second-, third- or fourth-line therapy in the European chart review. *ERG comment:* *Patients in the model by definition have only received one prior line of therapy on entry*
Third-line progression-free	Patients starting fourth-line treatment in the European chart review. *ERG comment:* *Patients in the model are by definition starting third-line treatment*		Patients progressed from third-line treatment in the European chart review. *ERG comment:* *Patients in the model are by definition progression-free in third-line*	
Fourth-line progression-free	Patients starting fourth-line treatment in the European chart review. *ERG comment:* *Evidence consistent with model*		Patients progressed from third-line treatment in the European chart review. *ERG comment:* *Evidence consistent with model*	
BSC	Not applicable		Patients progressed from third-line treatment in the European chart review. *ERG comment:* *Includes post-progression survival outcomes for patients receiving active therapy rather than BSC*	

BSC – best supportive care

The ERG also notes the following issues, each of which calls to question the credibility and value of the company's sequence-based model structure:

- The CS argues that there is no standard of care for WM, hence the inclusion of a blended comparator of rituximab/chemotherapy options. Thus, whilst patients with R/R disease may receive more than one subsequent line of therapy, this does not follow a well-defined sequence. In addition, the company's model uses subjective expert opinion, rather than objective data (for example, the European chart review[9]), to determine which treatment options are received in each line of therapy as well as the proportion of patients who receive BSC. The ERG also notes that the final NICE scope[7] does not request the development of a model based on an explicit sequence of therapies.
- The same pre-progression mortality probability is applied to the third- and fourth-line progression-free states. This is also the same as the post-progression survival probability for BSC. Therefore, despite the company's model adopting a sequence-based structure, survival following progression on second-line therapy is governed entirely by a single exponential function. In addition, the same probability of progression is applied to both the third- and fourth-line progression-free health states.
- The company's model assumes the same health utility score for all progression-free states irrespective of line of therapy, with a lower utility score assumed for BSC.

The ERG notes that the use of a partitioned survival approach may have resulted in a more parsimonious model structure. However, this would not have allowed for the inclusion of the company's assumption that the pre-progression mortality rate for ibrutinib reflects that of the general population (see critical appraisal point 5). Had such an approach been adopted, it is likely that external data (e.g. expert judgement) would have been required to estimate relative survival gains for ibrutinib versus rituximab/chemotherapy.

In response to a request for clarification from the ERG regarding the mismatch between the available data from Study 1118E and the company's sequence-based model structure (see clarification response,[14] question C6), the company stated that: *"Janssen believe this is an appropriate approach because given our licence is broad; should clinicians have access to ibrutinib, it is likely that ibrutinib will be used early in the treatment pathway due to its strong efficacy and tolerable safety profile. As such, we aimed to reflect likely clinical practice. Furthermore, in order to estimate the relative efficacy of ibrutinib using the European Chart Review data, patients in Study 1118E who had 5+ lines of treatment were removed from the comparison dataset which shifted the median prior lines of therapy patients were exposed to. Janssen believe that any uncertainty on the appropriateness of this modelling approach would be addressed via the MEA as the UK WM Registry should be able to*

demonstrate how ibrutinib is used in clinical practice and the associated efficacy, safety, and HRQoL data" (Clarification response,[14] question C6).

The ERG does not consider that the company's response addresses the issue regarding the suitability of the model structure given the available data.

(ii) Imposition of potentially inappropriate structural relationships between progression and death

The company's model imposes a structural relationship between PFS and pre-progression mortality which may not be appropriate. Within both groups, this firstly involves calculating the probability of being alive and progression-free at time *t* using the parametric PFS curve and subsequently applying the probability of pre-progression mortality to the modelled PFS probability. In other words, pre-progression mortality in the second-line progression-free state is modelled conditional on PFS: the PFS curve determines the probability of leaving the state, whilst the pre-progression curve mortality determines the proportion of those patients leaving the state who transit to the dead state. 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 (3.35 LYGs). 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. This is demonstrated in Table 51 across two scenarios: (a) the company's base case, and; (b) a scenario in which the general population mortality hazard is assumed to be zero. As shown in the table, the health gains generated during the second-line progression-free interval are identical, despite the use of different pre-progression mortality assumptions. The ERG does not consider this to reflect the best use of evidence and notes that it produces counter-intuitive model behaviour.

Table 51: Comparison of company's base case and scenario whereby general population mortality hazard is zero

Deterministic model - base case		
Health outcome	**Ibrutinib**	**Rituximab/chemotherapy**
Second-line progression-free survival (years)	[redacted]	[redacted]
Post-second-line progression-free survival (years)	[redacted]	[redacted]
Overall survival (years)	[redacted]	[redacted]
Deterministic model – zero pre-progression mortality hazard		
Health outcome	**Ibrutinib**	**Rituximab/chemotherapy**
Second-line progression-free survival (years)	[redacted]	[redacted]
Post-second-line progression-free survival (years)	[redacted]	[redacted]
Overall survival (years)	[redacted]	[redacted]

The ERG considers that given the underlying Markov structure adopted, the most appropriate approach would involve the independent modelling of time to progression (censoring for death) and pre-progression mortality (censoring for progression). This would however also require the re-estimation of the treatment effect on progression and/or pre-progression death separately.

(iii) Questionable structural assumptions and inconsistent data for post-progression survival

The company's Markov approach imposes a structural assumption whereby survival following progression on second-line treatment must follow an exponential distribution. This is due to the use of multiple intermediate health states within the company's model (third-line progression-free, fourth-line progression-free and BSC). Whilst it would have been possible to reflect time-variant event rates through the use of a semi-Markov design (using multiple tunnel states for incident patients entering each intermediate state), or through the use of patient-level simulation, this is not possible within the company's existing model structure. With respect to this assumption, the CS states *"A parametric fitting was conducted for the OS of this cohort; an exponential function (see Table 38) was found to be the best fit, which indicates a constant hazard of death regardless of treatment"* (CS,[1] page 87). However, the AIC for the log normal distribution is actually slightly lower than that for the exponential distribution. In addition, the CS does not present the fitted Kaplan-Meier plots, hence the ERG is unable to judge whether an alternative survivor function may provide a more appropriate extrapolation. If this was the case, the company's model structure would preclude their use. The ERG notes that the same structural issue applies to time to progression in the third- and fourth-line progression-free states.

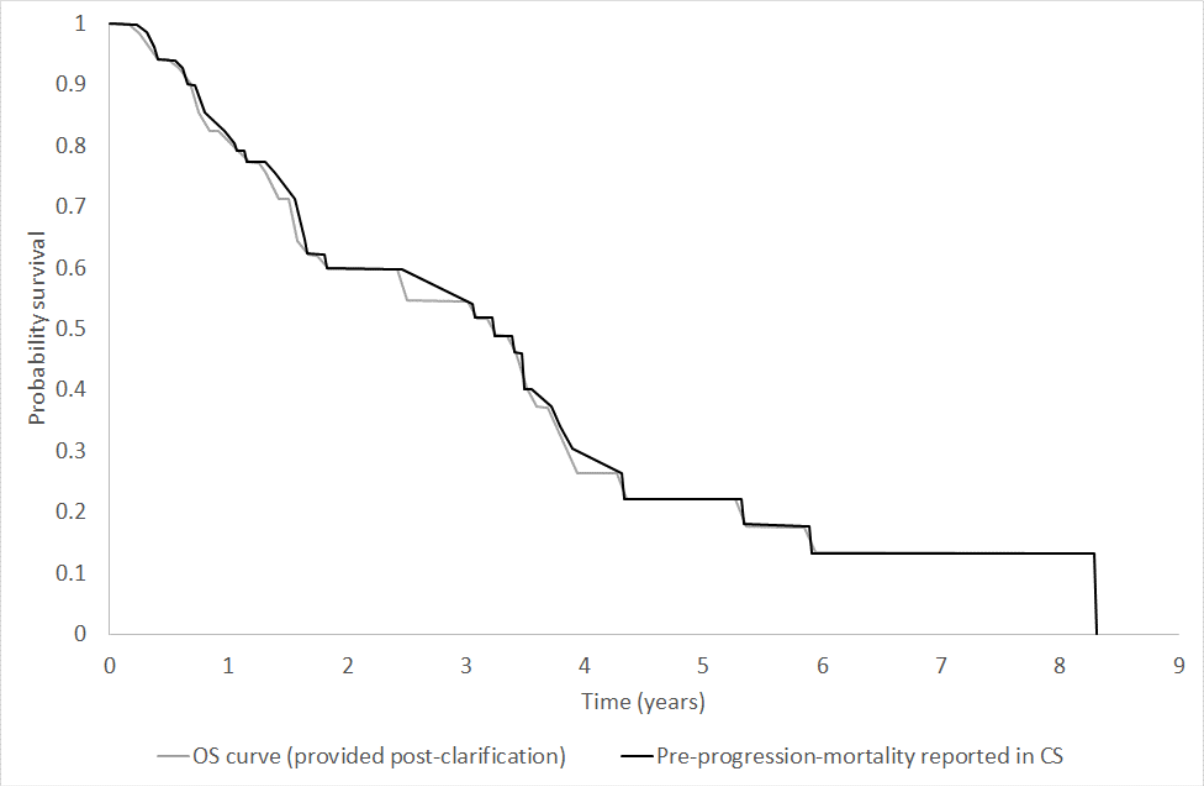
The ERG notes also that the survival curves used to inform the second-line pre-progression mortality and post-progression survival for rituximab/chemotherapy appear logically inconsistent (see Figure 16). Clinical advisors to the ERG stated that whilst survival prognosis would be expected to decrease following progression from each consecutive line of treatment, the parametric models used by the company suggest the opposite; the modelled survival prognosis for the rituximab/chemotherapy group following progression from second-line treatment is better than that assumed prior to progression (mean second-line pre-progression survival from log normal curve = 3.91 years, mean post-progression survival from exponential curve = [redacted]). The ERG also notes that for the rituximab/chemotherapy group, the similar trajectories of these two curves result in a situation whereby the HR for PFS affects the probability of being in the second-line progression-free state, but does not have a material impact on the overall survival gains for this group.

Figure 16: Modelled second-line pre-progression and post-progression survival assumed in company's model

(4) Potentially inappropriate data used to inform pre-progression mortality for rituximab/chemotherapy

The ERG has concerns that the data used to model pre-progression mortality for rituximab/chemotherapy relate to OS (without censoring for progression events). The consequence of using data relating to all deaths (rather than only those occurring before progression) is that the death rate in the rituximab/chemotherapy group would be artificially inflated, thereby erroneously improving the ICER for ibrutinib. The ERG sought clarification from the company regarding the data used to inform the pre-progression mortality curve in the model (see clarification response,[24] question C9). In response, the company stated that: *"The time to death for physician's choice presented in Section 5.3, Figure 21 represents the pre-progression death only, and does not take into account post-progression survival. Patients who progressed are censored."* (see clarification response,[24] question C9). In response to a further subsequent request for clarification by the ERG, the company provided the Kaplan-Meier OS curve from the matched European chart review cohort (n=175). The ERG digitally scanned the OS curve and the pre-progression mortality curve reported in the CS and plotted the data together (see Figure 17). The two curves appear to reflect the same data; this suggests that either the CS or the company's clarification response is inaccurate, and it remains unclear whether the model uses data on all deaths or only those occurring before progression to model pre-progression mortality for the rituximab/chemotherapy group. The ERG notes that if OS data have been used, the ICER for ibrutinib could be significantly higher than that reported in the CS.

Figure 17: Pre-progression mortality and overall survival data from the matched European chart review cohort (digitised by ERG)



(5) Questionable assumption of general population mortality rates for ibrutinib patients in the second-line progression-free state

The key driver of the ICER for ibrutinib versus rituximab/chemotherapy is the use of general population life tables to describe pre-progression mortality for the ibrutinib group. The company's assumption of general population mortality hazards was made on the basis that only three patients died within the 24-month follow-up period within Study 1118E (see Section 4.2.2.6 and Figure 7). The ERG notes that the CS does not present any comparative evidence to demonstrate a survival benefit for ibrutinib compared with any other WM treatment and the 24-month follow-up duration is short, thereby leading to considerable uncertainty.

The importance of this assumption is evident from the company's DSAs (see CS, Table 63, and CS Appendix 9, Table 52), whereby even at an HR for PFS of [redacted] (compared with an HR of [redacted] in the base case), the ICER is only increased from £58,630 per QALY gained to £59,460 per QALY gained. Table 52 and Table 53 present the broad health state summaries and cost-effectiveness results generated: (a) under the company's base case assumptions, and; (b) under the assumption that the HR for PFS for rituximab/chemotherapy versus ibrutinib is equal to 1.0 (i.e. no effect). As shown in Table 53, under the assumption of equivalent PFS gains, the ICER for ibrutinib versus

rituximab/chemotherapy is £74,615 per QALY gained; this is only around £15,000 higher than the base case. Table 52 demonstrates that the behaviour of the model is driven by four factors:

(a) The inverse of the HR is applied to the baseline ibrutinib PFS curve to estimate outcomes for second-line rituximab/chemotherapy – this means that the modelled health outcomes for the ibrutinib group are entirely independent of the HR for PFS;

(b) The use of a highly favourable survival trajectory for ibrutinib patients in the second-line progression-free state – given that mortality is modelled conditional on PFS, this leads to a considerable survival gain accruing beyond second-line progression;

(c) The proportion of patients leaving the second-line progression-free state that die is independent of the PFS curve;

(d) The similarity between the survival curves for second-line pre-progression mortality and post-second-line mortality for rituximab/chemotherapy (see Figure 16) – this means that the HR impacts on the probability of being in the second-line progression-free or post-progression states for rituximab/chemotherapy, but does not markedly impact on overall survival in this group.

Table 52: Modelled health outcomes assuming HR for PFS = 1.0 and HR for PFS = [redacted]

Deterministic model (HR for PFS=1.0)		
Health outcome	**Ibrutinib**	**Rituximab/chemotherapy**
Second-line progression-free survival (years)	[redacted]	[redacted]
Post-second-line progression-free survival (years)	[redacted]	[redacted]
Overall survival (years)	[redacted]	[redacted]
Deterministic model base case (HR for PFS = [redacted])		
Health outcome	**Ibrutinib**	**Rituximab/chemotherapy**
Second-line progression-free survival (years)	[redacted]	[redacted]
Post-second-line progression-free survival (years)	[redacted]	[redacted]
Overall survival (years)	[redacted]	[redacted]

HR – hazard ratio; PFS – progression-free survival

Table 53: Company's model results assuming HR for PFS = 1.0

Deterministic model (HR for PFS=1.0)					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£74,615**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-
Deterministic model base case (HR for PFS = [redacted])					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£58,630**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

HR – hazard ratio; PFS – progression-free survival; QALY – quality-adjusted life year

The ERG has two main concerns regarding this assumption and its application in the company's model: (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.

(i) Zero death rate assumed for first 6 model cycles

The ERG notes that within the second-line progression-free state, the hazard of death for patients receiving ibrutinib is assumed to be zero over the first 6 cycles (5.5 months). This means that no patients in the ibrutinib group (whilst remaining progression-free) can die during the first 24 weeks of treatment, hence the modelled pre-progression mortality rate is more favourable than that from age- and sex-matched general population life tables.[34] This appears to have occurred because the company's model assumes that patients are aged 64.5 years at model entry, but the company's =VLOOKUP() calculations for general population mortality begin at age 65. At best, this represents a programming error; at worst, it reflects a highly unreasonable judgement. Irrespective of whether this assumption was intended, the consequence is that the ICER for ibrutinib will be underestimated.

(ii) The observed death rate within Study 1118E was higher than that for the age- and sex-matched general population

Based on Study 1118E,[11] the company estimated the 1-year probability of death. Given 3 deaths in 63 patients and a total follow-up time of 122 years (mean follow-up of 1.93 years per patient), this leads to an estimated 1-year probability of death of 0.025.

Starting at age 64 years (broadly corresponding to the assumed starting age of 64.5 years within the company's model),

Table 54 shows the age- and sex-adjusted probability of dying between age *x* and *x*+1 (denoted "*qx*") from the 2012-2014 life tables for England[34] for males and females separately, as well as a weighted average assuming that 76.2% patients are male (in line with the company's model). As shown in the table, the estimated 1-year probability of death of 0.025 from Study 1118E is higher than that for the age- and sex-adjusted general population at model entry (*qx*=0.01 at age 64 years). The 1-year probability of death in the age- and sex-matched general population only exceeds that observed within Study 1118E for a population aged 74 years of age. However, by this point, the company's modelled PFS projection indicates that only 2% of patients will still be receiving ibrutinib.

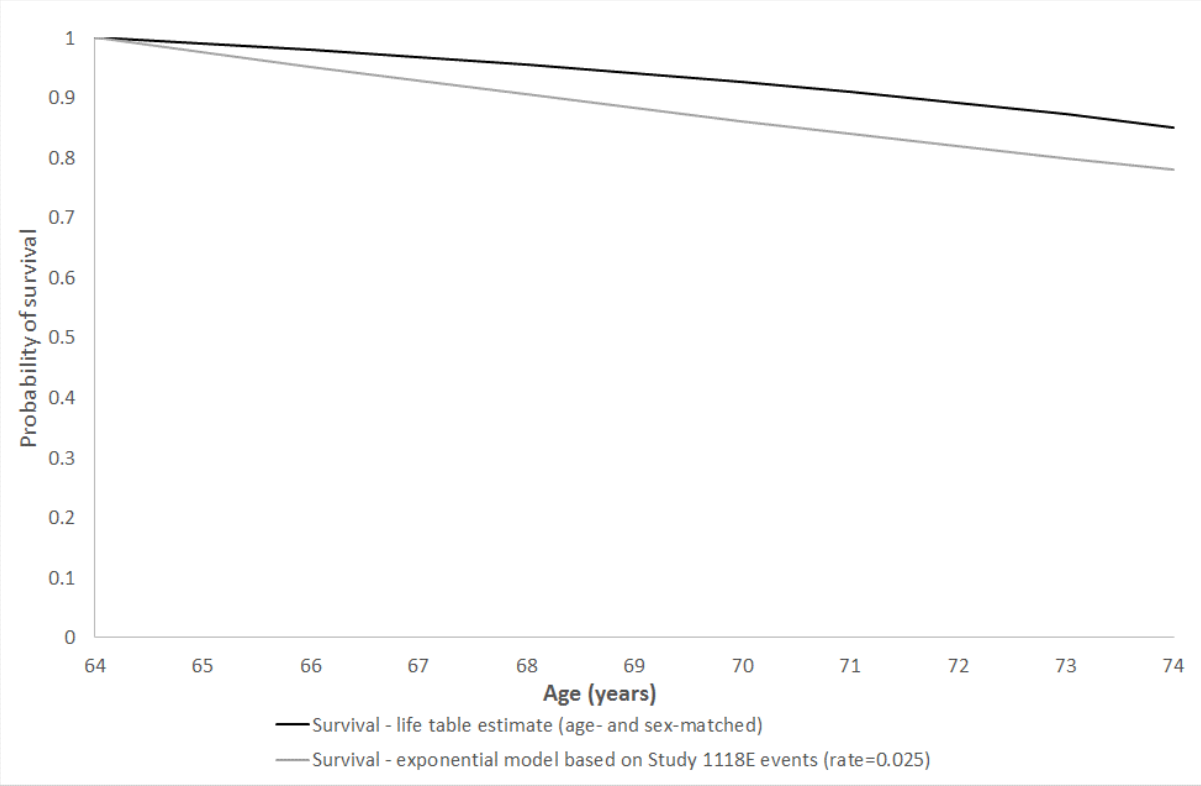
Table 54: General population annual death risk for patients aged 64 years and above

Age (x)	General population life tables for England 2012-2014		
	Males (*qx*)	Females (*qx*)	Sex-adjusted average (*qx*)
64	0.011	0.007	0.010
65	0.012	0.008	0.011
66	0.013	0.008	0.012
67	0.014	0.009	0.013
68	0.016	0.010	0.014
69	0.018	0.011	0.016
70	0.019	0.013	0.018
71	0.021	0.014	0.020
72	0.024	0.016	0.022
73	0.027	0.018	0.024
74	0.029	0.020	0.027

PFS – progression-free survival

Similarly, Figure 18 presents an estimated second-line pre-progression survivor function based on the age- and sex-adjusted life table survival estimates compared with an exponential survivor based on the constant death rate of 0.025 observed in Study 1118E. As shown in the figure, there is a marked separation of the two curves which reaches more than a 7% difference by age 74 years. This suggests that the company's model underestimates the pre-progression mortality rate for the ibrutinib group.

Figure 18: Modelled second-line pre-progression mortality based on age- and sex-adjusted life table estimates and estimated death rate within Study 1118E



Clinical advisors to the ERG noted that they would expect ibrutinib to produce additional survival benefits compared with standard therapies. One advisor to the ERG stated that the use of general population death rates to describe pre-progression mortality is not reasonable. The second clinical advisor considered that this assumption may be reasonable, but only whilst patients are responding to ibrutinib (CR or PR). Given the comparison presented in Figure 18, the ERG considers that this assumption biases the ICER in favour of ibrutinib. However, given the immaturity of the available survival data from Study 1118E and the lack of a randomised comparator, the extent of this bias remains unclear. As noted in critical appraisal point 3, the company's approach to modelling pre-progression mortality is questionable and produces model behaviour which is counter-intuitive.

During clarification, the ERG sought justification regarding the use of general population mortality rates within the company's model (see clarification response,[14] question C8). Within their response, the company stated that: *"We recognise that the trial data are limited and therefore an assumption had to be made on how best to capture this outcome. We believe that, should ibrutinib be recommended for the MEA during a minimum 2 year data collection period (aligning with the median follow-up period of Study 1118E), the data observed in the trial will be confirmed by the real world setting given the strong efficacy and safety data observed thus far with ibrutinib. This will confirm and/or replace the assumptions currently being used in the model."*

The ERG agrees that the available data are limited but notes that the company's approach reflects the most favourable assumption that could be made and that this is not supported by the limited survival data that are currently available.

(6) Limited clinical evidence available for ibrutinib versus rituximab/chemotherapy

The ERG has concerns regarding the limited evidence of clinical benefit for ibrutinib versus rituximab/chemotherapy. In particular, the ERG notes the following:

- There are no head-to-head RCTs comparing the clinical effectiveness of ibrutinib versus any other therapy, either for patients with R/R WM or treatment-naïve patients for whom chemo-immunotherapy is unsuitable. The CS includes outcomes for only one single-arm study (Study 1118E[11]). As such, any estimate of relative treatment effects must be derived from the use of external data.
- The CS presents a naïve indirect comparison of PFS outcomes for ibrutinib versus everolimus, rituximab, panobinostat, alemtuzumab, bortezomib, chlorambucil and fludarabine (see Figure 3, derived from the CHMP variation report[6]). However, the results of this indirect comparison are problematic in that they may be confounded by differences between the studies in terms of populations and study designs. The ERG notes that these concerns regarding potential confounding are also raised within the CS (see CS, Section 1.3).[1]

- The company has undertaken an adjusted arm-based indirect comparison of ibrutinib versus standard therapies regimens using the European chart review.[9] As noted in Section 4.4, the ERG has concerns regarding the robustness of this comparison, in particular: the potential for unadjusted confounders; the lack of a unique matched sample from the chart review and the exclusion of patients who had received five or more prior lines of treatment. In addition, the CS does not contain an analysis of the relative survival benefits of ibrutinib versus standard therapies.
- The overall survival data (DCO 19th December 2014) included only three deaths, all of which occurred prior to disease progression. The long-term survival prognosis of WM patients receiving ibrutinib is unknown.
- Study 1118E is based on a small patient population (n=63).
- Study 1118E did not include the use of a preference-based measure of HRQoL. The company's systematic review did not identify any HRQoL studies in WM. Clinical advisors to the ERG were also unaware of any HRQoL studies in this population. Based on their own experience of using the drug, the clinical advisors to the ERG did however consider that ibrutinib is generally better tolerated than current rituximab/chemotherapy options (whilst patients are receiving treatment) and that HRQoL improves with better disease control.

As a consequence of these issues, the ERG considers that any estimate of the relative benefits of ibrutinib on PFS, OS and HRQoL are highly uncertain. Given the strong assumptions regarding relative clinical benefits employed in the company's model, the ERG considers the company's economic analysis to be largely speculative.

(7) Concerns regarding company's estimation of time-to-event parameters

As noted in Section 5.2.3, the transition probabilities employed within the company's model were derived using survival modelling methods. Whilst the CS cites NICE Decision Support Unit Technical Support Document 14,[48] the ERG does not consider that this methodological guidance has been fully adhered to. The ERG's main concerns surrounding the estimation of time-to-event parameters are summarised in

Table 55.

Table 55: Summary of ERG's concerns regarding company's survival modelling

Health state	Outcome	Issues related to survival modelling presented in the CS
Second-line progression-free	PFS	• Several candidate survivor functions not tested (Gompertz, gamma, generalised gamma, generalised F) • Proportional hazards for PFS assumed without proper justification • Ibrutinib PFS function used as the baseline • Discrepancy between observed PFS curve presented in CS[1] and observed PFS curve presented in company's clarification response[14]
	Pre-progression mortality	• No parametric survival models fitted to available mortality data from Study 1118E • Several candidate survivor functions not tested for rituximab/chemotherapy group (Gompertz, gamma, generalised gamma, generalised F)
Third-/fourth-line progression-free	PFS	• Graphical comparison of candidate functions and observed Kaplan-Meier not presented • Goodness-of-fit statistics not presented
	Pre-progression mortality	• Broader set of parametric functions included compared with second-line PFS and pre-progression mortality, however some functions are still missing (gamma and generalised F) • Unclear whether progression events have been censored
BSC	Post-progression survival	

PFS – progression-free survival; CS – company's submission; BSC – best supportive care

Second-line PFS

PFS outcomes for patients receiving ibrutinib were extrapolated from the PFS data reported in Study 1118E (n=63).[11] However, only a selection of parametric function distributions (exponential, Weibull, log-normal, and log-logistic), were fitted to the available data. The ERG considers that other survivor functions, for example, the gamma, the generalised gamma, the generalised F and the Gompertz distributions should have also been tested; the CS does not present any justification with respect to this omission. It is possible that these models could have provided a better fit and a more plausible long-term projection compared with the parametric functions which were tested. In response to a request for clarification from the ERG (see clarification response,[14] question C7), the company provided the parameters and AIC/BIC statistics for the Gompertz and generalised gamma functions fitted to the PFS data from Study 1118E.[11] The company's clarification response notes that the generalised gamma did not converge and that the Gompertz was shown to have worse AIC and BIC than the Weibull, log-logistic and exponential functions. No additional analyses of the gamma or Gompertz functions were presented.

PFS outcomes for second-line rituximab/chemotherapy were estimated by applying the inverse of the HR derived from the company's multivariable Cox model to the fitted PFS curve for ibrutinib (see Section 5.2.3). The CS does not contain any justification regarding whether the proportional hazards

assumption holds, although this issue was later addressed in the company's clarification response[14] (question B27, as discussed in Section 4.4).

The ERG notes that the baseline PFS survivor function used in the company's model uses the PFS data from Study 1118E and applies the inverse of the HR for the effect of ibrutinib versus standard therapies on PFS estimated from the indirect comparison to generate the rituximab/chemotherapy PFS survivor function. The ERG considers that it would have been more appropriate for the baseline PFS function to reflect the survivor function for the target population receiving current standard therapies and to apply the HR to this curve to generate the survivor function for the experimental treatment (ibrutinib). This baseline PFS survivor function could have been derived from external sources relating to the target population, for example, the European chart review or some other source, thereby allowing for the inclusion of more data on long-term outcomes for these patients. In addition, this would have allowed for the assessment of a wider set of potentially plausible survival models than those considered by the company (e.g. fractional polynomials).

The ERG also notes that the PFS data for ibrutinib used in the curve-fitting presented in the CS do not match those presented in the company's clarification response (see Figure 19). The reasons underlying this discrepancy are unclear; the figure shown in the CS suggests that the final observations have not been included in the curve-fitting process and the cumulative survival probabilities do not match. Whilst the curve on the left reflect the IRRC assessment of PFS (DCO unclear), it is unclear who assessed the PFS outcomes used in the model.

Figure 19: Ibrutinib PFS curves presented in CS and company's clarification response

Second-line pre-progression mortality

As discussed in critical appraisal point 5, the ERG has concerns that the observed mortality rate for patients receiving ibrutinib in Study 1118E is higher than that estimated from age- and sex-matched life tables for the general population. The ERG considers that the company could have explored the

use of simple parametric models (e.g. exponential functions) using the observed data within Study 1118E. However, as noted above, the ERG would have preferred the rituximab/chemotherapy group to have been used as the baseline, with the relative survival benefits of ibrutinib quantified using Study 1118E and/or some external data source.

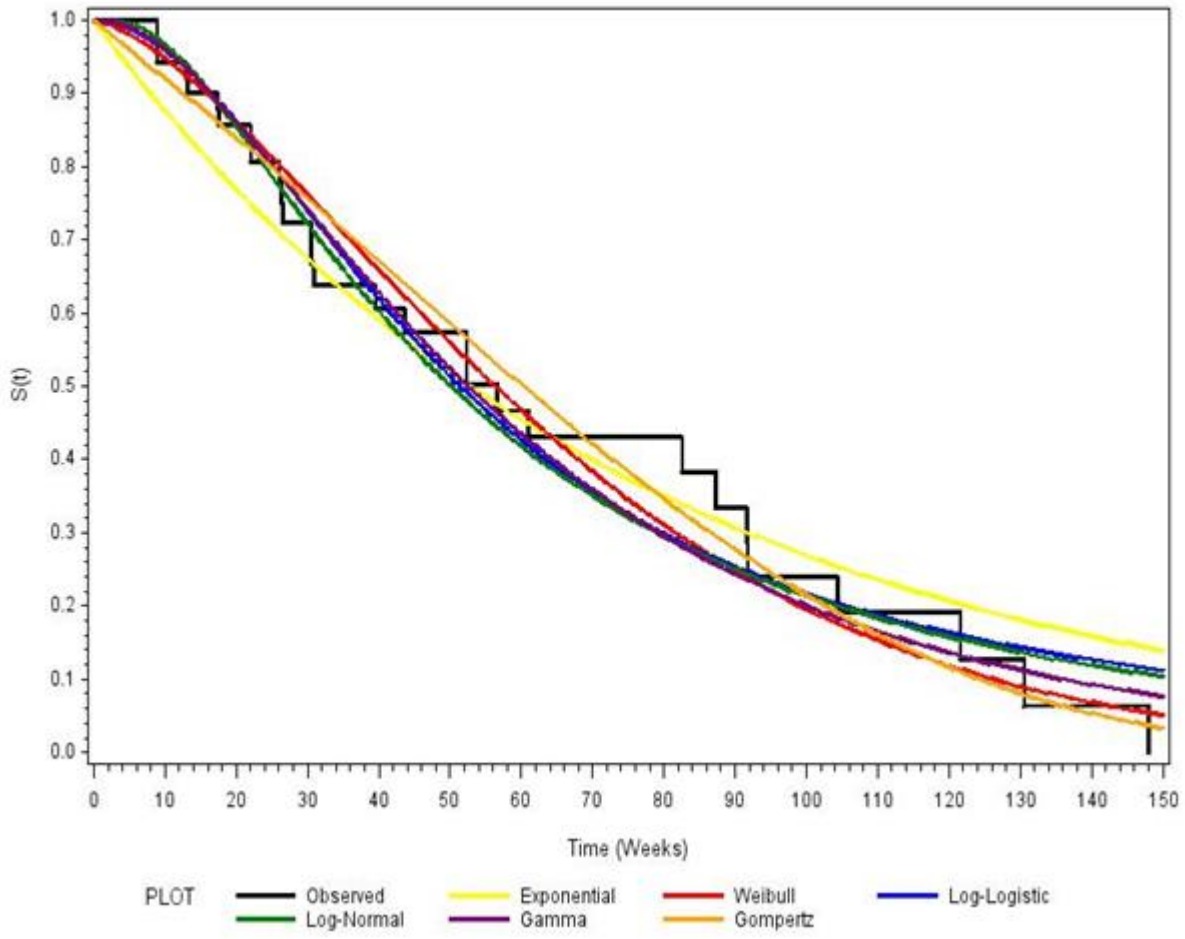
The survival modelling methods applied to the second-line rituximab/chemotherapy pre-progression mortality data were also limited (see Section 5.2). The CS details the parameters and AIC/BIC statistics for only a selection of potentially relevant parametric models (the exponential, Weibull, log normal, and log logistic functions). The ERG considers that other survivor functions, for example, the gamma, the generalised gamma, the generalised F and the Gompertz distributions should have also been tested. The use of more flexible models could have also have been explored.

Third- and fourth-line time to progression

The company's model assumes the same constant probability of progression for both third- and fourth-line treatments and the CS states that an exponential model provided the best fit. However, the CS does not present a graphical plot of the alternative candidate survivor functions against the observed Kaplan-Meier survival data. In addition, the AIC/BIC statistics for the alternative models are also not presented.

As part of the company's clarification response[14] (question C10), the company provided a comparative plot of the Weibull, log logistic, log normal, gamma, Gompertz and exponential models against the observed Kaplan-Meier curve for time to progression (see Figure 20). The company also provided AIC and BIC statistics for the Weibull, log logistic, log normal and exponential models (see Table 56); goodness-of-fit statistics were not reported for the gamma and Gompertz functions.

Figure 20: Time to progression – observed and parametric curves survivor functions (from the European chart review, reproduced from clarification response (question C10)



S(t) – cumulative survival probability

Table 56: Goodness-of-fit statistics – time to progression for third- and fourth-line rituximab/chemotherapy from European chart review (adapted from company's clarification response (question C10)

Survivor function	AIC	BIC
Weibull	[redacted]	[redacted]
Log normal	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]
Exponential	[redacted]	[redacted]

AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion

On the basis of visual inspection, Figure 20 suggests that the exponential survivor function provides the least appropriate model fit and produces a fatter tail which has not been observed in the time-to-event data. In addition, both the AIC and BIC statistics were highest for the exponential function, thereby indicating a worse fit relative to the other models assessed. As discussed in critical appraisal point 3, the company's model structure cannot however incorporate time-variant transition rates

except in the second-line progression-free health state. It appears that the company has selected the use of an exponential distribution for this event rate on the basis of convenience rather than a proper consideration of the available evidence.

Third- and fourth-line pre-progression mortality and post-progression survival in BSC

The model assumes a constant probability of death in the third- and fourth-line progression-free states and the BSC state. The CS states that an exponential function was found to be the best fit. Whilst the CS reports the AIC/BIC statistics for the candidate functions assessed (see Table 37), it does not present a graphical plot of the distributions against the empirical Kaplan-Meier survivor function. It is thus unclear whether the exponential survivor function is appropriate.

(8) Disconnect between sources used to estimate health gains and costs for rituximab/chemotherapy

The company's model estimates the effectiveness of rituximab/chemotherapy regimens and the resources required to generate those health benefits (that is, the total costs of treatment weighted by the proportionate use of each regimen) based on different sources. PFS outcomes for second-line rituximab/chemotherapy were estimated based on the inverse of the HR derived from the company's adjusted arm-based indirect comparison (see Section 4.4) based on Study 1118E[11] and the European chart review.[9] Conversely, the costs associated with second-line rituximab/chemotherapy were estimated as a weighted average of the distribution of treatments, based on the input from clinical experts (FCR - 11%; DRC - 31%; BR - 47%, and "other treatment" - 11%). This may produce some inconsistency between estimated health outcomes and the costs associated with generating those outcomes.

The ERG also notes that a considerably wider range of treatment regimens were received within the European chart review at second-line compared with those included in the model (see clarification response,[14] additional data provided in response to question B24), and that the company's survey of clinical experts also included additional treatments which have not been included in the company's costings (for example, bortezomib-based regimens and stem cell transplantation, see CS Appendix 4).

In response to a request for clarification from the ERG regarding the use of separate data sources for effectiveness and costs (see clarification response,[14] question C5), the company stated that *"Clinical opinion confirmed the efficacy data were plausible, that the treatment effect was plausible, and that the treatment regimens may be slightly different in the UK but the impact of this could be limited to the cost as opposed to the efficacy."*

The ERG accepts that the evidence for this appraisal is limited. However, it would have been prudent to consider two alternative scenarios: (i) a scenario in which only the least expensive comparator regimen is assumed, and; (ii) a scenario in which the proportionate use of each regimen was based on the European chart review.[9]

(9) Use of a blended comparator

The company's economic analysis is based on a blended comparison of ibrutinib versus eight alternative second-line rituximab/chemotherapy regimens. The ERG considers the use of blended comparisons to be inappropriate as they may produce misleading conclusions on the cost-effectiveness of health technologies. If all treatment regimens are truly equally effective, clinicians would simply select the least expensive regimen which can be tolerated by the patient. Clinical advisors to the ERG noted that in clinical practice, a range of regimens are used within this patient population, and that treatment options choices are typically guided by patient fitness and their ability to tolerate therapy: for example, BR is typically used in fitter patients, whilst chlorambucil tends to be used in very frail patients. It would have been preferable to present analyses of ibrutinib versus individual rituximab/chemotherapy regimens according to those patient characteristics which determine treatment choice. However, the ERG accepts that the data required to undertake such analyses are limited.

(10) Concerns regarding health utilities assumed in the model

The company's model assumes that the utility for patients in the progression-free states is 0.799, whilst the utility for patients on BSC is 0.665. These estimates were based on the RESONATE CLL trial[16] and Beusterien *et al*.[39] Clinical advisors to the ERG noted that given the lack of HRQoL data available for patients with WM, the use of utilities from a CLL study by proxy may be reasonable. However, 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 as a consequence of treatment-related toxicity. With the exception of the disutilities associated with AEs experienced during second-line treatment, the company's model does not account for any of these HRQoL effects. One clinical advisor to the ERG also noted that the utility score applied in the BSC state was lower than might be expected. Again, the ERG accepts that evidence in this area is absent.

(11) Errors and discrepancies relating to drug acquisition costs for rituximab/chemotherapy

The ERG has concerns regarding the estimation and application of costs in the company's model. Table 57 summarises the regimens assumed in the company's model. The right-hand column highlights inconsistencies and discrepancies identified by the ERG with respect to the calculation of these costs.

Table 57: Treatment regimens assumed in company's model (including ERG comments)

Regimen	Regimen details (from model)	Acquisition cost assumed in model	ERG comments
Ibrutinib	420 mg/day (3 capsules) daily	51.10 per capsule	• Calculations appear to be correct
FCR	Fludarabine: 25 mg/m^2 on days 2–4 every 28 days for six cycles Cyclophosphamide: 250 mg/m^2 on days 2–4 every 28 days for six cycles Rituximab: 375 mg/m^2 on day 1 of first cycle followed by 500mg/m^2 every 28 days for six cycles	Fludarabine (50mg/vial) = £147.10 Cyclophosphamide (500mg/vial) = £9.20 Rituximab (500mg vial) = £873.15	• Model assumes fludarabine 40mg/m^2 rather than 25mg/m^2 stated in the CS • Least expensive 500mg vial of cyclophosphamide is £9.66 rather than £9.20 • Model calculations actually use a 50:50 split of the 3-day schedule (mentioned in the CS) as well as a 5-day FCR schedule (not mentioned in the CS) • Model assumes rituximab dose is 500mg/m^2 for five of the six cycles (375mg/m^2 stated in CS) • Model assumes 3 rather than 4 IV administrations per 28-days
DRC	Dexamethasone: 20 mg IV on day 1 every 21 days for six cycles Rituximab: 375 mg/m^2 IV on day 1 every 21 days for six cycles Cyclophosphamide:100mg/m^2 orally on days 1–5 every 21 days for six cycles	Dexamethasone (3.8mg/1ml vial) = £1.99 Rituximab (500mg vial) = £873.15 Cyclophosphamide (500mg/vial) = £9.20	• Dexamethasone very slightly under-costed (should be £2.00) • Uses IV cyclophosphamide cost but should use least expensive cost of oral cyclophosphamide (£1.39 per 50mg tablet)
BR	Bendamustine: 70 mg/m^2 every 28 days for 6 cycles Rituximab: 375 mg/m^2 every 28 days for six cycles	Bendamustine (100mg vial)=£275.81 Rituximab (500mg vial)=£873.15	• Model uses 70mg/m^2 rather than 90mg/m^2 bendamustine as stated in CS Table 33, although this does not affect calculations due to the inclusion of wastage. • Bendamustine assumed to be given on 2 days of cycle rather than 1 (implied by CS Table 33) • Generic version of bendamustine costs £27.77 per 100mg vial; this is considerably less expensive than cost used in the model (£275.81) • Model includes 4 rather than 3 IV administrations per 28-days

Regimen	Regimen details (from model)	Acquisition cost assumed in model	ERG comments
Cladribine + R	Cladribine: 0.14 mg/kg every 28 days for 4 cycles Rituximab: 375 mg/m^2 every 28 days for 4 cycles	Cladribine (10mg vial) = £165.00 Rituximab (500mg vial) = £873.15	• Model assumes cladribine assumed given every 5 days but CS implies one dose • The model includes programming errors which erroneously add in the acquisition costs of other regimens to the cladribine+R costs • Model assumes 5 rather than 6 IV infusions per 28-days
Chlorambucil + R	Not stated in CS. Model indicates 0.2mg/kg chlorambucil for 7 days and 375mg/m^2 rituximab for 1 day. Repeated every 28 days for 6 cycles.	Chlorambucil (25 x 2mg tablets) = £40.51 Rituximab (500mg vial) = £873.15	• The least expensive version of chlorambucil in the current BNF is £42.87 per 25 tablets (2mg) • The formulae include an error in the dose-rounding formulae which increases the total dose to 350mg rather than (correct dose is 112mg per 28 days)
Rituximab monotherapy	Not stated in CS. Model indicates rituximab 375mg/m2 weekly for 4 weeks.	Rituximab (500mg vial) = £873.15	• Calculations appear to be correct
Chlorambucil monotherapy	Not stated in CS. Model indicates 0.2mg/kg chlorambucil daily for 56 days	Chlorambucil (25 x 2mg tablets) = £40.51 Rituximab (500mg vial) = £873.15	• The least expensive version of chlorambucil in the current BNF is £42.87 per 25 tablets (2mg) • The formulae include an error in the dose-rounding formulae which increases the total dose to 350mg rather than (correct dose is 112mg per 28 days)
Cladribine monotherapy	Not stated. Model indicates cladribine 0.14 mg/kg for 5 days every 28 days for 6 cycles.	Cladribine (10mg vial) = £165.00	• Calculations appear to be correct

As shown in Table 57, the ERG's main concerns are:

- The cost of bendamustine reflects the proprietary product; the cost of the generic version is markedly less expensive than that assumed in the company's model.
- Several of the drug costs did not match those reported in the current version of the BNF.
- The cost calculations for chlorambucil include errors which inflate the total waste-adjusted dose, thereby inflating the total cost of the chlorambucil regimens.
- The cost calculations for cladribine plus rituximab includes programming errors which dramatically inflate the estimated cost of the regimen.
- The administration costs are incorrect for several regimens.

The ERG also has concerns regarding the calculation and implementation of the third- and fourth-line treatment costs in the model. The company's model calculates the total cost of third- and fourth-line regimens over a 6-cycle period (the maximum duration of all regimens) and then down-weights these according to the probability of being alive and progression-free at time *t*, based on the third- and fourth-line PFS functions estimated using data from the European chart review.[9] This approach is not discussed in the CS. Strictly speaking, these costs should be calculated according to the time that the patient remains progression-free and on treatment, rather than based on a "front-loaded" total cost. This would however require a very different model structure which tracks incident cohorts of patients progressing into, and remaining in, the third- and fourth-line progression-free states over time. This approach is not possible in the company's model structure. The ERG also notes that the "front-loaded" costs are discounted twice: firstly at the point of calculating the total cost, and secondly at the point at which they are applied to the total costs for the treatment group. This is incorrect.

The ERG further notes that the total costs of the rituximab/chemotherapy regimens are calculated using the mean height and body mass of patients within Study 1118E.[11] The costs of each regimen should have been calculated according to the distributions of height and body mass observed in the study.[49]

(12) Incomplete characterisation of uncertainty

Whilst there is considerable uncertainty surrounding the decision problem, this has not been adequately characterised within the company's model. With respect to this issue, the ERG makes the following observations:

- Within the company's PSA (see Table 44), many uncertain parameters are held fixed. The most pertinent of these are: (i) the HR for PFS; (ii) the pre-progression mortality curve for second-line rituximab/chemotherapy, and; (iii) the pre-progression mortality function for ibrutinib.

- Health utilities for the progression-free states are modelled independently, despite being based on the same input data. This leads to problems of monotonicity being violated whereby sampled utility values applied to more advanced states are commonly better than those for less advanced states.
- The gamma distribution for routine follow-up costs appear to have been sampled incorrectly whereby the standard error is incorrectly specified as the number of visits per year.
- The company's scenario analyses are highly limited and include only the removal of age-adjustment for utilities, the use of two alternative HRs for PFS and the use of the log normal rather than the Weibull function for PFS for ibrutinib. With respect to the latter analysis, the ERG notes that the log normal is not a proportional hazards model; the application of an HR to an accelerated failure time distribution is inappropriate.
- The executable model only allows for a subset of parametric functions to be assessed.
- There is no consideration of structural uncertainty surrounding the company's assumption that pre-progression mortality rates for ibrutinib reflects those of the age- and sex-adjusted general population.

5.4 ERG's exploratory analysis

This section presents the methods and results of the exploratory analyses undertaken by the ERG. As noted in the critical appraisal section, the ERG has concerns regarding the structure and the use of evidence within the company's model. However, given the data available to the ERG, it was not possible to resolve these problems. The ERG would have preferred a model which: (i) appropriately deals with competing risks of events in the second-line setting using time to progression (censoring for death) and pre-progression mortality (censoring for progression); (ii) includes the estimation of a treatment effect for survival for ibrutinib versus standard therapies; (iii) is populated using evidence which is consistent with defined parameters of the model (e.g. second-line pre-progression survival informed by patients receiving second-line therapy, third-line PFS informed by data on patients receiving third-line therapy), and; (iv) allows for the full exploration of the uncertainty surrounding the decision problem. Given the weaknesses of the company's model and the evidence used to inform it, together with the lack of clarity surrounding which data have been used to inform pre-progression mortality for the rituximab/chemotherapy group, all ICERs presented in this section should be interpreted with some degree of caution.

All analyses use the confidential PAS price for ibrutinib ([redacted] per 120mg capsule). The results of the exploratory analyses based on the list price for ibrutinib are presented in Appendix 2. Unless otherwise stated, all ICERs reported in this section are based on the deterministic version of the model.

5.4.1 Exploratory analysis – methods

The ERG undertook ten sets of exploratory analysis:

- Exploratory analysis 1 – Re-estimation of drug acquisition and administration costs
- Exploratory analysis 2 – Correction of apparent errors surrounding follow-up costs
- Exploratory analysis 3 – Use of ibrutinib pre-progression mortality rate from Study 1118E
- Exploratory analysis 4 – ERG's preferred base case analysis (combining ERG exploratory analyses 1, 2 and 3)
- Exploratory analysis 5 - Use of alternative BSC utility value (using ERG's base case)
- Exploratory analysis 6 – Use of alternative HR for PFS of [redacted] from company's repeated Cox analysis (using ERG's base case)
- Exploratory analysis 7 – Assumption of equivalent pre-progression mortality for ibrutinib and rituximab/chemotherapy (using ERG's base case)
- Exploratory analysis 8 - Use of alternative costs for rituximab/chemotherapy (using ERG's base case)
- Exploratory analysis 9 - Use of the Weibull distribution for pre-progression mortality for rituximab/chemotherapy (using ERG's base case)
- Exploratory analysis 10 – Threshold analysis around HR for PFS

The methods used to implement each exploratory analysis are described in turn below. The technical details for implementing each analysis using the company's submitted model are detailed in Appendix 3.

Exploratory analysis 1 – Re-estimation of drug acquisition and administration costs

As noted in Section 5.3, the ERG has concerns regarding the accuracy and consistency of the drug acquisition and administration costs applied in the rituximab/chemotherapy group (see Table 57). Using input from the ERG's clinical advisors, these costs were recalculated for second-line and subsequent-line rituximab/chemotherapy. The unit costs of each product based on the current version of the BNF (August 2016) are presented in

Table 58. The overall summary of costs by regimen are presented in Table 59**.**

Table 58: Acquisition cost estimates used in ERG exploratory analyses

Product	Details	Pack contents	Cost per pack
Ibrutinib	Imbruvica 140mg capsules (Janssen-Cilag Ltd)	90 capsules	[redacted]
Fludarabine	Fludarabine phosphate 50mg powder for solution for injection vials (A A H Pharmaceuticals Ltd)	1 vial	£155.00
Cyclophosphamide (IV)	Cyclophosphamide 500mg powder for solution for injection vials (Alliance Healthcare [Distribution] Ltd / Baxter Healthcare Ltd)	1 vial	£9.66
Cyclophosphamide (oral)	Cyclophosphamide 50mg tablets (Alliance Healthcare [Distribution] Ltd / Baxter Healthcare Ltd)	100 tablets	£139.00
Rituximab	MabThera 500mg/50ml concentrate for solution for infusion vials (Roche Products Ltd)	1 vial	£873.15
Dexamethasone	Dexamethasone 3.8mg/1ml solution for injection vials (A A H Pharmaceuticals Ltd, Alliance Healthcare [Distribution] Ltd or Aspen Pharma Trading Ltd)	10 vials	£19.99
Bendamustine	Bendamustine 100mg powder for concentrate for solution for infusion vials (Actavis UK Ltd)	1 vial	£27.77
Cladribine	Litak 10mg/5ml solution for injection vials (Lipomed GmbH)	5 vials	£820.00
Chlorambucil	Chlorambucil 2mg tablets (A A H Pharmaceuticals Ltd, Alliance Healthcare [Distribution] Ltd or Aspen Pharma Trading Ltd)	25 tablets	£42.87

Table 59: Rituximab/chemotherapy costs applied in ERG's exploratory analyses

Regimen	Regimen component	Dose per administration	Treatment duration	Dose days per 28 days	Infusions per 28 days	RDI adjusted component cost per 28 days	RDI adjusted regimen cost per 28 days	RDI adjusted administration cost per 28 days
Ibrutinib	Ibrutinib (oral)	420mg o.d.	Until progression	28	0	[redacted]	[redacted]	£0.00
FCR*	Fludarabine (oral)	25mg/m^2	6 x 28-day cycles	3	0	£864.90	£2,527.74	£222.38
	Cyclophosphamide (oral)	250mg/m^2		3	0	£38.78		
	Rituximab (IV)	375mg/m^2		1	1	£1,624.06		
DRC	Dexamethasone (IV)	20mg	6 x 21-day cycles	1.33	1.33	£14.87	£2,249.23	£593.02
	Rituximab (IV)	375mg/m^2		1.33	1.33	£2,165.41		
	Cyclophosphamide (oral)	100mg/m^2		6.67	0	£68.94		
BR	Bendamustine (IV)	90mg/m^2	6 x 28-day cycles	2	2	£103.30	£1,727.36	£667.14
	Rituximab (IV)	375mg/m^2		1	1	£1,624.06		
Cladribine+ rituximab	Cladribine (IV)	0.14mg/Kg	4 x 28-day cycles	5	5	£1,525.20	£3,149.26	£1,334.29
	Rituximab (IV)	375mg/m^2		1	1	£1,624.06		
Cladribine	Cladribine (IV)	0.14mg/Kg	4 x 28-day cycles	5	5	£1,525.20	£1,525.20	£1,111.91
Rituximab	Rituximab (IV)	375mg/m^2	4 x 7-day cycles	4	4	£6,496.24	£6,496.24	£889.53
Chlorambucil	Chlorambucil (oral)	0.2mg/Kg	6 x 28-day cycles	7	0	£89.31	£89.31	£0.00
Chlorambucil + rituximab	Rituximab (IV)	375mg/m^2	6 x 28-day cycles	1	1	£1,624.06	£1,713.37	£222.38
	Chlorambucil (oral)	0.2mg/Kg		7	0	£89.31		

RDI – relative dose intensity; IV – intravenous

** One clinical advisor stated that they use an alternative FCR regimen including oral fludarabine 24mg/m^2 (days 1-5) and oral cyclophosphamide 150mg/m^2 (days 1-5)*

Exploratory analysis 2 – Correction of apparent errors surrounding follow-up costs

As noted in Section 5.3.3 (critical appraisal point 2), the company's model includes unexplained anomalies in the calculation of follow-up costs in the third- and fourth-line progression-free and BSC states. The ERG amended the model such that the costs of follow-up by year are the same irrespective of line of therapy (see Table 60).

Table 60: Routine follow-up costs applied in the ERG exploratory analysis

Parameter	**Annual resource use**		
	Years 1-2	**Years 3-5**	**Year 6+**
Annual total cost	£833.75	£667.00	£500.25
Cost per cycle	£63.92	£51.13	£38.35

Exploratory analysis 3 – Use of ibrutinib pre-progression mortality rate from Study 1118E

The company's model uses age- and sex-adjusted general population mortality rates to describe the proportion of patients leaving the progression-free state who die during each cycle. The ERG has concerns regarding this assumption (see Section 5.3.3, critical appraisal point 5). The ERG notes that the mortality rate observed within Study 1118E was consistently higher than the age- and sex-adjusted general population life table estimate. Within this exploratory analysis, the ERG estimated the pre-progression mortality rate based on the number of events, the number of patients and mean number of years of patient exposure (1-year probability = 0.025). This probability was converted to an instantaneous rate (λ=0.0019); pre-progression mortality was then modelled using an exponential distribution using this rate.

Exploratory analysis 4 – ERG's preferred base case analysis

The ERG preferred base case incorporates Exploratory Analyses 1, 2 and 3. This analysis was undertaken using both the probabilistic and the deterministic version of the company's model. The ERG notes that company's implementation of PSA is incomplete; this has not been resolved by the ERG. As such, the probabilistic ICER does not fully reflect the uncertainty surrounding the cost-effectiveness of ibrutinib.

Exploratory analysis 5 - Use of alternative BSC utility value (using ERG's base case)

The company's model assumes a utility value of 0.665 in the BSC state, based on the RESONATE trial.[16] However, clinical advisors to the ERG considered that this may represent an over-estimate as patients receiving BSC alone tend to have a lower level of HRQoL (although the ERG notes that there are no empirical HRQoL data in WM to either confirm or refute this). Within this analysis, the utility score for BSC was amended to a lower value of 0.50, based on clinical advice.

Exploratory analysis 6 – Use of alternative HR for PFS of [redacted] from company's repeated Cox analysis (using ERG's base case)

As noted in Section 4.4, the company's approach to the creation of a matched sample from the European chart review does not lead to a unique solution, and different matched samples of patients lead to different HRs. Within this analysis, company's estimated HR of [redacted] from the alternative matched sample cohort from the European chart review (see clarification response,[14] question B30) was applied in the model.

Exploratory analysis 7 – Assumption of equivalent pre-progression mortality for ibrutinib and rituximab/chemotherapy (using ERG's base case)

Given the uncertainty surrounding the survival benefits of ibrutinib, a pessimistic exploratory analysis was undertaken assuming that the pre-progression mortality curve for the ibrutinib group is the same as that for the rituximab/chemotherapy group (based on the log normal function applied in the company's base case).

Exploratory analysis 8 - Use of alternative costs for rituximab/chemotherapy (using ERG's base case)

Within this analysis, the cost of second-line rituximab/chemotherapy was assumed to reflect the least expensive comparator regimen (chlorambucil monotherapy, cost per 6-cycles = £535.86).

Exploratory analysis 9 - Use of the Weibull distribution for pre-progression mortality for rituximab/chemotherapy (using ERG's base case)

Within this analysis, the company's Weibull distribution was applied to model pre-progression mortality in rituximab/chemotherapy arm. The ERG was unable to assess the impact of alternative survivor functions for pre-progression mortality as these were not included in the company's model. In addition, the company's model only includes Weibull and log normal functions for PFS; given that the treatment effect is an HR, it is not appropriate to apply this to an accelerated failure time model. As the company's model does not include any other parametric functions for PFS, the ERG was also unable to explore the impact of using any distribution other than the log normal and the Weibull.

Exploratory analysis 10 – Threshold analysis around HR for PFS

Within this exploratory analysis, the HR for PFS for ibrutinib versus rituximab/chemotherapy was varied within the range 0.01 to 1.00.

5.4.2 Results of additional analyses undertaken by the ERG

Exploratory analysis 1 – Re-estimation of drug acquisition and administration costs

Table 61 presents the results of the exploratory analysis which includes the re-estimation of the drug acquisition and administration costs. Within this analysis, the total treatment costs are reduced in both groups compared with the company's base case. The revised costing has only a marginal impact on the model results; based on this analysis, the ICER for ibrutinib versus rituximab/chemotherapy is estimated to be £57,878 per QALY gained. This is slightly lower than the company's base case ICER for ibrutinib versus rituximab/chemotherapy of [redacted] per QALY gained.

Table 61: Exploratory Analysis 1 - Re-estimation of drug acquisition and administration costs

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£57,878**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

QALY - quality-adjusted life year

Exploratory Analysis 2 - Correction of apparent errors surrounding follow-up costs

Table 62 presents the results of an analysis in which the follow-up costs are assumed to be independent of line of therapy. As expected, the use of the amended follow-up costs (which are higher than those used in the company's model) increases the total costs in both groups. However, these cost differences have only a marginal impact on the model results; based on this analysis, the ICER for ibrutinib versus rituximab/chemotherapy is estimated to be £58,831 per QALY gained.

Table 62: Exploratory Analysis 2 - Correction of apparent errors surrounding follow-up costs

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£58,831**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

QALY - quality-adjusted life year

Exploratory Analysis 3 - Use of ibrutinib pre-progression mortality rate from Study 1118E

Table 63 presents the results of the exploratory analysis in which pre-progression mortality in the ibrutinib group is based on the rate observed within Study 1118E.[11] As expected, the use of a higher mortality rate reduces the total QALY gain in the ibrutinib group whilst also reducing the total costs. Within this scenario, the ICER for ibrutinib versus rituximab/chemotherapy is estimated to be £61,387 per QALY gained.

Table 63: Exploratory Analysis 3 - Use of ibrutinib pre-progression mortality rate from Study 1118E

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£61,387**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

QALY - quality-adjusted life year

Exploratory Analysis 4 – ERG-preferred base case

Table 64 presents the results of the ERG-preferred base case analysis. The probabilistic version of the model suggests that ibrutinib is expected to produce an additional [redacted] QALYs at an additional cost of [redacted] compared with rituximab/chemotherapy; the ICER for ibrutinib versus rituximab/chemotherapy is expected to be £61,219 per QALY gained. The results of the deterministic model are similar, with ibrutinib yielding an ICER of £61,050 per QALY gained compared with rituximab/chemotherapy.

Table 64: Exploratory Analysis 4 – ERG-preferred base case

Probabilistic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£61,219**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-
Deterministic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£61,050**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

QALY - quality-adjusted life year

Exploratory Analysis 5 - Use of alternative BSC utility value (using ERG's base case)

Table 65 presents the results of an analysis in which the utility score for BSC was assumed to be [redacted]. This increases the ICER for ibrutinib versus rituximab/chemotherapy to £63,340 per QALY gained.

Table 65: Exploratory Analysis 5 - Use of alternative BSC utility value (using ERG's base case)

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£63,340**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

QALY - quality-adjusted life year

Exploratory Analysis 6 - Use of alternative HR of [redacted] for PFS from company's repeated analysis (using ERG's base case)

Table 66 presents the results of an analysis using the higher HR for PFS of [redacted]. Within this analysis, the ICER is estimated to be £60,410 per QALY gained.

Table 66: ERG Exploratory Analysis 6 - Use of alternative HR of [redacted] for PFS from company's repeated analysis (using ERG's base case)

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£60,410**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

QALY - quality-adjusted life year

Exploratory Analysis 7 - Assumption of equivalent pre-progression mortality for ibrutinib and rituximab/chemotherapy (using ERG's base case)

Table 67 presents the results of the analysis in which pre-progression mortality is modelled using the same log normal distribution in both groups (thereby assuming no incremental survival gain for ibrutinib). This analysis results in a large reduction in the incremental QALY gain and hence and marked increase in the ICER. Under this pessimistic scenario, the ICER for ibrutinib versus rituximab/chemotherapy is estimated to be £390,432 per QALY gained.

Table 67: Exploratory Analysis 7 - Assumption of equivalent pre-progression mortality for ibrutinib and rituximab/chemotherapy (using ERG's base case)

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£390,432**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

QALY - quality-adjusted life year

Exploratory Analysis 8 - Use of alternative costs for rituximab/chemotherapy (using ERG's base case)

Table **68** presents the results of an analysis in which the treatment costs for rituximab/chemotherapy reflect the least expensive regimen (chlorambucil monotherapy). Within this analysis, the ICER for ibrutinib versus rituximab/chemotherapy is estimated to be £64,233 per QALY gained.

Table 68: Exploratory Analysis 8 - Use of alternative costs for rituximab/chemotherapy (using ERG's base case)

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£64,233**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

QALY - quality-adjusted life year

Exploratory Analysis 9 - Use of the Weibull distribution for pre-progression mortality for rituximab/chemotherapy (using ERG's base case)

Table 69 presents the results of an analysis in which the pre-progression mortality curve for rituximab/chemotherapy is modelled using the Weibull function. The use of this alternative survivor function increases the ICER for ibrutinib versus rituximab/chemotherapy to £64,628 per QALY gained.

Table 69: Use of the Weibull distribution for pre-progression mortality for rituximab/chemotherapy (using ERG's base case)

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£64,628**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

QALY - quality-adjusted life year

ERG Exploratory analysis 10 – Threshold analysis around HR for PFS

Figure 21 presents a range of ICERs for ibrutinib versus rituximab/chemotherapy based on an HR for PFS range of 0.01 to 1.00. This analysis suggests that based on the ERG's base case assumptions, the lowest possible deterministic ICER for ibrutinib versus rituximab/chemotherapy is estimated to be £59,620 per QALY gained (HR for PFS~[redacted]). Under the company's more favourable scenario which is based on general population mortality rates, the lowest possible deterministic ICER for ibrutinib versus rituximab/chemotherapy is estimated to be £56,917 per QALY gained (HR for PFS~[redacted]).

Figure 21: ERG Exploratory analysis 10 – Threshold analysis around HR for PFS

ICER – incremental cost-effectiveness ratio

5.5 Discussion

The CS includes a systematic review of published economic evaluations of treatments for WM together with a *de novo* health economic evaluation of ibrutinib versus rituximab/chemotherapy in adult patients with R/R WM. The company's review did not identify any full economic evaluations relating to ibrutinib or any other therapy for WM.

The company's *de novo* economic model adopts a sequence-based Markov approach to estimate the costs and health outcomes for ibrutinib versus rituximab/chemotherapy for patients with R/R WM from the perspective of the NHS and PSS over a 30-year (lifetime) horizon. The company's model includes five health states: (1) second-line progression-free; (2) third-line progression-free; (3) fourth-line progression-free; (4) BSC, and; (5) dead. The model uses parametric curves fitted to data on PFS, time to progression, pre-progression mortality and post-progression survival to inform transition rates between the health states. Transitions between states are modelled according to a 28-day cycle length (392 cycles). Patients enter the model in the second-line progression-free state and receive treatment with ibrutinib or rituximab/chemotherapy. Within the ibrutinib group, the probability of being progression-free at any time *t* is modelled using a parametric (Weibull) survivor function fitted to the empirical PFS data from Study 1118E.[11] Within the ibrutinib group, the probability that a patient leaving the second-line progression-free state dies during a given interval is modelled using age- and sex-adjusted general population mortality hazards derived from life tables. Within the rituximab/chemotherapy group, PFS in second-line is modelled using the inverse of the HR derived

from the multivariable Cox model applied to the ibrutinib PFS curve, whilst the probability that a patient leaving the second-line progression-free state dies is modelled using pre-progression mortality data derived from the matched European chart review cohort (1-4 prior lines of therapy).[9] Within both treatment groups, progression events in the third- and fourth-line progression-free states were estimated using data from the European chart review for patients who were starting fourth-line treatment, whilst the probability of death in all post-second-line progression-free states was based on data from the European chart review for patients who had progressed from third-line treatment.[9] A proportion of patients transit directly to BSC after progressing from each line of therapy. HRQoL is differentiated according to the presence/absence of disease progression, with a higher baseline utility value applied to each of the progression-free states compared with the BSC state. Disutilities associated with AEs are included only for second-line treatment; AEs associated with active subsequent-line treatment are not included in the model. The company's model includes costs associated with: (i) drug acquisition; (ii) drug administration (applied to the rituximab/chemotherapy regimens only); (iii) routine follow-up; (iv) the management of AEs; (v) BSC, and; (vi) terminal care.

Based on a re-run of the probabilistic version of the company's base case model by the ERG, ibrutinib is expected to produce an additional [redacted] QALYs at an additional cost of [redacted] compared with rituximab/chemotherapy; the ICER for ibrutinib versus rituximab/chemotherapy is expected to be £58,905 per QALY gained. The results of the deterministic model are similar, with ibrutinib yielding an ICER of £58,630 per QALY gained compared with rituximab/chemotherapy. Assuming a WTP threshold of £30,000 per QALY gained, the company's base case model suggests that the probability that ibrutinib produces more net benefit than rituximab/chemotherapy is approximately zero. The company's DSAs and scenario analyses indicate that the ICER for ibrutinib versus rituximab/chemotherapy is expected to be greater than £47,000 per QALY gained across all analyses.

The ERG critically appraised the company's economic analysis and partially double-programmed the deterministic version of the company's model. The ERG's critical appraisal identified several issues relating to the company's economic analysis and the evidence used to inform it. The most pertinent of these included: (i) the absence of any economic analysis of ibrutinib for treatment-naïve patients in whom chemo-immunotherapy is unsuitable; (ii) concerns regarding the company's modelling approach, in particular the use of a sequence-based model, the modelling of death conditional on PFS, and the mismatch between the evidence required for the model and the evidence available for the appraisal; (iii) ambiguity surrounding the data used to inform pre-progression mortality for rituximab/chemotherapy (iv) the company's use of general population life tables to model pre-progression mortality within the ibrutinib group; (v) the limited evidence to quantify the health gains associated with ibrutinib versus any other WM therapy; (vi) model errors and inconsistencies surrounding costs, and; (vii) the incomplete characterisation of uncertainty.

The ERG undertook ten sets of exploratory analyses using the company's submitted model. The ERG's preferred base case involved re-estimating drug acquisition and administration costs, rectifying an apparent error in the follow-up costs and applying the pre-progression mortality rate observed within Study 1118E to the ibrutinib group. The remaining exploratory analyses focussed on assessing the uncertainty surrounding the utility score for the BSC state, the HR for the effect of ibrutinib on PFS, the costs of rituximab/chemotherapy, the parametric function used to model pre-progression mortality for rituximab/chemotherapy and removing the modelled survival benefit for ibrutinib. As a consequence of concerns regarding the company's model structure and use of evidence therein, as well as uncertainty surrounding which data have been used to inform pre-progression mortality in the rituximab/chemotherapy group, the ERG advises that all analyses should be interpreted with caution.

The ERG's preferred analysis resulted in an ICER for ibrutinib versus rituximab/chemotherapy of £61,219 per QALY gained. The other exploratory analysis did not produce markedly different ICERs, with the exception of the scenario in which the survival gains for ibrutinib were removed from the model; within this analysis, the ICER for ibrutinib versus rituximab/chemotherapy was increased to £390,432 per QALY gained. The ERG's threshold analysis around the HR for the effect of ibrutinib on PFS suggests that under the ERG's base case assumptions, the lowest possible deterministic ICER for ibrutinib versus rituximab/chemotherapy is estimated to be £59,620 per QALY gained (HR~ [redacted]). Under the company's more favourable scenario which is based on general population pre-progression mortality rates, the lowest possible deterministic ICER for ibrutinib versus rituximab/chemotherapy is estimated to be £56,917 per QALY gained (HR~[redacted]).

The CS notes that the current evidence base is uncertain and that further data collection is required to address this uncertainty. The CS (Section 7) requests the inclusion of ibrutinib on the CDF and presents details regarding the establishment of a proposed MEA put forward by the company, based on the collection of additional evidence as an "add-on" to the Rory Morrison WM UK Clinical Registry (sponsored and owned by University College London Hospital). The CS states that this registry will collect, *inter alia*, data on demographics, characteristics of diagnosis and testing, treatments, symptoms of the disease and treatments given (across a number of lines of treatment from newly diagnosed to up to 8 lines of therapy), survival status, comorbidities, and Cumulative Illness Rating Scale-Geriatric (CIRS-G). The CS states that this registry will provide address five areas of uncertainty in the current evidence base:

- 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. The proposed instrument is not fully specified in the CS, although the FACT-Lym and EQ-5D are mentioned.

- Data on comparative effectiveness. The CS contains few details relating to this aspect of data collection and limited information is provided regarding how these data could be used to estimate the relative effectiveness of ibrutinib versus other treatments for WM.
- 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. No specific details are given, except that the CS states that the registry already collects data on first-line treatments for WM.

The CS states that the company will ensure that sufficient funding is available to the registry to collect and quality assure the required data and analysis to successfully deliver the proposal in time for a review of the NICE guidance on the use of ibrutinib in WM. The CS also states that the company would aim to also include any follow-up data from Study 118E[11] that becomes available during the course of the data collection period as well as relevant data from Arm C of the iNNOVATE trial[23] to further substantiate the evidence base.

With respect to the company's proposed MEA, the ERG agrees that the evidence base is highly uncertain. The ERG also advocates the collection of further data, provided that the collection of such data is valuable in terms of reducing decision uncertainty. Within the company's model, the OS trajectory for ibrutinib was based on general population life tables on the basis that there were only 3 events over the available follow-up period of Study 1118E.[11] As shown in the ERG's exploratory analyses, the difference in the pre-progression survival trajectories for ibrutinib and rituximab/chemotherapy is the key driver of cost-effectiveness; a less favourable survival trajectory for ibrutinib has the propensity to dramatically worsen the cost-effectiveness of ibrutinib relative to rituximab/chemotherapy. Importantly, the HR for the effect of ibrutinib PFS is not an influential parameter in the company's model; this may be explained in part by the company's questionable modelling approach. The ERG's exploratory threshold analyses suggest that even under the assumption of general population mortality whilst patients are receiving ibrutinib, the ICER for ibrutinib versus rituximab is not expected to be below £56,917 per QALY gained, irrespective of the HR for PFS. Other things being equal, this represents the best case scenario for the cost-effectiveness of ibrutinib versus rituximab/chemotherapy in the R/R WM setting. The ERG therefore considers it unlikely that further data collection will lead to a more favourable cost-effectiveness profile for ibrutinib.

6. END OF LIFE

The CS does not make a case that ibrutinib meets NICE's criteria for life extending therapies given at the end of life.[45]

7. DISCUSSION

Clinical effectiveness evidence

The CS reports results from three reviews: (i) a review of the efficacy and safety evidence from non-randomised and non-controlled studies; (ii) a review of efficacy evidence with the intention of informing an indirect comparison, and; (iii) a review of safety evidence from randomised and non-randomised studies in trials of ibrutinib in different populations. The reviews of the clinical efficacy and safety evidence were poorly reported and there was a lack of high quality evidence. There was no RCT or non-randomised controlled trial of ibrutinib in the relevant WM populations outlined in the final NICE scope. No empirical clinical evidence was submitted on treatment-naïve patients with WM who were unsuitable for chemo-immunotherapy. The clinical evidence consisted of one Phase II, single-arm, open-label study of ibrutinib in 63 adult patients with WM who had received at least one prior therapy: Study 1118E (PCYC-1118E). In this study, treatment was administered for a median of 19.1 months (range, 0.5 to 29.7 months) and 43/63 patients (68%) remained on treatment after the final DCO (19th December 2014). The median age of patients was 63.0 years (mean age = 64.5 years) and the majority were male (76.2%). The median time from diagnosis of WM to study entry was 76 months (range: 6 to 340 months). The median number of prior regimens was 2 (range: 1 to 9).

The principal efficacy outcomes were response and PFS. The reported ORR (any response) was 90.5% (95% CI 80.4% to 96.4%), which was achieved by 57/63 patients. Responders were categorised as follows: VGPR: n=10; PR: n=36; and minor response: n=11. The major response rate (defined as PR or better) was 73% (95% CI 60.3% to 83.4%). Based on data only available in the CSR, the Kaplan-Meier estimate for the event-free rate for all responders at 18 months was 80.9% (95% CI 64.9% to 90.2%), and the corresponding values for major responders were 86.7% (95% CI 67.9% to 94.9%). The CS presents subgroup analyses of ORR and major response rate and reports that response rates were "consistent across most subgroups" (e.g. by age, ECOG score at baseline, IPSSWM risk score). The Kaplan-Meier curve estimates the rate of PFS at 24 months to be 69.1% (95% CI 53.2% to 80.5%). By the end of data collection (19th December 2014 DCO), 60 of the 63 patients were still alive and the estimated rate of OS was 95.2% (95% CI 86% to 98.4%).

Treatment with ibrutinib also resulted in a significant decline in median percentage of bone marrow infiltration from 60% to 25% ($p<0.001$). There was no correlation between serum IgM levels and bone marrow involvement at 6 months ($r=0.03$, $p=0.83$), but there was at 12 months ($r=0.51$, $p<0.001$) and 24 months ($r=0.56$, $p<0.008$). At baseline, adenopathy and splenomegaly were identified by CT in 37/63 (59%) and 7/63 (11%) patients, respectively, and the number of patients with lymphadenopathy and splenomegaly were reduced after ibrutinib treatment. The CS concludes that, in terms of efficacy, the clinical data demonstrated benefit for the 63 patients with R/R WM

treated with ibrutinib. Treatment also resulted in rapid reduction in serum IgM and improvement in haemoglobin, reversing the principal underlying causes of treatment-related morbidities.

The ERG has a number of concerns about Study 1118E. It was generally well-reported but was at high risk of selection, performance and detection bias, not only on account of its study design but because of inadequate reporting of outcome measurement. The trial had only 63 patients, who were generally younger and had less severe disease than the R/R adults with WM who might routinely present in practice England. The outcome measures used were generally valid and reliable but the response criteria (the primary outcome) were "modified" from international standards and limited to serum IgM level only. The ERG notes that IgM response alone is insufficient as an outcome for WM.

Given the absence of randomised head-to-head evidence comparing ibrutinib versus any other WM treatment, the CS presented an adjusted arm-based indirect comparison of PFS data from Study 1118E and a matched cohort from a retrospective European chart review. This indirect comparison estimated the HR for PFS for ibrutinib versus standard therapies using a multivariable Cox model. The company's multivariable Cox model produced an estimated HR for PFS for ibrutinib versus standard therapies of [redacted]. The use of alternative imputation methods produced more favourable HRs for PFS ranging from [redacted] to [redacted]. The ERG has concerns regarding the reliability of this reported estimate of treatment effect, in particular: (i) the potential for unadjusted confounders; (ii) the lack of a unique matched sample from the chart review, and; (iii) the exclusion of patients who had received five or more prior lines of treatment. In addition, the CS does not contain an analysis of the relative survival benefits of ibrutinib versus any other therapy.

On account of the small number of patients (n=63) in Study 1118E, the CS also reported safety data from selected, supplementary studies in which patients with CLL or MCL received ibrutinib: RESONATE (PCYC-1112), RESONATE-2 (PCYC-1115), PCYC-1102, PCYC-1103 and PCYC-1104. AEs of any grade were very frequent in all trials: up to 100% of patients in any of the included studies experienced at least one AE and between 42% and 57% experienced the most frequent event, diarrhoea. Grade 3 and 4 AEs were experienced by 49% and 57% of patients in Study 1118E and RESONATE, respectively. The grade 3 and 4 events that occurred most often in Study 1118E were: neutropenia (14% of patients); thrombocytopenia (13%), and; pneumonia (8%). The findings of the supplementary studies were generally consistent with those of Study 1118E in terms of type and frequency of grade 3 and 4 AEs ($\geq$2%). In Study 1118E, 6 out of 63 patients (10%) discontinued treatment due to AEs (not including disease progression). The other ibrutinib studies reported a rate of between 4% and 11% discontinuation due to AEs. The proportion of deaths within the ibrutinib arms

of the included trials ranged from 2% to 11% but, according to the studies, none of the deaths were related to ibrutinib.

There is one single ongoing study: PCYC-1127-CA (iNNOVATE) (NCT02165397), an international (including UK), multi-centre, Phase III trial evaluating the safety and efficacy of ibrutinib in combination with rituximab in patients with WM, which includes a third arm of ibrutinib monotherapy, an open-label sub-study for 31 patients who are refractory to rituximab. The estimated study completion date is January 2019.

Cost-effectiveness evidence

Based on a re-run of the probabilistic version of the company's base case model by the ERG, ibrutinib is expected to produce an additional [redacted] QALYs at an additional cost of [redacted] compared with rituximab/chemotherapy; the ICER for ibrutinib versus rituximab/chemotherapy is expected to be £58,905 per QALY gained. The results of the deterministic model are similar, with ibrutinib yielding an ICER of £58,630 per QALY gained compared with rituximab/chemotherapy. Assuming a WTP threshold of £30,000 per QALY gained, the company's base case model suggests that the probability that ibrutinib produces more net benefit than rituximab/chemotherapy is approximately zero. The company's DSAs and scenario analyses indicate that the ICER for ibrutinib versus rituximab/chemotherapy is expected to be greater than £47,000 per QALY gained across all analyses.

The ERG critically appraised the company's economic analysis and partially double-programmed the deterministic version of the company's model. The ERG's critical appraisal identified several issues relating to the company's economic analysis and the evidence used to inform it. The most pertinent issues included: (i) the absence of any economic analysis of ibrutinib for treatment-naïve patients in whom chemo-immunotherapy is unsuitable; (ii) concerns regarding the company's modelling approach, in particular the use of a sequence-based model, the modelling of death conditional on PFS, and the mismatch between the evidence required for the model and the evidence available for the appraisal; (iii) ambiguity surrounding the data used to inform pre-progression mortality for rituximab/chemotherapy (iv) the company's use of general population life tables to model pre-progression mortality within the ibrutinib group; (v) the limited evidence to quantify the health gains associated with ibrutinib versus any other WM therapy; (vi) model errors and inconsistencies surrounding costs, and; (vii) the incomplete characterisation of uncertainty.

The ERG undertook ten sets of exploratory analyses using the company's submitted model. The ERG's preferred base case involved re-estimating drug acquisition and administration costs, rectifying an apparent error in the follow-up costs and applying the pre-progression mortality rate observed

within Study 1118E to the ibrutinib group. The remaining exploratory analyses focussed on assessing the uncertainty surrounding the utility score for the BSC state, the HR for PFS, the costs of rituximab/chemotherapy, the parametric function used to model pre-progression mortality for rituximab/chemotherapy and removing the modelled survival benefits for ibrutinib. As a consequence of concerns regarding the company's model structure and use of evidence therein, the ERG advises that these analyses should be interpreted with caution.

The ERG's preferred analysis resulted in an ICER for ibrutinib versus rituximab/chemotherapy of £61,219 per QALY gained. The other exploratory analysis did not produce markedly different ICERs, with the exception of the scenario in which the survival gain for ibrutinib was removed from the model; within this analysis, the ICER for ibrutinib versus rituximab/chemotherapy was increased to £390,432 per QALY gained. The ERG's threshold analysis around the HR for PFS suggests that under the ERG's base case assumptions, the lowest possible deterministic ICER for ibrutinib versus rituximab/chemotherapy is estimated to be £59,620 per QALY gained (HR~[redacted]). Under the company's more favourable scenario which is based on general population pre-progression mortality rates, the lowest possible deterministic ICER for ibrutinib versus rituximab/chemotherapy is estimated to be £56,917 per QALY gained (HR~[redacted]).

The CS requests the inclusion of ibrutinib on the CDF and presents details regarding a proposed MEA including additional data collection around clinical outcomes for treatment-naïve and R/R WM patients, HRQoL, and resource use. The ERG's exploratory threshold analyses suggest that even under the assumption of general population mortality, the ICER for ibrutinib versus rituximab is not expected to be below £56,917 per QALY gained, irrespective of the HR for PFS. Other things being equal, this represents the best case scenario for the cost-effectiveness of ibrutinib versus rituximab/chemotherapy in the R/R WM setting. The ERG therefore considers it unlikely that further data collection will lead to a more favourable cost-effectiveness profile for ibrutinib.

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Appendix 1: Cost-effectiveness results using ibrutinib list price

Table 70: Central estimates of cost-effectiveness

Probabilistic model*					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	2.26	£177,916	**£78,898**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-
Deterministic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	2.18	£171,430	**£78,647**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

** Produced from a re-run of the company's model by the ERG*

Figure 22: Cost-effectiveness plane – ibrutinib versus rituximab/chemotherapy

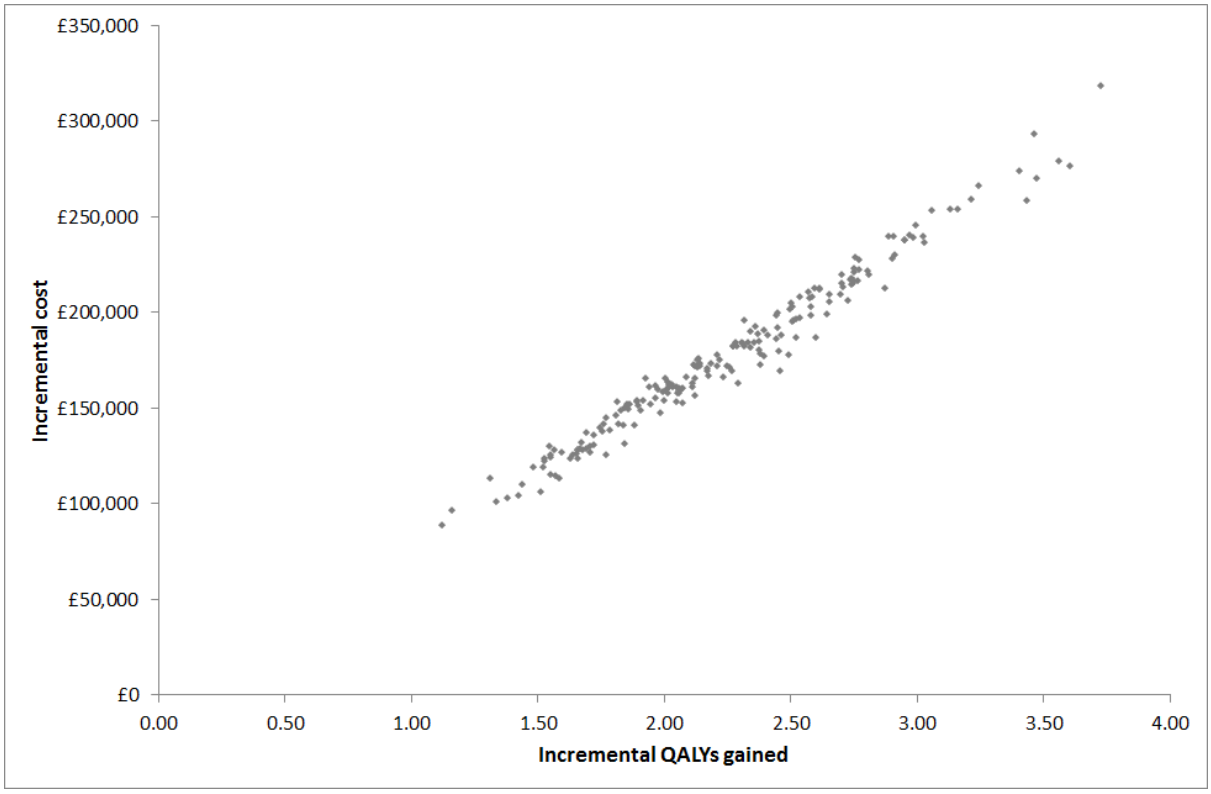


Figure 23: Cost-effectiveness acceptability curves – ibrutinib versus rituximab/chemotherapy

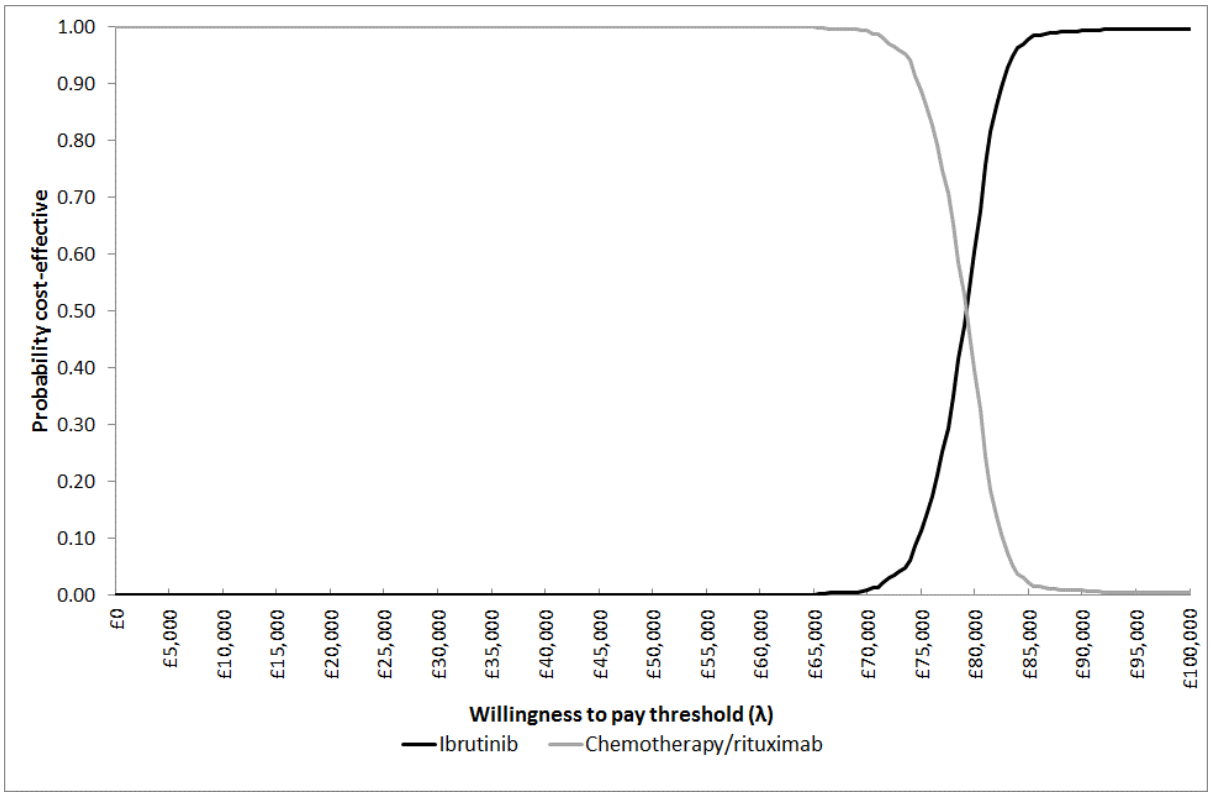


Figure 24: Deterministic sensitivity analysis tornado diagram (amended from company's model, not corrected by the ERG)

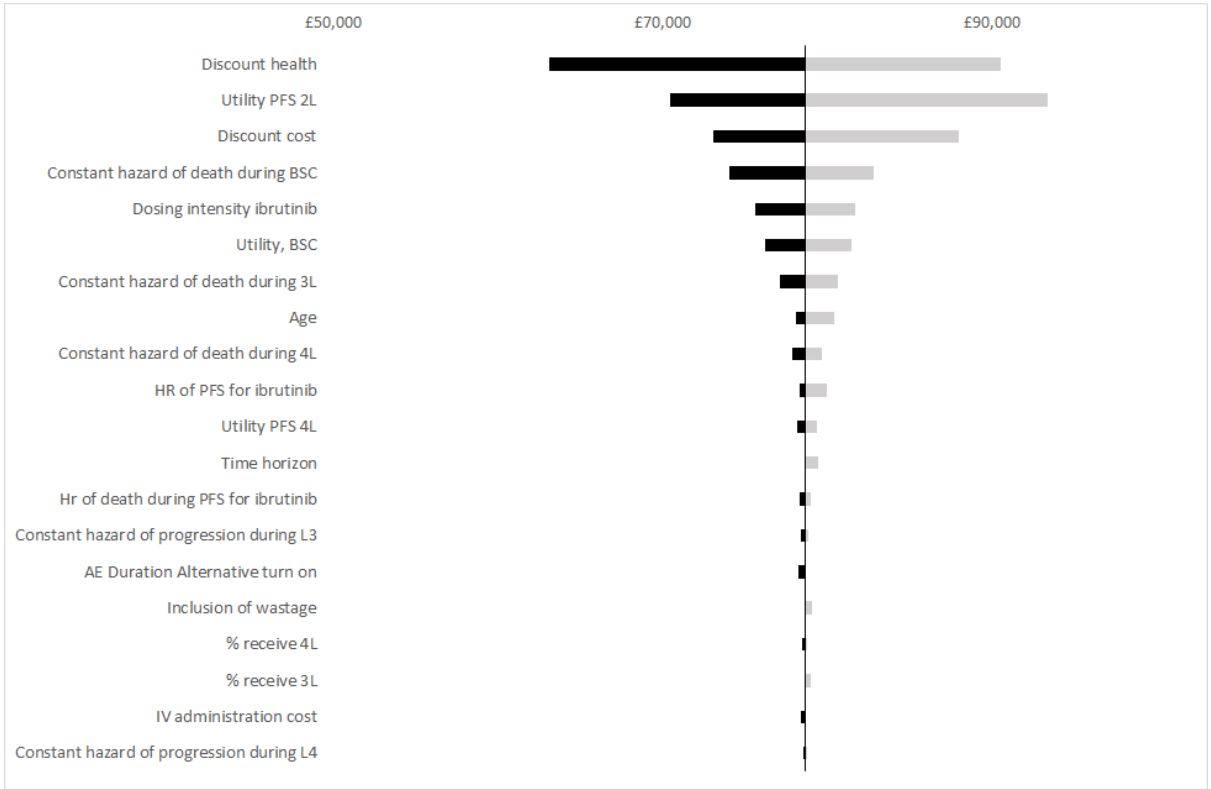


Table 71: Deterministic sensitivity analysis results (corrected by ERG)

Scenario	Base case value	Sensitivity analysis value	Incremental – ibrutinib versus rituximab/chemotherapy		
			Inc. QALYs	Inc. costs	ICER (per QALY gained)
Base case			[redacted]	[redacted]	£78,647
Discount health	3.5%	0%	[redacted]	[redacted]	£63,114
		6%	[redacted]	[redacted]	£90,531
Utility PFS 2L	0.799	0.62	[redacted]	[redacted]	£93,372*
		0.93	[redacted]	[redacted]	£70,456*
Discount cost	3.5%	0%	[redacted]	[redacted]	£87,952*
		6%	[redacted]	[redacted]	£73,091*
Constant hazard of death during BSC	[redacted]	[redacted]	[redacted]	[redacted]	£74,006
		[redacted]	[redacted]	[redacted]	£82,780
Dosing intensity ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	£75,647
		[redacted]	[redacted]	[redacted]	£81,648
Utility BSC	0.67	0.53	[redacted]	[redacted]	£81,489*
		0.79	[redacted]	[redacted]	£76,237*
HR of PFS for ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	£79,987*
		[redacted]	[redacted]	[redacted]	£78,296*
Constant hazard of death during 3L	[redacted]	[redacted]	[redacted]	[redacted]	£77,120
		[redacted]	[redacted]	[redacted]	£80,638
Utility PFS 3L	0.799	0.62†	[redacted]	[redacted]	£80,045
		0.93†	[redacted]	[redacted]	£77,648
Age	64.5	61.9	[redacted]	[redacted]	£78,078
		67.1	[redacted]	[redacted]	£80,385
Constant hazard of death during 4L	[redacted]	[redacted]	[redacted]	[redacted]	£77,846
		[redacted]	[redacted]	[redacted]	£79,667
Utility PFS 4L	0.799	0.62	[redacted]	[redacted]	£79,343*
		0.93	[redacted]	[redacted]	£78,142*
Time horizon	30 years	20	[redacted]	[redacted]	£79,413
		30	[redacted]	[redacted]	£78,647
Inclusion of wastage	Yes	No	[redacted]	[redacted]	£79,034*
		Yes	[redacted]	[redacted]	£78,647*
HR of death during PFS for ibrutinib	1	0.90	[redacted]	[redacted]	£78,311
		1.10	[redacted]	[redacted]	£78,987
Constant hazard of progression during 3L	[redacted]	[redacted]	[redacted]	[redacted]	£78,376*
		[redacted]	[redacted]	[redacted]	£78,849
Duration of AE disutility	14	180	[redacted]	[redacted]	£78,221
		14	[redacted]	[redacted]	£78,647
IV administration cost	£239	£239	[redacted]	[redacted]	£78,647*
		£389	[redacted]	[redacted]	£78,363*
Constant hazard of progression during 4L	[redacted]	[redacted]	[redacted]	[redacted]	£78,543
		[redacted]	[redacted]	[redacted]	£78,721
% receive 4L	70%	50%†	[redacted]	[redacted]	£78,467
		86%†	[redacted]	[redacted]	£78,791

2L – second-line; 3L – third-line; 4L – fourth-line; BSC – best supportive care; PFS – progression-free survival; HR – hazard ratio; AE – adverse event; IV – intravenous; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; inc. - incremental

** value reported in CS incorrect – corrected values produced by ERG*

† ranges reported in CS incorrect – corrected values applied to generate results

Table 72: Scenario analysis results

Scenario	Base case	Scenario analysis	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Base case			[redacted]	[redacted]	£78,647
Age adjustment for utilities	Yes	No	[redacted]	[redacted]	£75,986
Distribution for PFS of ibrutinib	Weibull	Log-logistic	[redacted]	[redacted]	£82,418
HR PFS in 2L. Imputed patient characteristics. No individual clinical measurement (risk category only)*	[redacted]	[redacted]	[redacted]	[redacted]	£78,865
HR PFS in 2L Scenario 2: sample with complete patient characteristics, no imputation. All Variable (individual clinical measurements & risk category)*	[redacted]	[redacted]	[redacted]	[redacted]	£79,137

** Results differ slightly from those reported within the CS due to a rounding error*

Appendix 2: ERG exploratory analysis results using list price for ibrutinib

Table 73: Exploratory analysis 1 – Re-estimation of drug acquisition and administration costs to remove errors and inconsistencies

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£77,896**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

Table 74: Exploratory analysis 2 – Correction of apparent errors surrounding follow-up costs

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£78,849**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

Table 75: Exploratory analysis 3 – Use of ibrutinib pre-progression mortality estimates observed within Study 1118E

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£82,581**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

Table 76: Exploratory analysis 4 – ERG's preferred base case (combining ERG exploratory analyses 1, 2 and 3)

Probabilistic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£82,441**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-
Deterministic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£82,245**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

Table 77: Exploratory analysis 5 - Use of an alternative utility value for BSC (using ERG's base case)

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£85,330**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

Table 78: Exploratory analysis 6 – Use of alternative HR of [redacted] for PFS from company's repeated analysis (using ERG's base case)

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£81,080**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

Table 79: Exploratory analysis 7 – Assumption equivalent pre-progression survival curves for ibrutinib and rituximab/chemotherapy (using ERG's base case)

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£542,578**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

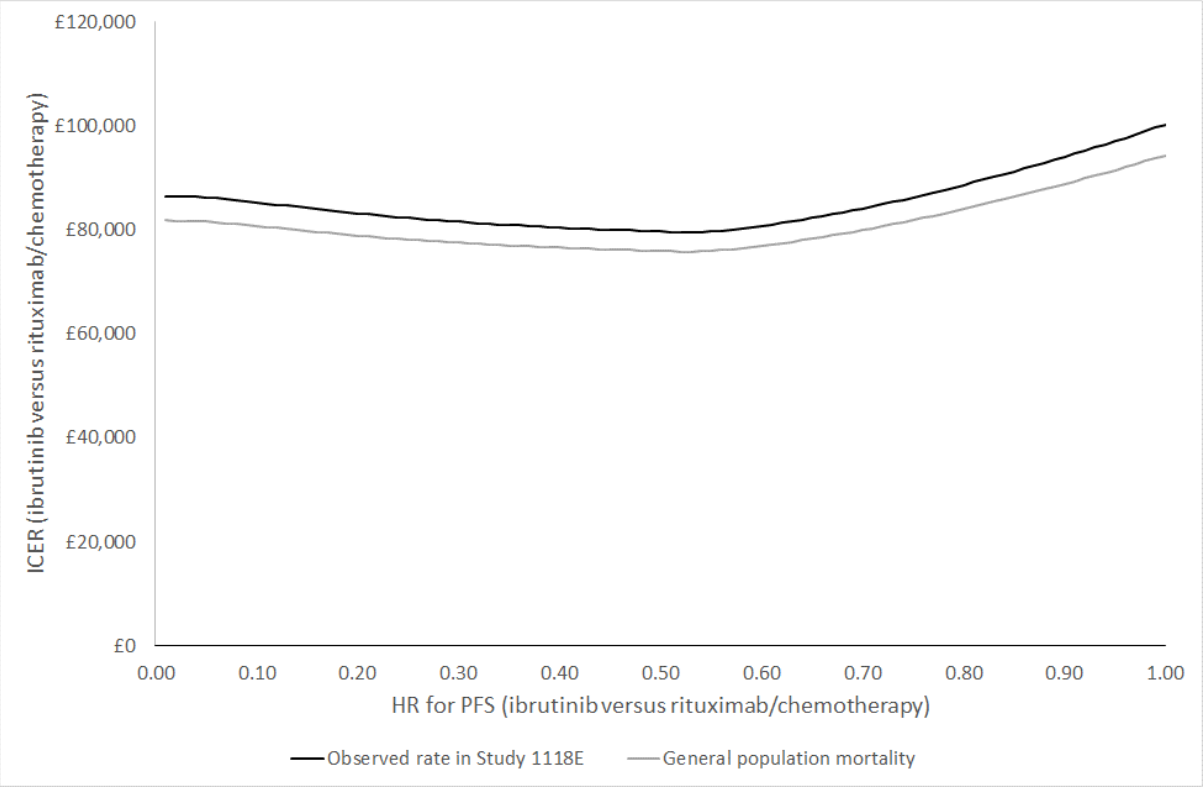
Table 80: Exploratory analysis 8 - Use of alternative costs for rituximab/chemotherapy (using ERG's base case)

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£85,428**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

Table 81: Exploratory analysis 9 - Use of the Weibull distribution for pre-progression mortality for rituximab/chemotherapy (using ERG's base case)

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£87,248**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

Figure 25: ERG Exploratory analysis 10 – Threshold analysis around HR for PFS



ICER – incremental cost-effectiveness ratio

Appendix 3: **Technical details for implementing ERG exploratory analyses**

Exploratory analysis 1 – Re-estimation of drug acquisition and administration costs to remove errors and inconsistencies
Go to the "Cost Inputs" worksheet
In cell G24 change the value to [redacted]
Go to the "Drug cost calc" worksheet
Change the values in cells DK12:DK17 to £2,527.74
Change the values in cells DL12:DL15 to £2,249.23, DL16 to £1,124.61 and DL17 to 0
Change the values in cells DM12:DM17 to £1,727.36
Change the values in cells DN12:DN15 to £3,149.26 and DN16:DN17 to 0
Change the values in cell DO12 to £2,456.03, DO13: DO15 to £831.97, DO16: DO17 to £450.67
Change the values in cell DP12 to £2,766.31, DP13: DP17 to £600.89
Change the values in cells DS12:DS17 to £222.38
Change the values in cells DT12:DT15 to £593.02, DT16 to £296.51 and DT17 to 0
Change the values in cells DU12:DU17 to £667.14
Change the values in cells DV12:DV15 to £1,334.29 and DN16:DN17 to 0
Change the values in cell DW12 to £555.96, DW13: DW15 to £333.57, DW16: DW17 to £55.60
Change the values in cell DX12 to £370.64, DX13: DX17 to £74.13
In cell DZ12 insert value 1
Fill down

Exploratory analysis 2 – Correction of apparent errors surrounding follow-up costs
Go to the "Cost Inputs" worksheet
In cell G24 change the value to [redacted]
Go to the "Parameter" worksheet
In cell F151 apply the following formula ='Cost Inputs'!I64
In cell F152 apply the following formula ='Cost Inputs'!I65
In cell F156 apply the following formula ='Cost Inputs'!K64
In cell F157 apply the following formula ='Cost Inputs'!K65
In cell F161apply the following formula ='Cost Inputs'!M64
In cell F162 apply the following formula ='Cost Inputs'!M65

Exploratory analysis 3 – Use of ibrutinib pre-progression mortality estimates observed within Study 1118E
Go to the "Cost Inputs" worksheet
In cell G24 change the value to [redacted]
Go to the "Clinical Data" worksheet
In cell R5 change the value to 0.00190864187654582
In cell R12 apply the following formula = MAX(lifetable!U8*ProbDeath_HR,R5)
Copy down

Exploratory analysis 4 – ERG's preferred base case (combining ERG exploratory analyses 1, 2 and 3)
Apply changes detailed in Exploratory Analyses, 1-3.

Exploratory analysis 5 - Use of an alternative utility value for BSC (using ERG's base case)
Use the model generated in Exploratory Analysis 4
Go to the "Utility" worksheet
In cell J15 change the value to 0.5

Exploratory analysis 6 – Use of alternative HR for PFS of [redacted] from company's repeated analysis (using ERG's base case)
Use the model generated in Exploratory Analysis 4
Go to the "Options" worksheet

In cell C13 change the value to [redacted]

Exploratory analysis 7 – Assumption equivalent pre-progression survival curves for ibrutinib and rituximab/chemotherapy (using ERG's base case)
Use the model generated in Exploratory Analysis 4
Go to the "Clinical Data" worksheet
In cell R12 apply the following formula =J12
Copy down

Exploratory analysis 8 - Use of alternative costs for rituximab/chemotherapy (using ERG's base case)
Use the model generated in Exploratory Analysis 4
Go to the "Drug cost calc" worksheet
Change the values in cells DK12:DO17 to £89.31
Change the values in cells DS12:DW17 to 0

ERG Exploratory analysis 9 - Use of the Weibull distribution for pre-progression mortality for rituximab/chemotherapy (using ERG's base case)
Use the model generated in Exploratory Analysis 4
Go to the "Clinical Inputs" worksheet
Choose Weibull from the drop-down menu in cell I20

ERG Exploratory analysis 10 – Threshold analysis around HR for PFS
Use the model generated in Exploratory Analysis 4
Go to the "Options" worksheet
Change the value in cell C13 in increments of 0.01 from 0.01 to 1

ERG Exploratory analysis using list price
Repeat the above analyses using the value in cell G24 in the "Cost Inputs" worksheet as 51.1

Ibrutinib for treating Waldenström's macroglobulinaemia: A Single Technology Appraisal

Erratum in response to the fact check

Produced by School of Health and Related Research (ScHARR), The University of Sheffield, UK

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5th September 2016

economic analysis focusses specifically patients with R/R WM who have received one prior line of therapy.

The comparator considered in the company's health economic model includes a blend of alternative second-line rituximab/chemotherapy options. Specifically, the model includes: (i) bendamustine and rituximab (BR); (ii) dexamethasone, rituximab and cyclophosphamide (DRC); (iii) fludarabine, cyclophosphamide and rituximab (FCR); (iv) cladribine and rituximab; (v) cladribine monotherapy; (vi) rituximab monotherapy; (vii) chlorambucil and rituximab, and; (viii) chlorambucil monotherapy. This set of options is broadly in line with the final NICE scope, with the exceptions that rituximab and fludarabine (without cyclophosphamide) is not considered as a treatment option and chlorambucil is assumed to be given either in combination with rituximab or as monotherapy (rather than only as monotherapy).

The CS presents analyses according to the following outcomes: overall survival (OS); progression-free survival (PFS); response rate; duration of response/remission; adverse events (AEs), and; health-related quality of life (HRQoL). With respect to the relative effectiveness of ibrutinib versus other treatments for WM, a comparison is only made in terms of PFS. OS gains associated with ibrutinib compared with rituximab/chemotherapy can be inferred from the company's health economic model but are not presented comparatively as part of the clinical evidence review within the CS. With the exception of pre-planned subgroup analyses of overall response and major response within Study 1118E, the CS does not contain any subgroup analyses.

The CS does not present an argument that ibrutinib satisfies NICE's End-of-Life criteria within the WM indication. Within the CS, the company requests that ibrutinib is included on the Cancer Drug Fund (CDF) and sets out a proposed managed entry agreement (MEA) including the collection of additional data.

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS identified one relevant single-arm study. In Study 1118E, 63 previously-treated adult patients with WM from across three sites in the USA were allocated to receive the licensed 420mg/day dose. Treatment was administered for a median of 19.1 months (range, 0.5 to 29.7 months) and 43/63 patients (68%) remained on treatment after the final data cut-off (DCO) on 19th December 2014. The median age was 63.0 years (mean age = 64.5 years); the majority of patients were male (76.2%). The median time from diagnosis of WM to study entry was 76 months (range: 6 to 340 months). The median number of prior regimens was 2 (range: 1 to 9).

The principal efficacy outcomes were response and PFS. The reported overall response rate (ORR,

rituximab/chemotherapy can be inferred from the company's health economic model but are not presented comparatively as part of the clinical evidence base within the CS.

3.5 Economic analysis

The CS[1] includes the methods and results of a *de novo* model-based health economic analysis to assess the incremental cost-effectiveness of ibrutinib versus a blended comparator of rituximab/chemotherapy regimens for the second-line treatment of adults with R/R WM. As stated in Section 3.1, no economic analysis is presented for the first-line treatment of adults with WM for whom chemo-immunotherapy is unsuitable. The company's health economic analysis is detailed and critiqued in Chapter 5.

3.6 Subgroups

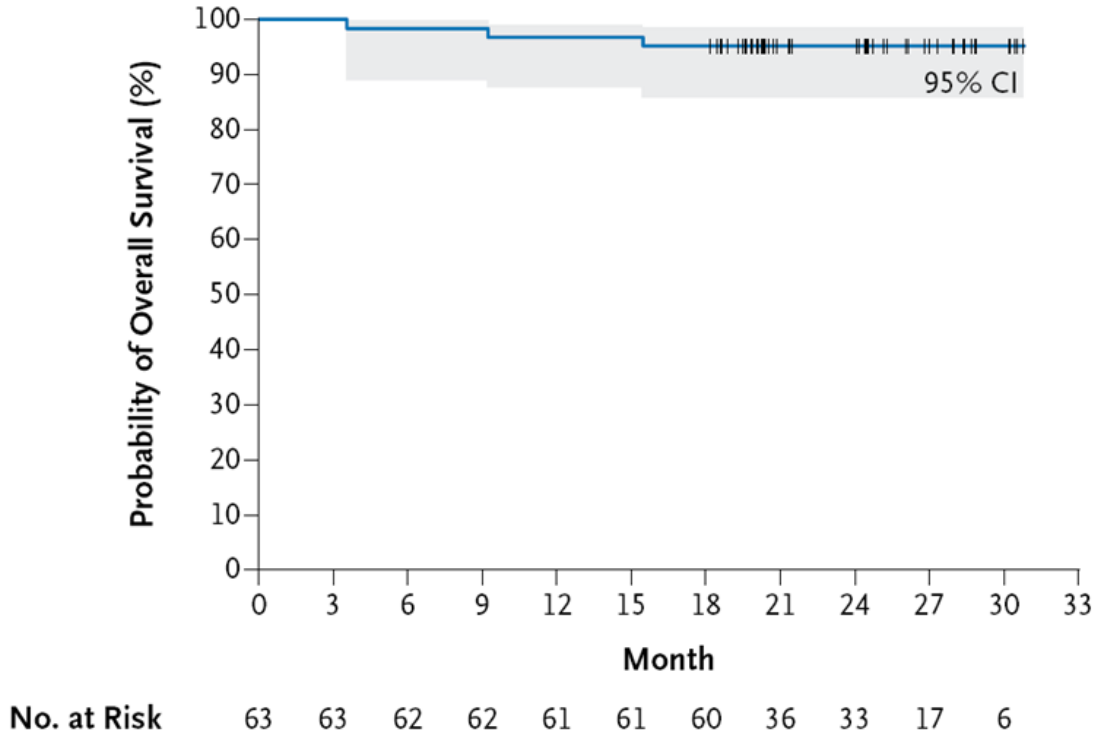
With the exception of pre-planned subgroup analyses of overall response and major response within Study 1118E (see CS[1] pages 47-48), the CS does not contain any subgroup analyses.

3.7 Special considerations

The CS notes that WM is a disease of the elderly and that the current most effective therapies are generally more suitable for younger fitter patients. Given that such treatments are toxic or immunosuppressive, these may be unsuitable for patients with a poor performance status and/or significant comorbidities. The CS also highlights that patients are currently managed with off-label treatments that do not target disease-specific abnormalities, but which are generally aimed at managing disease symptoms.

The CS does not present an argument that ibrutinib satisfies NICE's End-of-Life criteria within the WM indication. Within the CS, the company requests that ibrutinib is included on the CDF and sets out a proposed managed entry agreement (MEA) including additional data collection; this is discussed further in Section 5.5.

Figure 1: Kaplan-Meier curve of OS in Study 1118E (reproduced from CS, Figure 11)



4.3 Additional study used to inform the company's indirect comparison

The CS includes an adjusted arm-based indirect comparison of patient-level data from Study 1118E and a European chart review study; the CS reports data from this study based on a published poster[29] and the company's data on file.

The European chart review was an analysis of retrospective observational data. Physicians retrospectively produced electronic records for WM patients. The inclusion criteria for the study were:

- Confirmed WM (International Workshop on WM (IWWM)-2 criteria[30]);
- Symptomatic disease at treatment initiation;
- Front-line treatment initiated January 2000 - January 2014;
- Availability of complete clinical/biologic evaluation at diagnosis/initial therapy.

The full chart review included 454 patients. Of these, patients were from: France (n=92); the UK (n=72); Germany (n=66); Spain (n=60); Italy (n=56); Greece (n=25); the Netherlands (n=25); Poland (n=21); Austria (n=19); and the Czech Republic (n=16). Baseline characteristics for the overall cohort and the UK cohort are summarised in **Error! Reference source not found.**.

4.4.2 Critique of the company's indirect comparison

The ERG acknowledges that that there are no RCTs in this patient population and that a conventional network meta-analysis is not possible. Consequently, in order to make inferences about relative treatment effects, it is necessary to consider alternative methods of analysis. To this end, the company made use of evidence from the European chart review[9] and attempted to adjust for important prognostic factors that could have affected the treatment effect. The ERG has a number of concerns regarding the company's indirect comparison.

(i) The indirect comparison method may not adjust for all potential confounders

The CS highlights that there was considerable variation in PFS between the countries included in the European chart review (see CS,[1] Table 19). In addition, whilst the matching process was based on matching the number of lines of therapy received by the cohort to Study 1118E, the multivariable Cox model does not include line of treatment as a factor. Overall, the ERG considers that other confounders may remain, hence the company's approach may not consider all sources of uncertainty that contribute towards an unbiased estimate of treatment effect.

(ii) Creation of the matched European chart review cohort

The methods used to select patients in the European chart review cohort are not clear. According to the CS, two criteria were employed in the creation of the matched dataset: *"(i) the same patient from the chart review was not allowed to be in two lines at the same time, and; (ii) the distribution across lines of therapy of the final subset of patients selected from the chart review matched the distribution of patients from Study 1118E"* (CS,[1] page 56). However, the ERG notes that the criteria applied to the matched European cohort do not define a unique sample of patients; there may be many combinations of patients who meet the company's matching criteria. In response to a request for clarification (question B30),[14] the company presented a sensitivity analysis using an alternative sample of patients who also met the matching criteria defined above. This analysis produced an HR of [redacted]; this is less favourable than the HR presented in the CS and the confidence interval is wider. The ERG thus has concerns regarding the reliability of this treatment effect estimate and whether it reflects the true uncertainty surrounding the treatment comparison.

(iii) Different definitions of disease progression in Study 1118E and the European chart review

The definition of progression differed between Study 1118E and the European chart review. The impact of this on the estimated treatment effect is unclear.

(iv) Reduced sample size for Study 1118E cohort

The CS notes that 16 patients in Study 1118E received five or more prior lines of treatment. The company's indirect comparison excluded these patients. Consequently, inferences should be made only with respect to this restricted patient population rather than all patients unless the treatment benefit can assumed to be independent of the number of prior lines of treatment. The ERG also notes that excluding patients from the analyses will lead to increased uncertainty surrounding the estimated treatment effect.

(v) Mismatch between the estimated treatment effect and its application in the health economic model

The evidence used to inform the effect of ibrutinib versus rituximab/chemotherapy on PFS has been derived from cohorts of patients who had received between one and ~~three~~ four prior lines of therapy. However, within the company's health economic model, this treatment effect is applied to patients receiving second-line therapy (see Section 5.2). The assumption underlying the use of this HR in the model is that the number of prior lines of therapy received is not a treatment effect modifier; this assumption is however contradicted in the use of evidence to inform progression rates in the subsequent states of the model (see Section 5.3).

(vi) Use of the proportional hazards assumption

By definition, the company's Cox model assumes that the PFS hazard in the ibrutinib group is proportional to that in the matched European chart review cohort. This is a potentially strong assumption. In response to a request for clarification from the ERG (see clarification response,[14] question B27), the company confirmed that whilst not discussed in the CS, the proportional hazards assumption was tested between the PFS of ibrutinib in Study 1118E and the PFS of the matched European chart review cohort. The company's clarification response states that all statistical tests (visual examination of the log of negative log of estimated survivor functions and the Epanechnikov Kernel-smoothed hazard function, and the Kolmogorov-Smirnov test) showed that the proportionality assumption should not be rejected. However, the ERG notes that an absence of evidence against the proportionality assumption is not the same as evidence in support of it, and that the analysis is based on very few patients and events (**Error! Reference source not found.**). A consequence of making this assumption is to assume that the treatment effect is maintained for the lifetime of patients.

(vii) Treatment effect estimated only for PFS

The company's indirect comparison is limited to estimating an HR for PFS between Study 1118E and the European chart review cohort. However, as described in Section 5.2, the company's health economic model includes benefits of treatment both in terms of PFS and OS. It is unclear whether the company's matched indirect comparison approach could have been used to estimate the relative benefits of ibrutinib versus standard therapies on OS; given the limited number of events, it is likely

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page ix of ERG report: "The principal efficacy outcomes were response and PFS." Page 65 of ERG report: "The principal efficacy outcomes were response and PFS."	"The ~~principal~~ primary efficacy outcomes were overall response rate and major response rate. Secondary efficacy endpoints included PFS."	Clarification of primary and secondary endpoints explored in Study 1118E. This amendment is aligned with the answer provided by Janssen to ERG clarification question B17. The word "principal" may be confusing; it is important to clarify the difference between primary and secondary outcomes with respect to statistical powering. PFS was the only efficacy outcome from Study 1118E that was used as a model input in the economic section of the CS.	This is not a factual inaccuracy. Response is specified as the primary outcome on pages xi, 19, 24 (Table 8), 27 and 56 of the ERG report. The first line on page 26 of the ERG report specifies PFS as "the main secondary outcome"
The ERG referred to the modelled population and comparators as "second-line" whereas the population modelled (and consequently the comparators selected) relates to the broader relapsed/refractory (R/R) WM population, i.e. WM patients eligible for second-line and subsequent lines of therapy. Page ix of ERG report: "The comparator considered in the company's health	Replace "second-line" by "relapsed/refractory": Page ix of ERG report: "The comparator considered in the company's health economic model includes a blend of alternative ~~second-line~~ relapsed/refractory rituximab/chemotherapy options." Page 73 of ERG report: "The company's model assesses the cost-effectiveness of second-line ibrutinib versus a blend of ~~second-line~~ relapsed/refractory rituximab/chemotherapy options (referred to as "physician's choice" in the CS) for the treatment of patients with R/R	The population modelled was based on the population from Study 1118E, which received 1 to 9 lines of prior treatment; therefore it was not limited to patients having received 1 line of prior treatment i.e. second-line treatment only.	This is not a factual inaccuracy. The company's proposed amendment is misleading as the model relates specifically to the evaluation of alternative treatments in second-line, with different rituximab/chemotherapy options in subsequent lines. The fact that the data relate to patients who have received differing numbers of prior therapies reflects a mismatch between the model structure and the evidence used to populate it.

economic model includes a blend of alternative second-line rituximab/chemotherapy options." Page 73 of ERG report: "The company's model assesses the cost-effectiveness of second-line ibrutinib versus a blend of second-line rituximab/chemotherapy options (referred to as "physician's choice" in the CS) for the treatment of patients with R/R WM."	WM."		
Page 15 of ERG report: "The CS reports the methods and results of three reviews: (i) A review of the efficacy and safety evidence from non-randomised and non-controlled studies (see CS, Sections 4.1 and 4.10); (ii) A review of the efficacy evidence from randomised, non-randomised and non-	Page 15 of ERG report: "The CS reports the methods and results of ~~three~~ a systematic literature review~~s~~: ~~(i) A review~~ of the efficacy and safety evidence from ~~non-randomised and non-controlled~~ studies conducted in WM patients (see CS, Sections 4.1, ~~and~~ 4.10, 4.11, Appendices 1 and 2); ~~(ii) A review of the efficacy evidence from randomised, non-randomised and non-controlled studies for the purposes of an indirect comparison (see CS,~~	In two instances the ERG mentioned that three clinical reviews were presented by the manufacturer, while only one review, a systematic literature review (SLR), was conducted to identify clinical evidence (both efficacy and safety data): - The SLR presented in Sections 4.1 and 4.10 is the same review as that presented in Section 4.11, introducing the indirect comparison - As stated at the top of page 37 of CS and in eligibility criteria presented in Table 2 page 4 of Appendix 1 of the CS, the scope	This is not a factual inaccuracy. The ERG agrees that the search was for "studies conducted in WM patients", which covered both reviews, but the reviews were distinct. The first was a review of ibrutinib in WM patients, while the second was a review of ibrutinib and comparators in WM patients. The first is contained within the second, but is also distinct. They are thus reported in different sections (4.10 and 4.11). Re: the safety review. The description of (iii) is accurate and the situation regarding the additional five trials is described fully on page 45 of the ERG report: *"However, it is not clear how these additional studies were identified or selected by the company, or*

controlled studies for the purposes of an indirect comparison (see CS, Sections 4.1 and 4.11), and; (iii) A review of safety evidence from randomised and non-randomised studies, including five additional trials of ibrutinib in different populations (see CS, Section 4.12)." Page 149 of ERG report: The CS reports results from three reviews: (i) a review of the efficacy and safety evidence from non-randomised and non-controlled studies; (ii) a review of efficacy evidence with the intention of informing an indirect comparison, and; (iii) a review of safety evidence from randomised and non-randomised studies in trials of ibrutinib in different populations. The reviews of the clinical efficacy and	~~Sections 4.1 and 4.11), and;~~ ~~(iii) A review of safety evidence from randomised and non-randomised studies, including five additional trials of ibrutinib in different populations (see CS, Section 4.12).~~" The evidence base for the safety of ibrutinib in WM patients was substantiated by evidence from five ibrutinib trials conducted in CLL and MCL." Page 149 of ERG report: "The CS reports results from ~~three reviews: (i)~~ a systematic literature review of the efficacy and safety evidence from ~~non-randomised and non-controlled~~ studies conducted in WM patients; ~~(ii) a review of efficacy evidence with the intention of informing an indirect comparison, and; (iii) a review of safety evidence from randomised and non-randomised studies in trials of ibrutinib in different populations.~~ The evidence base for the safety of ibrutinib in WM patients was substantiated by evidence from five ibrutinib trials conducted in CLL and MCL.	of the SLR, in terms of outcomes, included both efficacy and safety outcomes in WM studies - No additional review was conducted, as part of this submission, to identify ibrutinib safety data *outside* the WM disease area; ibrutinib safety data reported in this submission for the chronic lymphocytic leukaemia (CLL) and mantle cell lymphoma (MCL) indications were taken from trials identified by the ongoing ibrutinib CLL [ID749] and MCL [ID753] NICE manufacturer submissions (see answer to ERG clarification question B31).	*whether further relevant studies have been excluded (one other study was included in the integrated dataset in the CHMP's consideration of safety [CS,[1] page 65]: 04753, a Phase 1, open-label, multicentre, dose-escalation study of ibrutinib in subjects with a variety of B-cell malignancies, including four subjects with previously treated WM). It is also unclear what processes were followed in the extraction and checking of data. Furthermore, no quality assessment of these studies is presented in the CS. In response to a request for clarification from the ERG (see clarification response,[14] question B31), the company reported that the identification and selection process for these additional studies was reported in the submissions for two other NICE appraisals (CLL - ID749 and MCL - ID753)."*

safety evidence were poorly reported and there was a lack of high quality evidence."	The reviews~~~~ of the clinical efficacy and safety evidence ~~were~~ was poorly reported and there was a lack of high quality evidence."		
The description of the sensitivity analyses conducted around the primary indirect comparison (IDC) analysis, and in particular the description of the second sensitivity analysis, is unclear. Page 46 of ERG report: "The CS also presents two sensitivity analyses using the Cox model based on alternative imputation approaches: (i) no imputation (n=89), and; (ii) imputation, no individual clinical measurement."	The manufacturer suggests taking the wording directly from the CS (page 58): "Two sensitivity analyses were conducted in addition to the primary analysis: i. Cox regression analysis based on the matched chart review cohort that excluded patients with missing data (i.e., n = 86 patients were excluded and the remainder with complete data, n=89, were included) ii. Cox regression analysis based on the full matched chart review cohort (n = 175), in which missing data were imputed using a subset of the covariates used in the primary analysis, i.e. using risk categories only, not individual clinical measurements (e.g., haemoglobin ≤11 g/L)."	The wording used by the ERG to describe the sensitivity analyses conducted around the primary indirect comparison analysis is unclear and therefore does not give a fair account of the attempt of the manufacturer to explore, via sensitivity analyses, the uncertainty around the outcome of the primary IDC analysis.	This is not a factual inaccuracy. The text is abridged, but not inaccurate. More detailed information about the scenarios is already provided in Table 47 of the ERG report.

The description of the "matched" cohort used to conduct the IDC is incorrect. Page 48 of ERG report: "The CS notes that 16 patients in Study 1118E received five or more lines of treatment. The company's indirect comparison excluded these patients. […] The evidence used to inform the effect of ibrutinib versus rituximab/chemotherapy on PFS has been derived from cohorts of patients who had received between one and three prior lines of therapy."	"The CS notes that 16 patients in Study 1118E received five or more prior lines of treatment. The company's indirect comparison excluded these patients. […] The evidence used to inform the effect of ibrutinib versus rituximab/chemotherapy on PFS has been derived from cohorts of patients who had received between one and ~~three~~ four prior lines of therapy."	Page 57 of the CS states: "In addition, patients from Study 1118E that had 5 or more prior lines of therapy were excluded from the analyses given that patients from the chart review had received at most four prior treatments."	The ERG agrees – both points have been amended.
Page xi and page 64 of ERG report: "The CS states that interim results are expected in April 2017 at the earliest, but some efficacy and safety data were presented in the	"The CS states that interim results are expected in April 2017 at the earliest, but some efficacy and safety data were presented for Arm C of the trial in the CS."	In line with text on page 67 of CS, clarification that iNNOVATE trial data presented to date only relate to one arm of the trial, arm C, an open label sub-study for patients who are refractory to rituximab and therefore, not eligible for randomisation.	This is not a factual inaccuracy. The data are from the iNNOVATE study, irrespective of which arm they are drawn from.

CS." The ERG report refers repeatedly to Study 1118E "protocol", primarily with regards to the definitions of the outcomes of Study 1118E. While the manufacturer has provided outcomes definitions based on Study 1118E protocol, as part of the answers to the clarification questions, the manufacturer is the opinion that in several cases there is an incorrect use of this term as it is often used to refer to the Treon 2015 publication, which reports the findings of Study 1118E. An example of is can be quoted from page 26 in Table 8 of ERG report. In this table, one of the "Response categories" is labelled as "Treon et al, Study 1118E NEJM Protocol" Another example can be	Review ERG report and remove references to the protocol for Study 1118E when appropriate.	Incorrect use of the word "protocol" in relation to Study 1118E is misleading as it suggests: • An incorrect source for the data presented by the manufacturer in its submission • And potentially that the ERG has had access to the study protocol, which is incorrect (only the CSR was shared with the ERG/NICE).	This is not a factual inaccuracy. It is a correct use of the word protocol. This reference is provided to distinguish the protocol available with the NEJM publication, from the ClinicalTrials.gov protocol and the protocol provided by the company. It can be accessed via a link on the electronic version of the Treon *et al* 2015 article, p.1431, in the NEJM, located in the following text: "The first author designed the study, and all the authors vouch for the integrity of the data and adherence to the protocol (available with the full text of this article at NEJM.org)." Here, the company will find the following document: "Protocol. This trial protocol has been provided by the authors to give readers additional information about their work. Protocol for: Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenström's macroglobulinemia. N Engl J Med 2015;372:1430-40. DOI: 10.1056/NEJMoa1501548."

found on page 28 of ERG report: "According to the protocol, "death from any cause or initiation of a new anti-neoplastic therapy was also considered to be a progression event" (Treon protocol, Section 9.1.2)."			
Manufacturer modelling approach and key assumptions described in "Table 55: Summary of ERG's concerns regarding company's survival modelling" (page 123) of ERG report reflects status in CS but does not take systematically into account the clarifications provided by Janssen in their answer to ERG clarifications questions. Examples are the first two bullet points in the table: "Several candidate survivor functions not tested (Gompertz,	Either amend title of Table 55 to clarify that table presents concerns prior to manufacturer answering ERG clarification questions or remove/amend points in table which have been clarified by manufacturer as part of answers to ERG clarification questions.	While the text below Table 55 describes the instances in which the manufacturer has provided clarification and therefore waived concerns from the ERG (e.g. page 123-124: "The CS does not contain any justification regarding whether the proportional hazards assumption holds, although this issue was later addressed in the company's clarification response14 (question B27, as discussed in Section 4.4)"), this is not apparent in Table 55 as a stand-alone table. Evidence presented in Table 55 without text below could lead to misinterpreting the scope of the evidence and the modelling approach followed by the manufacturer.	The ERG disagrees. The heading of the right-hand column of Table 55 already mentions that the issues relate to the content of the CS. The subsequent text includes discussion of additional information provided following the clarification process.

gamma, generalised gamma, generalised F)" "Proportional hazards for PFS assumed without proper justification"			
The name of Study 1118E was incorrectly misspelled as "Study 118E" on three occasions in the ERG report: Page ix: "With the exception of pre-planned subgroup analyses of overall response and major response within Study 118E, the CS does not contain any subgroup analyses." Page 14: "With the exception of pre-planned subgroup analyses of overall response and major response within Study 118E (see CS pages 47-48), the CS does not contain any subgroup analyses."	Replace "Study 118E" with "Study 1118E".	Name of the pivotal study has been spelled incorrectly and should be corrected.	The ERG agrees – these typographical errors have been corrected.

Page 42: "The CS includes an adjusted arm-based indirect comparison of patient-level data from Study 118E and a European chart review study; the CS reports data from this study based on a published poster and the company's data on file."			
Page 47 of ERG report: "In response to a request for clarification (question B30), the company presented a sensitivity analysis using an alternative sample of patients who also met the matching criteria defined above. This analysis produced an HR [redacted] […]."	"[redacted]"	The value for the lower bound of the HR provided in answer to ERG clarification question B30 is incorrect.	The ERG agrees – this transcription error has been corrected.