NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ibrutinib for treating relapsed or refractory mantle cell lymphoma [ID753]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ibrutinib for treating relapsed or refractory mantle cell lymphoma [ID753]

Contents:

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Ibrutinib for treating relapsed or refractory mantle cell lymphoma

This premeeting briefing presents:

- 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.

Key issues for consideration

Clinical effectiveness

- The NICE scope included rituximab plus chemotherapy (R-chemo) options as comparators for ibrutinib. However, there appears to be no accepted standard of care for patients with relapsed or refractory mantle cell lymphoma (R/R MCL). Does the committee agree with the company that R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) is the most commonly used regimen? Is it reasonable for the company to assume that R-chemo regimens have equal efficacy?

- No randomised controlled trials (RCTs) were identified that compared ibrutinib with any of the comparators listed in the NICE scope. The sole RCT compared

ibrutinib with temsirolimus, which does not appear to be used in clinical practice. To what extent can temsirolimus be used as a proxy for UK current care?

- Of the 3 ibrutinib studies, only 1 study was an RCT (RAY), the other 2 were single arm studies (PCYC1104 and SPARK). All 3 were open-label and the ERG considered they were prone to performance and measurement bias although it considered RAY to be well-designed and of adequate quality. All studies addressed the issue of measurement bias by having an assessment of the primary outcome by an independent review committee (IRC) and were sufficiently large and adequately powered for the primary endpoint of PFS(RAY) or overall response rate (SPARK and PCYC1104). What is the committee's view of the quality of the studies?

- The ERG considered that the populations of the 3 ibrutinib trials reflect the demographic characteristics of the R/R MCL population that would be eligible for ibrutinib treatment but that, in practice, patients may have more co-morbidities than trial patients. Studies were international, with a small proportion of patients from the UK (27 in RAY, 21 in PCYC1104 and 6 in SPARK). What is the committee's view on the generalisability of the studies to the UK clinical setting?

- The company reported that the populations in the 3 clinical trials of ibrutinib were sufficiently similar in terms of baseline characteristics to allow for pooling of data. Due to the paucity of evidence for ibrutinib for the treatment of R/R MCL, the ERG considered it acceptable to combine the studies. What is the committee's view of the pooled analyses?

- The company conducted an indirect comparison comparing ibrutinib with physician's choice of treatment in which patients received a range of single-agent chemotherapy regimens. The company adjusted the treatment effect from the indirect comparison to account for the increased effectiveness expected by clinical experts with the addition of rituximab to chemotherapy. The ERG did not agree with the company's 2 stage approach to estimating treatment effects for ibrutinib compared with R-chemo and considered that a single stage approach using random effects network meta-analysis would provide a better representation of

the uncertainty in the resulting treatment comparisons. Due to concerns regarding the evidence used to inform the indirect comparisons, the ERG considered that the results should be interpreted with caution. What is the committee's view of the indirect comparisons? Which approach does the committee prefer?

- The ERG considered that there was considerable uncertainty in the clinical evidence for ibrutinib, driven by: (a) the absence of RCT comparisons for ibrutinib versus R-chemo and the limitations of the indirect comparison; (b) the presence of treatment switching within RAY; (c) immaturity of the available OS data; and (d) the use of other therapies beyond disease progression which are not used in England. What is the committee's view of the strength of the clinical evidence for ibrutinib?

Cost effectiveness

- The ERG raised concerns about the company's model structure, in particular that the Markov approach makes a number of restrictive structural assumptions which lead to a poor model fit to the available overall survival (OS) data for ibrutinib, and that the use of post-progression survival may introduce selection bias. What is the committee's view of the company's model structure?

- The ERG had several concerns regarding the company's parametric survival modelling, in particular the limited set of survivor functions considered for PFS and that the hazards of pre-progression mortality and post progression survival (PPS) were assumed to be constant. What is the committee's view of the parametric survival modelling?

- The ERG was concerned about the company's approach to modelling time to treatment discontinuation or death (TTD/D), and considered that none of the fitted parametric survival curves provided a reasonable fit to the observed Kaplan-Meier curve. The ERG considered that the Weibull function, used in the base case analysis, led to a much longer tail compared with the observed Kaplan-Meier curve, leading to an overestimation of the modelled drug costs for ibrutinib, thereby inflating the ICER for ibrutinib compared with R-chemo. What is the committee's view on the company's methods for modelling TTD/D?

- The ERG raised concerns about the reliability of the HRQoL estimates used in the company's model, including uncertainty surrounding progression-free (0.78) and post-progression (0.68) utility values, and issues with the duration of the disutility (0.20) associated with R-chemo. However, it acknowledged that these factors did not have a material impact on the ICER. What is the committee's view of the HRQoL estimates used?

- The company was concerned that HRQoL values elicited with the EQ-5D may underestimate the true utility gain associated with ibrutinib. The ERG acknowledged that there may be disconnect between the EQ-5D evidence from RAY and clinical experience using ibrutinib. Does the committee consider that HRQoL is adequately captured by the EQ-5D?

- The ERG raised concerns regarding the validity of the company's sequential model which compared ibrutinib followed by R-chemo against R-chemo alone in a secondary analysis, and believed that this analysis should be disregarded. What is the committee's view of this analysis?

- The ERG highlighted that the company's model-predicted OS did not appear to provide a good visual fit to the observed Kaplan-Meier OS curve, overestimating OS up to around 15.6 months and under-predicting OS beyond this timepoint, suggesting that the survival gain in the ibrutinib group is likely to be underestimated. The ERG therefore expressed concern about the credibility of the results. Does the committee support this view?

- The results from the company's model showed that the deterministic ICER for ibrutinib compared with R-CHOP was £75,317 per QALY gained and the probabilistic ICER was £75,878 per QALY gained. The ERG undertook 2 sets of exploratory analyses. The first set ("Set A") involved amending the parameter values of the company's model. The ERG's preferred analysis within Set A involved using the hazard ratio for PFS for ibrutinib versus R-CHOP from the ERG's random effects network meta-analysis, the use of the Kaplan-Meier curve instead of a parametric (Weibull) curve to model time to treatment discontinuation or death (TTD/D) for ibrutinib, and the truncation of the R-chemo QALY loss upon

treatment discontinuation. This analysis resulted in a probabilistic ICER for ibrutinib compared with R-CHOP of £63,340 per QALY gained. The use of alternative utility values sourced from the literature for the progression-free and post-progression states within the ERG's preferred analysis produced ICERs for ibrutinib versus R-CHOP ranging from £59,952 to £60,417 per QALY gained. What is the committee's view of the ICERs estimated by the company and by the ERG using the company's model? Which assumptions does the committee consider to be most plausible?

- The ERG considered that the company's subgroup analysis according to number of prior LOTs indicated the potential for an improved cost-effectiveness profile for ibrutinib. Using the ERG's preferred analysis within Set A, the ICER for ibrutinib compared with R-CHOP for the subgroup of patients who had 1 prior LOT was £44,711 per QALY gained (or £64,755 when estimated by the company), considerably lower than for the overall population. However, the ERG was concerned about the post hoc nature of the subgroup analyses and poor fit of the PFS survivor function to the 1 prior LOT subgroup. What is the committee's view of the subgroup analyses?

- The ERG's second set of exploratory analyses ("Set B") explored the impact of using a partitioned survival approach and involved amending the structure of the company's model such that OS data for ibrutinib from the pooled dataset was used as an input. The ERG considered that this approach provided a better fit to the OS data but involved using the outputs of a highly uncertain random effects network meta-analysis. In this analysis, ibrutinib was dominated by R-CHOP. In addition, the ERG estimated that, for the ICER to be below £50,000 per QALY gained, the hazard ratio for OS for ibrutinib compared with R-CHOP would need to be 0.39-0.40. What is the committee's view of the ERG's exploratory analyses Set B?

- Which approach to modelling the cost-effectiveness of ibrutinib does the committee prefer? What is the committee's view on the most plausible ICER for ibrutinib compared with R-chemo and the robustness of the estimates?

Other

- The company considered ibrutinib to be innovative in the management of R/R MCL as it offers the opportunity for daily dosing whilst minimising the duration of side effects, and addresses a significant unmet need within the MCL treatment pathway. The oral administration of ibrutinib also reduces the patient, carer and NHS burden associated with current intravenous MCL treatments. Does the Committee consider ibrutinib to be an innovative therapy?

- The company stated that ibrutinib meets all the criteria to be considered a life-extending treatment at the end of life. Is the Committee satisfied that all the criteria have been met, the estimates presented by the company are robust enough and the assumptions used in the model are plausible, objective and robust?

- The company suggested that ibrutinib might be suitable for cancer drugs fund (CDF) funding with the collection of some specific additional data. However, subsequent to this, the company indicated that it is applying for baseline commissioning, not CDF funding. Does the committee consider that CDF funding is appropriate?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of ibrutinib within its marketing authorisation for treating relapsed or refractory mantle cell lymphoma.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	Adults with R/R MCL.	Adults with R/R MCL.	The company felt that the decision problem matched the final scope	Same as the NICE scope. Studies presented were relevant to the population, intervention and outcomes of the decision problem.
Int.	Ibrutinib.	Ibrutinib.	The company felt that the decision problem matched the final scope	Same as the NICE scope. Studies presented were relevant to the population, intervention and outcomes of the decision problem.
Com.	• Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) • Rituximab, cyclophosphamide, vincristine and prednisolone (R-CVP) • Fludarabine, cyclophosphamide and rituximab (FCR) • Rituximab and cytarabine (RC).	• Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) • Rituximab, cyclophosphamide, vincristine and prednisolone (R-CVP) • Fludarabine, cyclophosphamide and rituximab (FCR) • Rituximab and cytarabine (RC).	The company felt that the decision problem matched the final scope	Same as the NICE scope. No studies providing comparator data reflecting UK clinical practice were identified.
Out.	• Overall survival (OS) • Progression-free survival	• OS • PFS	The company felt that the decision problem matched	Same as the NICE scope. Studies presented were relevant

	(PFS) • Overall response rates (overall response rate) • Duration of response (DOR)/remission • Time to new anti-lymphoma treatment/time to progression • Adverse effects of treatment • Health-related quality of life (HRQoL).	• Overall response rate • DOR/remission • Time to new anti-lymphoma treatment/time to progression • Adverse effects of treatment • HRQoL.	the final scope	to the population, intervention and outcomes of the decision problem.
Abbreviations: ERG, evidence review group; Pop, population; Int, intervention; Com, comparators; Out, outcomes ; R/R MCL: relapsed or refractory mantle cell lymphoma, RC: rituximab and cytarabine, R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone, R-CVP: rituximab, cyclophosphamide, vincristine and prednisolone, FCR: fludarabine, cyclophosphamide and rituximab; OS: overall survival; PFS: progression-free survival; ORR: overall response rate; DOR: duration of response; HRQoL: health-related quality of life				

2 The technology and the treatment pathway

2.1 Ibrutinib (Imbruvica, Janssen) is an inhibitor of a protein called Bruton's tyrosine kinase, which stops B-cell (lymphocyte) proliferation and promotes cell death. It has a marketing authorisation in the UK for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (R/R MCL) as well as for chronic lymphocytic leukaemia and Waldenström's macroglobulinaemia. Ibrutinib is administered orally once daily until disease progression or unacceptable toxicity (see Table 2).

2.2 The company has agreed a patient access scheme with the Department of Health involving a single confidential discount applied to the list price of ibrutinib. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

Table 2 Technology (adapted from Table 9 in the company submission)

	Ibrutinib	**Source**
Marketing authorisation	Treatment of adult patients with R/R MCL	SmPC
Administration method and dose	Oral; 4 x 140 mg capsules (560 mg) once daily until disease progression or unacceptable toxicitie	SmPC
Acquisition cost (excluding VAT)	List price: • £4,599.00 for 90 × 140 mg capsules (£51.10 per capsule) • £6,132.00 for 120 × 140 mg capsules (£51.10 per capsule) Discounted price: [redacted]	BNF 2016
Average cost of a course of treatment	List price: £78,550.92 (based on a 30-day month, therefore assuming a cost of £6,132.00 for a one month supply, and 12.81 months [median PFS from the pooled analysis] of treatment) Discounted price: [redacted] (based on a 30-day month, therefore assuming a cost of [redacted] for a one month supply, and 12.81 months [median PFS from the pooled dataset] of treatment)	BNF 2016, Pooled analysis of data
Abbreviations: SmPC: summary of product characteristics, VAT: value added tax, BNF: British National Formulary, PAS, patient access scheme;		

2.3 The draft NICE guidelines on the diagnosis and management of non-Hodgkin's lymphoma note that MCL is a relatively rare disease and that there is no accepted standard of care for patients with this condition (publication of the final NICE guideline is expected July 2016). This is supported in the company submission through reference to the haematological malignancy research network (HMRN) audit, whereby across the 79 patients who received chemotherapy for R/R MCL, 19 different approaches were used. The company reports that response to first-line chemotherapy is often temporary and relapse rates are high. Choice of treatment depends mainly on patient age and fitness. Younger patients who are fit enough for high dose chemotherapy and autologous peripheral blood stem cell transplantation in first remission should receive a high dose cytarabine-containing regimen to achieve an optimal remission, followed by allogeneic transplantation at relapse. An advisory board held by the company highlighted that in clinical practice R-CHOP is most commonly used as first relapse treatment for patients who are able to tolerate it. For elderly and less fit patients R-CVP is the most common treatment and for very frail patients R-chlorambucil is used. Other options may include R- chlorambucil and R-bendamustine. Where the patient has received one previous line of treatment, a different regimen would typically be chosen following relapse.

2.4 Clinical guidelines by the European Society for Medical Oncology (ESMO) strongly recommend newer targeted approaches in cases of early relapse including drugs such as temsirolimus, bortezomib and ibrutinib. Other than ibrutinib, temsirolimus is the only agent licensed for use in R/R MCL in the EU; however is not used in clinical practice in the UK. Bortezomib is only recommended by NICE for treating MCL in previously untreated patients (technology appraisal 370).

3 Comments from consultees

3.1 The professional groups noted that there is an inevitable pattern of a relapse with no curative therapy available for the majority of patients with

MCL. It was noted that there was no standard of care for R/R MCL although an alternative immune-chemotherapeutic from first line treatment was normally employed. In the case of a very young and fit patient an allogeneic transplant can be considered at relapse and this is curative in around 30-40%. The professional groups also noted that there are 4 novel licensed drugs for R/R MCL: bortezomib, lenalidomide, temsirolimus and ibrutinib but the relative efficacy of these drugs as single agents across comparative trials shows that ibrutinib is significantly more active with the highest response rate, complete response rate and longest progression free survival.

3.2 The professional groups noted that ibrutinib has the most favourable side effects profile of the 4 drugs and that it appears to benefit all risk groups irrespective of line of therapy. Therefore, it can be used to treat old, frail patients where the conventional options are the least effective and most toxic. In contrast it can also be used in very young patients as an effective salvage therapy before an allogeneic transplant.

3.3 The professional groups noted that treatment is easy to deliver but requires supervision in secondary care preferably through a specialist lymphoma clinic. They noted no particular testing requirements for patients and that monitoring for response was no different from that used with conventional therapies. No specific education is required as the drug has been widely used via the expanded access programme from the company and the cancer drugs Fund.

3.4 The professional group noted that ibrutinib increases bruising and bleeding in patients and that this requires cautious care with any form of anti-coagulation and withdrawal of ibrutinib during operative procedures.

3.5 A statement from a patient organisation highlighted the severity and diversity of symptoms experienced by patients with advanced R/R MCL and the severe detrimental effects on quality of life in some cases. Treatment options are limited which results in generally very poor

outcomes for patients. Current treatment options available on the NHS were said to be associated with increased toxicity, lower tumour-reduction capability, and unpleasant side-effects. A significant proportion of carers also reported the significant impact that current treatments have on day-to-day life of both patients and carers alike.

3.6 The patient group also highlighted that the milder side effects and improved efficacy of ibrutinib allowed patients to regain a good quality of life, have fewer hospital visits/less travel and contribute more to society. This had a corresponding impact on carers and patients' families. Given that ibrutinib is administered orally (which is convenient and preferable to most patients as set against traditional chemotherapy regimens), and has limited and manageable side-effects and a well-tolerated toxicity profile, the patient group viewed it as a step-change in the management of MCL.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company identified 3 clinical trials of ibrutinib in the population considered in this appraisal, that is, people with relapsed or refractory mantle cell lymphoma (R/R MCL). One of the studies (RAY [MCL3001], described hereafter as ‘RAY’, was a randomised controlled trial, the other 2 studies (PCYC1104 and SPARK (MCL2001), described hereafter as ‘SPARK’, were single arm studies.

4.2 RAY was a randomised, open-label, multicentre study that compared ibrutinib with temsirolimus in patients who had received at least one prior rituximab-containing chemotherapy regimen. Temsirolimus was chosen as the comparator because it was the only therapy licensed in the European Union for R/R MCL when the trial was initiated. The trial included centres in 21 countries with 27 patients from 9 sites in the UK. Patients (n=280) were stratified by previous therapy and simplified MCL international prognostic index (MIPI) score and randomly assigned in a

1:1 ratio to ibrutinib (n=139) or temsirolimus (n=141). All 139 patients in the ibrutinib group and 139 of the 141 people in the temsirolimus group received the assigned treatment (1 withdrew consent and 1 patient experienced an adverse event before start of treatment).

4.3 The baseline demographics were similar in the 2 treatment groups. Over 70% of patients in both arms were male, approximately 62% were aged >65 years and over 80% in both arms had stage IV disease at study entry. The median number of prior lines of systemic therapy for MCL was 2 (range: 1-9 lines) in both arms and the median time from end of last prior therapy to randomisation was 8.25 months in the ibrutinib arm and 7.03 months in the temsirolimus arm. In both arms, Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 48% of patients and 1 in 51% of patients.

4.4 Ibrutinib (560 mg) was administered orally once a day on a continuous 21 day cycle whereas temsirolimus (175 mg) was administered intravenously (IV) on days 1, 8 and 15 of the first cycle, followed by 75 mg IV on days 1, 8 and 15 of each subsequent 21-day cycle. Both groups continued treatment until disease progression or unacceptable toxic effects. The trial protocol was amended to allow patients in the temsirolimus arm with confirmed progression of disease to formally crossover to receive treatment with ibrutinib until disease progression or unacceptable toxicity.

4.5 The primary outcome of RAY was progression free survival (PFS) defined as the interval from the date of randomisation to the date of disease progression as assessed by the independent review committee (IRC), or date of death, whichever occurred first. Progressive disease was determined according to the revised International Working Group Criteria for non-Hodgkin's lymphoma. Secondary outcomes included PSF2, defined as the time interval between the date of randomisation and the date of an event, where an event was defined as progressive disease assessed by the IRC after the next line of therapy, death from

any cause, or start of subsequent therapy if no disease progression is noted. Secondary outcomes also included overall survival (OS), defined as the duration from the date of randomisation to the date of death from any cause. The survival time of patients still alive was censored on the last date they were known to be alive or lost to follow-up. Other secondary outcomes included one year survival rate, overall response rate (overall response rate - the proportion of patients who had a complete response or partial response as best overall response), time to next treatment, duration of response, health related quality-of-life assessed by EQ-5D and FACT-Lym, and safety.

4.6 In the 2 non-randomised, single-arm studies (PCYC1104 and SPARK) ibrutinib 560 mg was administered orally once a day until disease progression or unacceptable toxicity. The PCYC1104 trial (n=115) included 18 centres in 4 countries (21 patients from 4 UK centres) and included patients with R/R MCL classified as receiving prior bortezomib treatment (≥2 cycles) or not receiving bortezomib treatment (<2 complete cycles or no treatment). Patients had a median age of 68 years and had received a median of 3 prior therapies. The SPARK trial enrolled 120 patients at 38 centres worldwide (6 patients from 2 UK centres) but only included patients with R/R MCL who had received prior bortezomib therapy. As this reflects a subset of the ibrutinib licensed indication, the company felt that SPARK was less relevant than the RAY and PCYC1104 studies. Patients in SPARK had a median age of 67.5 years and had received a median of 2 prior therapies. The primary endpoint in both SPARK and PCYC1104 was overall response rate.

4.7 The clinical evidence is supported by 2 real-world studies: a Compassionate Use Programme (CUP), which recruited 715 patients worldwide, including 154 in the UK (the highest level of enrolment globally), and an Early Access Programme (EAP), which recruited 149 patients in the United States (see pages 101-105 of the company submission).

ERG comments – overview of clinical trials

4.8 The ERG reported that the company had identified all relevant trials and that the studies presented were relevant to the population, intervention and outcomes of the decision problem. Of the 3 included ibrutinib studies, only 1 study was an RCT, the other 2 were single arm, lower quality studies subject to selection bias. All 3 studies were open-label which made them prone to performance and measurement bias although the ERG considered RAY to be well- designed and of adequate quality. However, all studies addressed the issue of measurement bias by having an assessment of the primary outcome by an independent review committee (IRC) and were sufficiently large and adequately powered for their primary endpoint of PFS.

4.9 The ERG highlighted that no RCTs were identified by the company comparing ibrutinib with any of the comparators listed in the NICE scope. The sole RCT included compared ibrutinib to temsirolimus, a drug not used in clinical practice in the UK.

4.10 The ERG noted that the populations of the 3 included trials reflect the demographic characteristics of the R/R MCL population that would be eligible for ibrutinib treatment. However, in practice, patients may have more co-morbidities than trial patients. Studies were international, with a small proportion of patients from the UK; therefore there may be differences between the treatment pathways of trial patients and those in current practice in England.

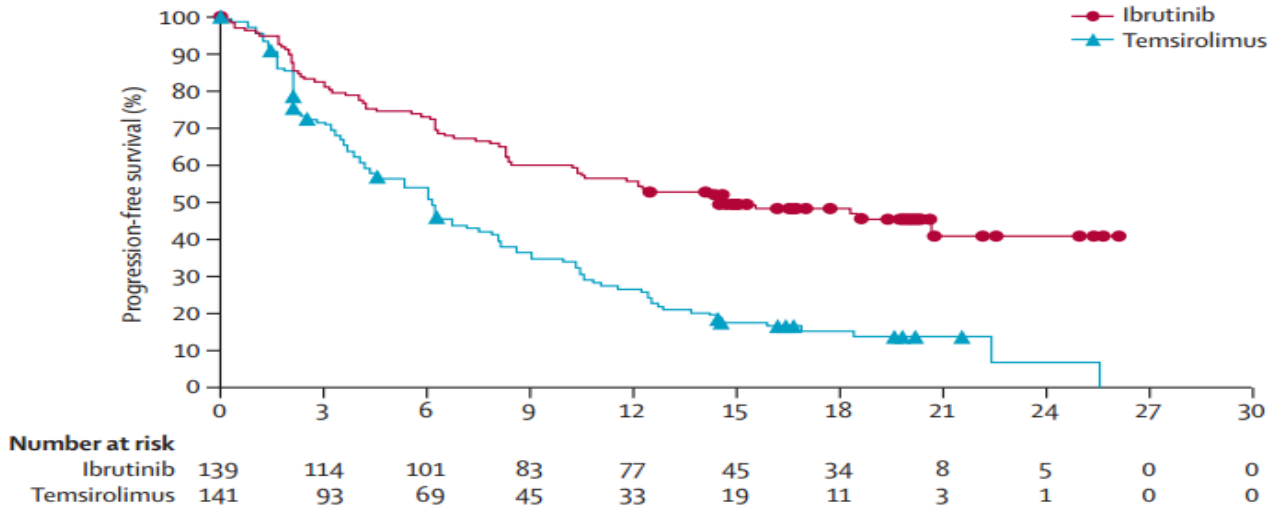
Clinical trial results

Randomised controlled trial results - RAY

4.11 All analyses on data from the RAY trial were performed on the ITT population. The clinical cut-off for the primary analysis of PFS was defined as the time at which approximately 178 PFS events were observed (April 2015), at which time median follow up was 20 months.

4.12 The study met its primary endpoint, demonstrating a PFS benefit of ibrutinib compared with temsirolimus (median PFS 14.6 months versus 6.2 months) and providing a 57% reduction in the risk of disease progression or death (hazard ratio [HR] 0.43, 95% confidence interval [CI] 0.32 to 0.58, p<0.0001). Forty-one percent of patients in the ibrutinib arm remained progression-free at 2 years compared with 7% in the temsirolimus arm. The company reported that pre-planned subgroup analyses showed internal consistency of the primary endpoint across all subgroups.

Figure 1 Kaplan- Meier plot of PFS by IRC at 2 years in RAY (taken from CS, Figure 9, page 67)



4.13 For the secondary outcome of PFS2 (for definition, see section 4.5), values were significantly longer for ibrutinib than for temsirolimus (19.1 months compared with 11.3 months, HR 0.49, 95% CI 0.36 to 0.69, p<0.0001). The company considered that the PFS2 results indicate how treatment with ibrutinib or temsirolimus differentially affects the clinical benefit of subsequent-line therapy, thereby providing an additional measure of overall treatment effect.

4.14 After a median follow-up of 20.0 months, median OS has not been reached in the ibrutinib arm, indicating that more than 50% of patients were still alive at study cut-off. In contrast, median OS was 21.3 months in the temsirolimus arm. The company reported that this represents a

24% reduction in the risk of death with ibrutinib (HR 0.76, 95% CI 0.53 to 1.09, p=0.1324), which was observed despite the crossover of 32 patients (23%) in the temsirolimus arm to the ibrutinib arm, thereby confounding the estimate of OS for temsirolimus. The company explained that the OS data for ibrutinib from RAY is immature and does not reach statistical significance. However, the study was not powered to observe a statistical OS benefit at interim analysis and the final data cut is scheduled for November 2016 and will provide more mature data. The company also highlighted that OS might be influenced by the clinical benefit of subsequent anticancer therapies received following progression on ibrutinib or temsirolimus, as these may affect post-progression survival. Subsequent anticancer systemic therapy was received by 31.7% of patients in the overall ibrutinib arm (60% of those who progressed or died) and by 58.2% in the overall temsirolimus arm (74% of those who progressed or died).

4.15 The overall response rate as determined by the IRC was significantly higher for the ibrutinib arm (71.9%) compared with the temsirolimus arm (40.4%). Median duration of response however was not reached for patients who received ibrutinib at the time of clinical cut-off and was 7.0 months for patients in the temsirolimus group. Further details of secondary outcomes results are given on pages 67-73 of the company submission.

4.16 The company reported that a post-hoc analysis of PFS and overall response rate by number of prior lines of therapy (LOT) demonstrated a substantial PFS benefit for patients who received ibrutinib following 1 prior therapy compared with 2 or more (see Figure 15, page 79 of the company submission). It also reported that the proportion of patients achieving a complete response rather than a partial response was higher when ibrutinib was used earlier in the treatment pathway (24.6% of patients in the 1 prior LOT subgroup had a complete response, compared with 18.4% in the 2 prior LOTs subgroup and 11.4% in the 3 or more prior LOTs subgroup).

4.17 Health-related quality of life (HRQoL) was assessed using FACT-Lym, a cancer-specific, non-preference based measure, with a lymphoma-specific subscale, and EQ-5D, a generic preference-based measure. Ninety percent of the study population completed the FACT-Lym at baseline with 61.9% of patients treated with ibrutinib achieving a clinically meaningful improvement in lymphoma symptoms compared with 35.5% of patients treated with temsirolimus ($p<0.0001$). Median time to improvement was reached in 6.3 weeks (95 % CI 3.6 to 9.7 weeks) with ibrutinib compared with 57.3 weeks (95% CI 15.3 to 107.7 weeks) with temsirolimus (HR 2.19, 95% CI 1.52 to 3.14, $p<0.0001$). Conversely, significantly fewer ibrutinib patients (26.6%) experienced a clinically meaningful worsening of lymphoma symptoms compared with 51.8% of temsirolimus patients ($p<0.0001$). Symptom worsening occurred significantly more slowly with ibrutinib than temsirolimus (median time to worsening not reached versus 9.7 weeks, respectively (HR 0.27; 95% CI: 0.18, 0.41, $p<0.0001$). At baseline, EQ-5D mean utility values were 0.73 for both treatment arms. A statistically significant difference in EQ-5D utility score favouring ibrutinib over temsirolimus was observed within 4 weeks and maintained through to week 49. EQ-5D utility values for ibrutinib did not return to baseline level at any time point up to week 40; in contrast mean change from baseline values with temsirolimus were negative at all time points up to week 106, the longest available time point at the clinical data cut-off as shown in Figure 2. The company stated that as mean EQ-5D-5L domain-level change was <1 unit, this may not equate to a change in EQ-5D health state and hence utility for many patients.

Table 3: Least square mean (95% CI) change from baseline in EQ-5D-5L utility score over time in RAY (MCL3001), ITT analysis set (company submission, table 24, page 75)

	Ibrutinib		Temsirolimus		Temsirolimus vs Ibrutinib	P value
Analysis set (ITT)	139		141		-	-
Baseline score, mean (SD)	130	0.73 (0.2)	120	0.73 (0.2)	-	-
	n	**LS mean change from baseline (95% CI)**	**n**	**LS mean change from baseline (95% CI)**		
Week 4	108	0.03 (-0.00, 0.05)	84	-0.07 (-0.10, -0.05)	-0.09 (-0.13, -0.05)	<0.0001
Week 7	101	0.02 (-0.00, 0.05)	71	-0.07 (-0.09, -0.04)	-0.09 (-0.13, -0.05)	<0.0001
Week 10	94	0.02 (-0.00, 0.05)	59	-0.06 (-0.09, -0.03)	-0.09 (-0.12, -0.05)	<0.0001
Week 13	93	0.02 (-0.01, 0.05)	48	-0.06 (-0.09, -0.03)	-0.08 (-0.12, -0.05)	<0.0001
Week 16	88	0.02 (-0.01, 0.05)	41	-0.06 (-0.09, -0.03)	-0.08 (-0.12, -0.04)	<0.0001
Week 19	79	0.02 (-0.01, 0.04)	40	-0.06 (-0.09, -0.03)	-0.08 (-0.11, -0.04)	<0.0001
Week 22	78	0.02 (-0.01, 0.04)	30	-0.06 (-0.09, -0.03)	-0.07 (-0.11, -0.04)	0.0001
Week 31	64	0.01 (-0.01, 0.04)	23	-0.05 (-0.08, -0.02)	-0.06 (-0.10, -0.03)	0.0010
Week 40	53	0.01 (-0.02, 0.04)	21	-0.05 (-0.08, -0.02)	-0.05 (-0.09, -0.01)	0.0073
Week 49	52	0.00 (-0.03, 0.03)	17	-0.04 (-0.08, -0.01)	-0.05 (-0.09, -0.00)	0.0387
Week 58	45	-0.00 (-0.03, 0.03)	13	-0.04 (-0.07, 0.00)	-0.04 (-0.08, 0.01)	0.1327
Week 82	12	-0.01 (-0.05, 0.03)	1	-0.02 (-0.07, 0.03)	-0.01 (-0.07, 0.05)	0.7340
Week 106	3	-0.02 (-0.07, 0.02)	2	-0.01 (-0.07, 0.05)	0.02 (-0.06, 0.09)	0.6857

LS: least squares, CI: confidence interval, TEM: temsirolimus.
Source: RAY (MCL3001) CSR[59]

Table 4: Summary of clinical trial outcomes from RAY (MCL3001)

	RAY(MCL3001)	
	Ibrutinib (n=139)	**Temsirolimus (n=141)**
Progression-Free Survival - PFS (ITT analysis)		
Median: months (95% CI)	14.6 (10.4; NE)	6.2 (4.2; 7.9)
HR (95% CI)	0.43 (0.32; 0.58), p<0.0001	
Progression-free survival rate (at 2 years)	41%	7%
Progression-Free Survival in next line therapy - PFS2 (ITT analysis)		
Median PFS2, months	19.1	11.3
HR (95% CI)	0.49 (0.36; 0.69), p<0.0001	
Overall Survival-OS (ITT analysis)		
Median OS, months	Not reached	21.3
HR (95% CI)	0.76 (95% CI: 0.53; 1.09) p=0.1324	
Overall survival rate (at 12 months)	68%	61%
Overall Response Rate - Complete Response (CR) OR Partial Response (PR)- ORR		
Overall response rate (CR or PR), n (%)	100 (71.9%)	57 (40.4%)
OR (95% CI)	3.98 (2.38, 6.65)	
Duration of response-DOR		
Median (95% CI)	NE (16.2, NE)*	7.0 (4.2, 9.9)*
18-month DOR rate (95% CI)	0.58 (0.46–0.68)*	0.20 (0.09–0.35)*
Quality of life (QoL)- FACT-Lym		
Median time to improvement, weeks (95% CI)	6.3 (3.6, 9.7)	57.3 weeks (15.3, 107.7)
HR (95% CI)	2.19(1.52, 3.14), p<0.0001	
Quality of life (QoL)- EQ-5D		
Least square mean (95% CI) change from baseline in EQ-5D utility score at week 4	0.03 (-0.00, 0.05) n=108	0.03 (-0.00, 0.05) n=84
Least square mean (95% CI) change from baseline in EQ-5D utility score at week 40	0.01 (-0.02, 0.04) n=53	-0.05 (-0.08, -0.02) n=21
ITT: intention-to-treat, CI: Confidence interval, HR: Hazard ratio, OR: Odd's ratio NE: Not estimable, PFS: Progression-free survival, TEM: temsirolimus * Duration of response was derived for patients who achieved complete response or partial response (ibrutinib (n=100) and temsirolimus(N=57))		

Single arm trials - results

4.18 Results from the single arm PCYC1104 study (described in section 4.6) showed that, at a median follow-up of 15.3 months, the investigator assessed overall response rate was 68% in the total patient cohort (67%

in patients who had received prior bortezomib (that is, ≥2 cycles) and 68% in bortezomib-naive patients (that is, people who had received <2 complete cycles or no bortezomib treatment). This overall response rate was maintained at the final analysis performed at median follow-up of 26.7 months. Secondary outcomes for the interim and final analysis are shown in Table 5. The company reported that the median PFS of 13.0 months (from the final analysis) is consistent with that observed in RAY (14.6 months) and that, due to the long-term follow-up, the study provided an estimate of median OS of 22.5 months.

Table 5: PCYC1104 secondary end-points (company submission, table 33, page 92)

Variable	No prior treatment with bortezomib (n=63)	Prior treatment with bortezomib (n=48)	All patients (n=111)
Median DOR (95% CI), months			
At 15.3 month follow-up	15.8 (5.6, NE)	NE	17.5 (15.8, NE)
At 26.7 month follow-up	NR	NR	17.5 (14.9, NE)
Median PFS (95% CI), months			
At 15.3 month follow-up	7.4 (5.3, 19.2)	16.6 (8.3, NE)	13.9 (7.0, NE)
At 26.7 month follow-up	NR	NR	13.0 (7.0, 17.5)
Median OS (95% CI), months			
At 15.3 month follow-up	NE (10.0-NE)	NE (11.9-NE)	NE (13.2, NE)
At 26.7 month follow-up	NR	NR	22.5 (13.7, NE)

NE: Non evaluable, PFS: progression-free survival, OS: overall survival, NR: not reported.
Source: Wang, 2013[37]; Wang 2015[36]

4.19 Results from the single arm SPARK study (described in section 4.6) showed that the overall response rate was 62.7% in the response evaluable (RE) population (n=110) of which CR was 20.9%, and 57.5% in the treated population (n=120). The median PFS was 10.5 months and median OS was not reached at a median follow-up of 14.9 months. The company reported that an estimated 61% of patients were alive 18 months after initiation of ibrutinib treatment.

4.20 SPARK demonstrated quality of life improvements with ibrutinib treatment. [redacted]

Both measures of EQ-5D-5L: VAS and utility values showed small but gradual improvement from baseline over the duration of the study.

ERG comments – clinical trial results

4.21 The ERG noted that at the time of the company's submission, median OS had not been reached in the ibrutinib arm of the RAY or SPARK trials but the OS rate at 18 months for ibrutinib-treated patients was similar across studies (RAY - [redacted]; PCYC1104 - 58.2%; SPARK - 61%). The ERG was uncertain if the lack of a significant OS benefit in RAY was due to the use of subsequent therapies beyond progression (including treatment switching in the temsirolimus arm) or the lack of adequate power for this outcome. The ERG highlighted that the temsirolimus arm in RAY reported better outcomes than those reported in the temsirolimus arms of the trial used in the indirect comparison (OPTIMAL study) and the HMRN audit. The ERG was uncertain how much of this difference was due to temsirolimus treatment, differences in populations between trials and routine practice, and the use of other therapies.

4.22 The ERG agreed that median PFS and overall response rate assessed by IRC was similar for ibrutinib treated patients across studies. It also agreed that the evidence from both RAY and SPARK showed clinically meaningful improvement in HRQoL for approximately [redacted] of patients treated with ibrutinib. The ERG noted that there are potential advantages for both patients and clinicians with ibrutinib as it is administered orally, and that this may impact on HRQoL.

Meta-analyses/indirect comparison/MTC

Pooled analysis of RAY, SPARK and PCYC1104

4.23 The company reported that the populations in the 3 clinical trials of ibrutinib were sufficiently similar in terms of baseline characteristics to allow for pooling of data for PFS, OS and overall response rate outcomes. This was on the basis that all the studies evaluated patients with R/R MCL, inclusion and exclusion criteria were similar across the

trials, and prior exposure to bortezomib before ibrutinib treatment (the key difference between SPARK and the other 2 studies, see section 4.6) was found not to be prognostic in secondary analyses.

4.24 An estimate of the efficacy of ibrutinib was carried out through exploratory analyses conducted using Kaplan–Meier estimates for PFS and OS. Univariate and multivariate analyses were also conducted with hazard ratios to allow for comparisons of variables. A total of 370 patients were included in the analysis. The company reported that the analysis demonstrated consistency of results across the trials and informs estimates of long-term survival, by making use of the longer-term data from PCYC1104.

4.25 The results of the pooled analysis for PFS and OS are shown in Table 6 for both IRC and investigator assessments. The company reported that the results of the pooled dataset demonstrate similar estimates of median PFS and OS to the individual trials informing the analysis. Median OS was 25.0 months (95% CI 21.59 to not evaluable) compared with the median OS of 22.5 months reported in PCYC1104. Median PFS results across RAY, PCYC1104 and SPARK were 14.6 months (95% CI 10.4 to not evaluable), 13.0 months (95% CI 7.0 to 17.5) (at longest available follow-up) and 10.5 months (95% CI 4.4 to 15.0), respectively. The company reported that the pooled median PFS by IRC of 12.81 (8.48, 16.56) is therefore consistent with these results. A pooled overall response rate estimate of 66.22% was also derived (see Table 7), compared with the 68% and 71.9% response rates observed in PCYC1104 and RAY respectively.

Table 6: Pooled analysis PFS and OS (company submission, table 40, page 107)

	PFS IRC * Median (95% CI)	PFS INV Median (95% CI)	OS Median (95% CI)
Overall population (n=370)	12.81 (8.48, 16.56)	[redacted]	25.00 (21.59, NA)
1 LOT (n=99)	[redacted]	[redacted]	[redacted]
>1 LOT (n=271)	[redacted]	[redacted]	[redacted]

LOTs: lines of treatment, PFS: progression-free survival, CI: confidence interval, OS: overall survival, ORR: overall response rate, NE: not evaluable, IRC Independent Review Committee, INV: Investigator.
* No IRC-assessed PFS available for PCYC-1104, therefore for INV-assessed PFS I used for PCYC-1104

Table 7: Pooled analysis overall response rates (based on updated datacut of PCYC1104 and SPARK, company submission, table 41, page 108)

	IRC ORR	INV ORR
Overall population (n=370)	[redacted](66.22%)	[redacted]
1 LOT (n=99)	[redacted]	[redacted]
>1 LOT (n=271)	[redacted]	[redacted]

LOTs: lines of treatment, ORR: overall response rate, IRC Independent Review Committee, INV: Investigator.
Based on updated data-cut of PCYC1104 and SPARK

4.26 In addition, results for the pooled analysis of the subgroups of patients who received 1 prior line of therapy (LOT) and >1 prior LOT indicate that, for all 3 outcomes (PFS, OS and overall response rate), the results were improved when R/R MCL patients received ibrutinib early in the treatment pathway. The company reported that this reinforces the findings of the *post-hoc* analysis of RAY (see section 4.14).

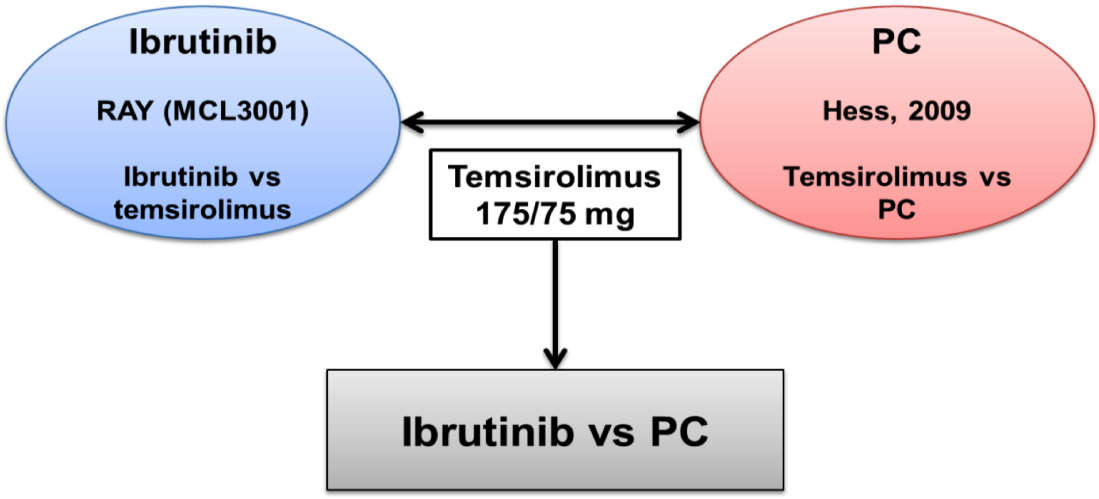
Indirect and mixed treatment comparisons

4.27 Due to the lack of direct head-to-head trial evidence for ibrutinib against a comparator reflective of current UK clinical practice, the company presented an indirect treatment comparison (ITC) based on Bucher et al. comparing ibrutinib with physician's choice (PC) of treatment in the OPTIMAL study (Hess, 2009). This was the only study identified by the company's systematic literature review that contained a potentially relevant comparator and permitted an ITC to ibrutinib via a shared temsirolimus comparator with the RAY study. OPTIMAL was a multicentre open-label randomised controlled trial that compared

temsirolimus with single agent treatment as per PC in patients with R/R MCL after 2 to 7 prior therapies. The study included 2 temsirolimus treatment arms with different dosing (175/75 mg and 175/25 mg [results of the 175/25 mg arm were not considered in the ITC, as the dose did not match the temsirolimus dose used in RAY]) and a PC arm in which patients received a range of single-agent chemotherapy regimens (primarily gemcitabine IV [42%] and fludarabine IV [23%]). The company acknowledged that, although there is no standard of care for R/R MCL, the most prominent therapies used in current clinical practice combine rituximab with chemotherapy (R-chemo) and that the single agent chemotherapy regimens used in the PC arm of OPTIMAL therefore do not fully reflect current UK clinical practice.

4.28 Data from OPTIMAL that informed the ITC included the IRC-assessed overall response rate odds ratio, IRC-assessed PFS hazard ratio, and the OS hazard ratio. The IRC-assessed overall response rate odds ratio, IRC-assessed PFS hazard ratio, and the OS hazard ratio for ibrutinib compared with temsirolimus from the clinical study report of the RAY study were used. The ITC is shown diagrammatically below in Figure 2:

Figure 2: ITC between ibrutinib (RAY and PC (OPTIMAL) via temsirolimus (company submission, figure 16, page 83)



4.29 The ITC produced hazard ratios for ibrutinib compared with PC of 0.19 for PFS and 0.59/0.61 for OS (depending on the time point for OS presented in OPTIMAL). The results are shown in Table 8.

Table 8: ITC results (company submission, table 28, page 84)

	Ibrutinib vs PC		
Outcome	**ORR**	**PFS**	**OS**
Result	60.26 [7.07, 513.4]	0.19 [0.1, 0.36]	July 19th 2007: 0.59 [0.31, 1.09] February 1st 2008: 0.61 [0.34, 1.1]
PC: Physician's choice, ORR: overall response rate, PFS: progression-free survival, OS: overall survival			

4.30 The company adjusted the treatment effect from the ITC to account for the increased effectiveness expected by clinical experts with the addition of rituximab to chemotherapy. This was based on information on the benefit of R-chemo compared with single agent chemotherapy derived from the Haematological Malignancy Research Network (HMRN) audit of 118 first line MCL patients, which estimated that the hazard ratio associated with adding rituximab to chemotherapy on PFS (adjusted for differences in patient characteristics) was 0.69 (95% CI 0.42-1.13). The final PFS hazard ratio, estimated for ibrutinib versus R-chemo using data from the ITC with the effect of adding rituximab from the HMRN audit, was 0.28.

ERG comments – meta-analysis/indirect comparison

4.31 The ERG noted that pooling of trials should be conducted at the treatment effect level, but that this is not possible for PCYC1104 and SPARK as the single-arm studies do not provide an estimate of treatment effect. However, due to the paucity of evidence for the use of ibrutinib for the treatment of R/R MCL, the ERG considered it acceptable to combine the ibrutinib studies.

4.32 The ERG had a number of concerns about the evidence used to inform the company's indirect comparison. For example, patients in OPTIMAL

were more heavily pre-treated than patients in RAY, and patients in the temsirolimus arm of OPTIMAL had more prior LOTs than patients in the temsirolimus arm of RAY. In addition, the company had performed an adjustment to the hazard ratio for PFS to account for the additional effectiveness of using rituximab alongside chemotherapy using data from the HMRN audit, which does not specifically relate to patients with R/R MCL, does not differentiate between chemotherapy regimens and has been estimated only in patients achieving a response (n=108). The ERG noted that no such adjustment for the use of rituximab was conducted for OS, and that this could have been done using OS data on rituximab plus fludarabine, cyclophosphamide and mitoxantrone (FCM) compared with FCM alone in people with R/R MCL from Forstpointner *et al*. The ERG also noted that the indirect comparison assumed that all R-chemo options have equivalent efficacy, whereas an adviser to the ERG suggested that R-bendamustine would be the treatment of choice rather than R-CHOP.

4.33 The ERG did not agree with the company's 2 stage approach to estimating treatment effects for ibrutinib compared with R-chemo and considered that a single stage approach using a random effects network meta-analysis (NMA) would provide a better representation of the uncertainty in the resulting treatment comparisons. Based on additional analyses performed by the ERG, ibrutinib was associated with a slower rate of disease progression, compared with R-chemo, but with considerable uncertainty (random effects HR = 0.27, 95% CI 0.06 to 1.26). The ERG estimated that the hazard ratio for OS when ibrutinib was compared with R-chemo ranged from 0.98 to 1.96. The ERG reported that this illustrates the high level of uncertainty for this comparison with large differences in the median hazard ratio depending on the data source used for the rituximab arm of the network (HMRN or Forstpointner). Due to concerns regarding the evidence used to inform the indirect comparisons, the ERG considered that the results should be interpreted with caution.

Adverse effects of treatment

4.34 Although median duration of treatment exposure was nearly 5-fold higher in the ibrutinib arm compared with the temsirolimus arm in RAY, the overall incidence of treatment emergent adverse effects was lower in the ibrutinib arm. There were 94 (68%) ibrutinib patients with grade 3 or higher adverse effects compared with 121 (87%) patients on temsirolimus. In the ibrutinib arm, 6.5% of patients discontinued treatment due to adverse effects compared with 25.5% in the temsirolimus arm. Overall, the most common adverse effects in the ibrutinib arm (≥ 20% of patients) were diarrhoea (29%), cough (22%) and fatigue (22%). The most frequently occurring grade 3 or higher adverse effects (≥ 10% of patients in any treatment arm) were neutropenia (ibrutinib: 12.9%, temsirolimus: 16.5%), thrombocytopenia (ibrutinib: 9.4%, temsirolimus: 42.4%), anaemia (ibrutinib: 7.9%, temsirolimus: 20.1%), and [redacted] Non-randomised data from the 2 single arm ibrutinib studies followed a similar safety profile to RAY, and the safety profile of ibrutinib from 2 real-world studies (see section 4.7) was consistent with those found in the clinical trials.

ERG comments – adverse effects of treatment

4.35 The ERG agreed that there was an improved adverse event profile in the ibrutinib arm of RAY compared with temsirolimus, and that the results were broadly consistent across the ibrutinib studies.

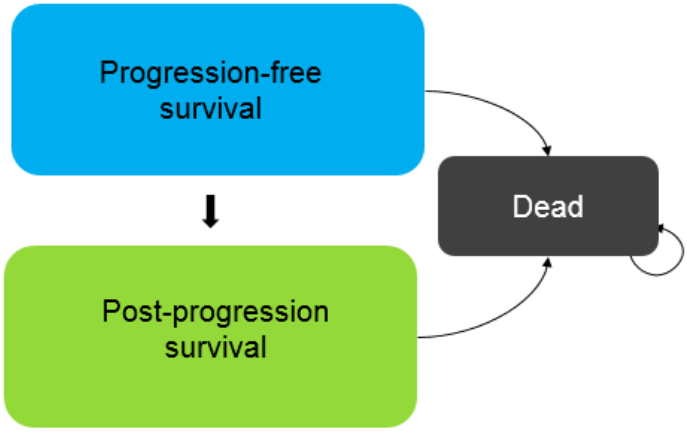
5 Cost-effectiveness evidence

Model structure

5.1 The company developed a de novo cost effectiveness model to assess the cost-effectiveness of ibrutinib for treating R/R MCL compared with R-

chemo (R-CHOP in the base case, R-CVP, FCR, RC and a blended comparison of all 4 R-chemo options weighted according to expected usage in scenario analyses). The company used a Markov model comprising 3 health states: pre-progression, post-progression and death as shown in Figure 10. It used 4-week cycle lengths (with half-cycle corrections), a time horizon of 15 years, and discounted costs and outcomes at a rate of 3.5%.

Figure 3: Model diagram (company submission, figure 29, page 130)



ERG comments – model structure

5.2 The ERG raised 3 main concerns with respect to the company's model structure: (a) the hazard of pre-progression mortality is assumed to be constant; (b) the use of PPS may introduce a selection bias, and; (c) the Markov approach imposes structural constraints which may produce bias. These are discussed below:

- In the company model, pre-progression mortality is modelled assuming an exponential distribution and the hazard ratio for patients dying prior to progression is constant. The company submission however, does not report any evidence to support this assumption. In response to a request for clarification from the ERG (see clarification response, question C22), the company provided a log-cumulative hazard plot and Kaplan-Meier survival curve for pre-progression mortality. The company's clarification response suggests that the log cumulative

hazard shows an approximately straight line with a gradient of 1 (45 degrees), which supports the use of an exponential distribution. The company's clarification response also suggests that due to the small numbers of patients experiencing pre-progression death, "*using [a] more complicated methodology would not be supported by the available evidence*." Given the company's choice of model structure and the evidence available, the ERG considered this to be a reasonable assumption although it would have been preferable to consider the use of sensitivity analysis to explore alternative survivor functions.

- Regression models fitted to Kaplan-Meier data for PPS use data only for those patients who have progressed; patients who have not yet progressed are excluded from the dataset. The ERG considered that selection bias may result if there is a true difference in survival outcomes between patients who progress earlier and those who progress later. Within the company's model, this problem may be mitigated by the fact that the same PPS rate is assumed in both the ibrutinib and R-chemo groups, although the true impact of the potential bias is not clear. The ERG also noted that the limitations in the evidence base, particularly for OS, restrict the potential for producing robust estimates of treatment effect for ibrutinib compared with R-chemo.
- The ERG noted that the company's PFS-based model makes a number of restrictive structural assumptions which lead to a poor model fit to the available OS data for ibrutinib. In the company model, PPS is assumed to follow an exponential distribution which does not reflect the PPS data well and other parametric functions may provide a statistically better fit and a more plausible extrapolation. The ERG noted that the use of a Markov design imposes several structural constraints which in some instances can preclude the model from making the best use of available evidence. The ERG undertook a partitioned survival analysis (Exploratory Analysis Set B, see section

5.37) which it considered provided a better fit to the OS data but which involved using the outputs of a highly uncertain network meta-analysis.

Model details

5.3 The pooled dataset for RAY, SPARK and PCYC1104 was used to inform the efficacy of ibrutinib, however, limited data on the effectiveness of the comparators listed in the NICE scope was available. Data from the pooled ibrutinib dataset (see sections 4.23 to 4.26) was used to estimate the baseline patients' characteristics, the proportion of people in the different states, the proportion experiencing adverse effects and the mortality rate.

5.4 The progression free health state included patients whose disease had completely responded, partially responded or who had stable disease, and was directly informed by the progression free survival curves projected based on parametric fitting of 4 distributions (exponential, Weibull, log-logistic or log-normal) to the patient level data from the pooled database for ibrutinib. The survival curves were then extrapolated beyond the trial period to derive transition probabilities. Transitions between states were derived from the proportion of patients that were reflected by the areas under the PFS and OS curves. The area between the PFS and OS curves represented the proportion of people in the post-progression state. Weibull was selected for use within the base case analysis based upon clinicians' feedback, and the impact of alternative curve fit selection was tested within scenario analyses.

5.5 Comparator efficacy was obtained by applying a hazard ratio to the relevant parametric curve selected. Due to non-availability of efficacy data for individual treatment regimens, all rituximab containing regimens were assumed to have equal effectiveness. Two approaches were tested to estimate effectiveness for comparator therapies and to calculate the PFS hazard ratio for R-chemo, as shown in Table 9. In the first approach (used in the base case analysis), the effectiveness of R-chemo was taken from the indirect comparison (described in sections

4.27 to 4.30). The hazard ratio for PFS for ibrutinib compared with R-chemo (0.28) was applied to ibrutinib in the pooled dataset.

5.6 In its second approach to estimating the effectiveness of comparator therapies, the company used temsirolimus as a proxy for UK current care using the hazard ratio directly from the RAY trial. Although the company recognised that temsirolimus is not used in UK clinical practice, it considered that this scenario allowed use of the only direct comparative RCT data available for ibrutinib.

5.7 A fixed risk of death during PFS was applied to the 2 arms in the model, which was calculated based on information from the ibrutinib clinical trials (In the base case: 0.71% for ibrutinib and 1.4% for R-chemo [equal to that of temsirolimus in RAY]).

Table 9: Approaches taken to estimate comparative efficacy (adapted from table 53, page 131 of the company submission)

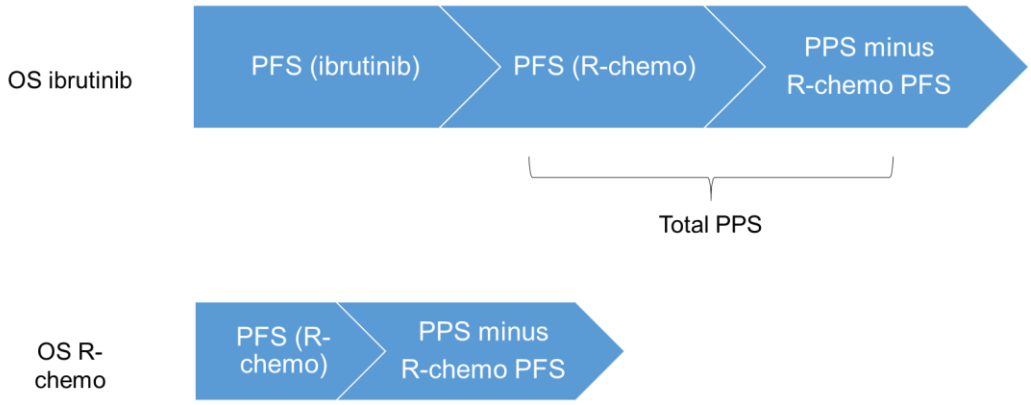
	Scenario 1 (base case) **Hess and RAY ITC**	**Scenario 2** **Efficacy of temsirolimus**
Approach	• Using results of an ITC from a published RCT including a PC arm (Hess 2009) and RAY. Results of the ITC are adjusted for the expected impact of rituximab from HMRN data • PFS HR for ibrutinib versus R-chemo = 0.28	• Assuming R-chemo is equivalent to temsirolimus within RAY (MCL3001) • PFS HR for ibrutinib versus R-chemo = 0.43
Strengths	• Provides a comparison to R-chemo • Use of a formal ITC maintains randomisation and provides a statistically robust comparison	• Uses information directly from the ibrutinib RCT undertaken in a R/R MCL population • Use of treatment effect from RAY (MCL3001) provides a statistically robust comparison
Weaknesses	• Single chemotherapy agents as used in Hess, 2009 do not reflect standard UK clinical practice • The HR for the rituximab treatment effect is based on a different population sample in newly diagnosed MCL (HMRN data) – these data can be viewed as an upper bound for the effectiveness of the addition of rituximab to chemotherapies in R/R MCL	• Temsirolimus is not a relevant comparator in UK clinical practice • No evidence is available to determine whether temsirolimus is more or less effective than R-chemo
ITC: indirect treatment comparison, RCT: randomised controlled trial, PC: physician's choice, R-chemo: rituximab plus chemotherapy, HMRN: haematological malignancy research network, R/R		

	Scenario 1 (base case) Hess and RAY ITC	Scenario 2 Efficacy of temsirolimus
MCL: relapsed or refractory mantle cell lymphoma, TEM: temsirolimus, HR: hazard ratio, PFS: progression-free survival		

5.8 Survival data from the trial were not directly extrapolated due to uncertainty around the estimates and the immaturity of the data. The company tested 2 methods to estimate long term survival in the ibrutinib and R-chemo arms. The fixed PPS approach (PFS + PPS applied in the same way in both arms) was used in the base case analysis and was considered by the company to be conservative as it assumes that patients will receive benefit from use of ibrutinib alone and not from additional treatments. PPS was calculated by fitting an exponential curve to the pooled dataset assuming a constant rate of mortality throughout the time horizon (10.83% per cycle). The median PPS observed within the pooled dataset was considered to be representative of what would be expected for R-chemo in UK clinical practice.

5.9 The sequential approach was used in a secondary analysis (PFS of ibrutinib + PFS of R-chemo after ibrutinib + PPS) and captures that ibrutinib offers an additional line of treatment to current chemotherapy regimens. PFS for ibrutinib was calculated as described in section 5.4. PFS for R-chemo was estimated using the exponential curve fitted to PFS data for the ibrutinib pooled dataset and the hazard ratio used for R-chemo compared with ibrutinib (outlined in section 5.5). The result was then used to inform the PFS for subsequent R-chemo in the ibrutinib arm, assuming that once patients progress on ibrutinib, they go on to receive R-chemo. To calculate such benefit, PPS in the ibrutinib arm was split into 2 portions: PFS for subsequent R-chemo treatment for R/R MCL and PPS post subsequent R-chemo treatment for R/R MCL as shown in Figure 4.

Figure 4: OS using the sequential approach (ibrutinib and R-chemo (taken from figure 34, page 144 of the company submission)



5.10 IRC-assessed response rates were included in the model to inform estimation of costs and resource use during PFS based upon the pooled clinical data. Comparator response rates were estimated using a variety of data sources, primarily the HMRN audit.

ERG comments – model details

5.11 The ERG had several concerns regarding the company's parametric survival modelling:

- ***Limited set of survivor functions for PFS***: The company considered the exponential, Weibull, log normal and log logistic survivor functions when modelling PFS. The ERG believed that other survivor functions, for example, the Gompertz, the generalised gamma, the gamma and the generalised F models should have been considered. In response to a request for clarification from the ERG (see clarification response, question C24), the company explored the use of the Gompertz and generalised gamma functions. Whilst the generalised gamma curve provided the best fit to the observed data in terms of Akaike Information Criterion (AIC), the company reported that both the generalised gamma and Gompertz survivor functions produced clinically implausible PFS projections. The company's clarification response also reported that the generalised F function could not be fitted using SAS (the statistical package used to undertake the company's survival analysis). The ERG

considered that this could have been fitted using an alternative software package.

- ***Application of hazard ratios to accelerated failure time models***: Within the company's scenario analyses, the hazard ratio for PFS derived from the indirect comparison was applied to the log logistic and log normal PFS functions. The ERG judged this to be inappropriate as these are accelerated failure time (AFT) models which do not assume proportional hazards. The ERG highlighted the company's clarification response that, given the implausibility of these functions, this issue was a secondary consideration (see clarification response, question C27) and considered that the company's view was reasonable.
- ***Pre-progression mortality and PPS hazards assumed to be constant:*** The ERG noted that the company's model assumes that the hazards of pre-progression mortality and PPS are constant. It does not allow for the incorporation of time-dependent transitions for PPS, hence it was not possible to explore the impact of alternative survivor functions for PPS in the company's model.

5.12 The ERG considered that none of the fitted parametric survival curves provided a reasonable fit to the observed Kaplan-Meier curve for TTD/D, and that this was unsurprising given that the hazard of treatment discontinuation or death appeared to decrease slightly between 0 and 25 months, and then increase sharply beyond this point (see Figure 24 in the ERG report). The ERG noted that, within the base case model, the company selected the use of the Weibull function, which does not provide a good visual fit to the data and leads to a much longer tail compared with the observed Kaplan-Meier curve. Using the Weibull TTD/D function, approximately 7% of patients would still be receiving treatment at 50 months, whilst the empirical Kaplan-Meier curve indicates that all patients discontinued by around 32 months. The ERG highlighted that this led to an overestimation of the modelled drug costs for ibrutinib, thereby inflating the ICER for ibrutinib compared with R-chemo. The ERG agreed that the tail of the TTD/D curve is uncertain,

and considered that the best estimate of the cumulative survival probability for this outcome is estimated using the observed Kaplan-Meier data directly rather than a parametric model which does not provide a good fit to those data. The impact of using the observed Kaplan-Meier curves for TTD/D is presented as part of the ERG's exploratory analyses (see Section 5.4 of the ERG report).

5.13 The ERG considered that, irrespective of the approach used to model the effectiveness of ibrutinib against R-chemo, the resulting estimates of incremental health gain would be subject to considerable uncertainty due to the limitations of the evidence base for ibrutinib. The ERG considered the uncertainty to be driven by 4 main issues: (a) the absence of randomised head-to-head trial comparisons for ibrutinib versus R-chemo and the limitations of the indirect comparison (see sections 4.31- 4.33) (b) the presence of treatment switching within RAY; (c) immaturity of the available OS data within the pooled ibrutinib dataset and; (d) the use of other therapies beyond disease progression which are not used in England.

5.14 The ERG raised concerns regarding the validity of the company's sequential model which compares ibrutinib followed by R-chemo against R-chemo alone. Due to the strong assumptions and structural constraints applied in the model as well as significant errors in calculations, the ERG considered that the results of this analysis be disregarded.

5.15 The ERG noted that the company's scenario analyses included the use of a blended comparison of 3 alternative R-chemo options. The ERG considered blended comparisons to be inappropriate as they may lead to misleading conclusions on the cost-effectiveness of ibrutinib in the R/R MCL population.

Health-related quality of life

5.16 Health-related quality of life (HRQoL) values were based on post baseline EQ-5D pooled data from RAY and SPARK and were used to inform both PFS and PPS HRQoL within the model. All utility values were calculated based on time to death and progression-based states. Utility values obtained for both the pre-progression and post-progression health states for ibrutinib already accounted for decrements due to adverse effects; therefore no additional decrements were applied to the ibrutinib arm in the model to avoid double counting. Utility decrements derived from clinical opinion were applied to the R-chemo arm to reflect the toxic effect of receiving chemotherapy and the impact on patients' HRQoL and functioning. Utilities were also adjusted to account for the natural decline in HRQoL associated with age. The company highlighted that the modelled EQ-5D utility value for progression free patients (0.78) represents a utility gain of only 0.05 from the 0.73 baseline EQ-5D utility observed in RAY (see section 4.17). By contrast, the company reported that clinical experts expected utility values for MCL patients on treatment with ibrutinib to be similar to the general population. The company was therefore concerned that values elicited with the EQ-5D may underestimate the true utility gain associated with ibrutinib, observed with FACT-Lym and by clinical experts. The utility values used in the model are reported in Table 10.

Table 10: Summary of utility values used in the base case of the company model taken from table 65, page 151 of the company submission)

State	Utility value: mean (SE)	HRQoL per 28 days	95% CI	Reference in submission (section)	Justification
Pre-progression	0.78	0.060	0.762 – 0.799	Section 5.41	Pooled ibrutinib EQ-5D data from first treatment for R/R MCL
Post-progression	0.68	0.052	0.634 – 0.727	Section 5.41 **Error! Reference source not found.**	
R-chemo decrement	0.2	0.015	0.1 - 0.3	Section 5.41	Clinician feedback[11]

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

ERG comments - HRQoL

5.17 The ERG raised concerns regarding the company's approach to modelling HRQoL data and the reliability of the estimates; however it acknowledged that these were driven largely by the limitations of the available evidence base.

5.18 The ERG highlighted that the disutility associated with R-chemo reflects clinicians' judgements which have not been derived using a preference-based method. This is parameterised in the company's model as a QALY loss per 4-week cycle without age-adjustment. The ERG highlighted that the company had conducted a sensitivity analysis in which the QALY decrement was calculated by subtracting the EQ-5D VAS valuation reported in a study of patients with progressed disease with CLL and MCL by Schenkel *et al*. (VAS estimate=0.61) from the progression-free utility of 0.78 derived from the RAY (MCL3001) and SPARK (MCL2001) studies. This results in a slightly lower QALY loss of 0.013 per 4-week period. However, the ERG noted that the quality of life estimate reported by Schenkel et al relates to a mixed population of patients (52 of 75 patients had CLL rather than MCL) and the EQ-5D VAS does not estimate utility as it is not a preference-based instrument.

5.19 The ERG highlighted the uncertainty surrounding progression-free and post-progression utility values used in the company model. It noted that patients in the R-chemo group who are progression-free experience a lower level of HRQoL than patients on ibrutinib who are progression-free because of disutility associated with chemotherapy-related toxicity and fatigue. Therefore, modelled patients in the R-chemo group experience a lower level of HRQoL whilst progression-free (utility=0.58 [0.78 minus 0.20]) compared with patients who have experienced disease progression and have discontinued treatment (utility=0.68). The ERG noted that only 36 patients contributed data to the post-progression utility

value (compared with 234 patients who contributed data to the progression-free utility value).

5.20 The ERG noted that patients were assumed to receive chemotherapy for a maximum of 6 cycles but that the disutility for the R-chemo group was applied to the entire duration of the TTD/D curve. Whilst clinical advisors to the ERG stated that the effects of toxicity may persist beyond treatment cessation (ranging from 3-12 months), the ERG noted that beyond 6 cycles the TTD/D curve for R-chemo does not reflect time to progression or time on treatment since all patients have discontinued R-chemo before this time-point. The ERG also disagreed with the company's assumption that quality of life would return to normal immediately upon ending R-chemo treatments. However, the ERG highlighted that the assumed disutility duration does not have a material impact upon the ICER for ibrutinib compared with R-chemo (see sections 5.36-5.37).

5.21 Due to the uncertainty surrounding available HRQoL estimates, the ERG considered that the company should have explored the use of utility estimates from patients with other types of lymphoma and not limited evidence to R/R MCL. The ERG noted that the company assumed alternative utility values of 0.45 to 0.636 for the post-progression state in their response to clarification (question C2). The ERG highlighted that these additional analyses indicate that the utility value applied in the progression state does not materially impact upon the ICER for ibrutinib compared with R-chemo (assuming post-progression utility scores of 0.45 and 0.636 resulted in ICERs of £73,865 and £75,035 per QALY gained, respectively).

5.22 The ERG acknowledged that there may be a disconnect between the EQ-5D evidence from RAY and clinical experience using ibrutinib but it was not aware of any other evidence of the benefits of ibrutinib using a preference-based measure of HRQoL in the R/R MCL population.

Cost and healthcare resource use

5.23 The company included costs reflecting the clinical management of R/R MCL in an NHS setting which included treatment costs, monitoring and follow up, management of complications and adverse effects and terminal care. Drug acquisition costs were taken from common UK sources, from the electronic market information tool (eMit) and the monthly index of medical specialities (MIMS) and administration costs were sourced from NHS reference costs or the Personal Social Services Research Unit 2015 (PSSRU). The analyses presented by the company incorporated the agreed patient access scheme for ibrutinib.

5.24 Costs associated with resource use based upon clinicians' feedback were estimated using data generated via a custom, on-line survey launched in November and December 2014. The survey was completed by actively practising NHS haematologists and oncologists and the outcomes validated by expert opinion from leading UK haematologists experienced in MCL.

5.25 For the comparator costs, the company calculated the average number of vials of IV drugs per patient using body surface area data from the pooled dataset of RAY, SPARK and PCYC1104 and assumed that patients received only whole vials with no vial sharing. In order to accurately estimate the proportion of patients receiving ibrutinib treatment during each model cycle, information for the observed time on treatment was derived from the pooled dataset. R-chemo patients were modelled to stay on treatment for the maximum number of cycles permitted for the specific chemotherapy that was received and ibrutinib was administered in patients until progression or unacceptable toxicity. For consistency within the model, the same curve fit was selected for time on treatment as for PFS (Weibull).

5.26 The cost of subsequent therapy was not included within either arm of the model except when modelling OS using the sequential approach for ibrutinib where both the costs and benefits of including an additional line

of R-chemo are included within the ibrutinib arm (see section 5.9). This was due to the small proportion of patients in the pooled dataset who received subsequent therapy as well as limited information available on the use of subsequent treatment for R-chemo. The incidence of adverse events was derived from the pooled dataset for ibrutinib and available literature for R-chemo (see Table 64 in section 5.4 of the company submission). All grade 3 or higher adverse events that occurred in at least 5% of the patients treated with ibrutinib within the pooled clinical trial data were included in the model, unless regarded clinically irrelevant by clinical experts. In addition, clinicians identified several clinically meaningful adverse events which occur at lower rates with either ibrutinib or R-chemo that were included in the model. The company reported that the NHS reference costs codes used to derive adverse effects costs were consistent with the adverse events reported in the company submission for technology appraisal 370 in first-line MCL. Lastly, the company applied a one-off terminal care cost within the model based on Nuffield 2014 inflated to reflect current prices (using the hospital and community health service (HCHS) inflation indices reported within the PSSRU). 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.

ERG comments – costs and healthcare resource use

5.27 The company's base case model did not include the costs of subsequent-line therapies in either group. Clinical advisors to the ERG noted that patients whose disease progresses after R-chemo or ibrutinib are likely to receive further treatment using a different chemotherapy regimen (in combination with rituximab if not refractory). Given that no adjustment has been made to account for the survival contribution of post-progression therapies to PPS, the ERG considered that the costs of these subsequent-line therapies should have been included in the company's base case model. The ERG noted that a scenario analysis by the company was presented in which FCR was included as subsequent-

line therapy for both model groups resulting in a slightly reduced ICER (see Table 17 in company clarification response).

Company's base-case results and sensitivity analysis

5.28 The company used the comparator R-CHOP in its base case economic analyses on the assumption that the 3 comparator therapies in use in UK practice would rank as follows in terms of effectiveness (most effective first): R-CHOP, R-CVP, FCR (advice from clinical experts suggested that RC is not used for R/R MCL). Despite lack of clinical effectiveness data for each comparator, the availability of individual costs for each treatment allowed for their inclusion in scenario analyses.

5.29 The company identified errors in the results presented in its submission and provided corrected results in its clarification response. Base case results for ibrutinib compared with R-CHOP showed that ibrutinib provided an additional [redacted] life years and [redacted] quality-adjusted life years (QALYs). The incremental cost was £70,522 resulting in an ICER of £75,317 per QALY gained.

5.30 Probabilistic sensitivity analyses (PSA) were performed to assess the uncertainty around the variables included in the model. The results led to a probabilistic ICER of £75,878 per QALY gained for ibrutinib compared with R-CHOP. Overall the average incremental QALYs gained from ibrutinib was 0.94 with a mean incremental cost of £71,243. The cost-effectiveness acceptability curves showed that the probability that ibrutinib was cost effective at a maximum acceptable ICER of £50,000 per QALY gained was approximately 0%.

5.31 The company reported that the results from the scenario analyses which tested the structural uncertainty within the model were consistent with the base case results. Across all but one of the scenario analyses, the ICER for ibrutinib compared with R-CHOP was greater than £70,000 per QALY gained. The model was most sensitive to the PPS assumed for R-chemo (assumed to be the same as ibrutinib in the fixed PPS approach),

with the ICER reducing to £59,345 per QALY gained when HMRN data were used to inform PPS. This minimised the difference between the median OS within the model and the median survival reported within the HMRN data (estimated to be 8.4 months for patients on 2nd line treatment). The model was also sensitive to the dataset used to inform the PFS of R-chemo. Using the PFS of temsirolimus from RAY as a proxy for R-chemo increased the ICER to £74,833 per QALY gained as the estimate used to inform R-chemo was higher than the one in the base case. The company highlighted that key uncertainties within the model parameterisation surrounded the parametric curve fits to time on treatment and PFS as well as the hazard ratio assumed for comparative efficacy within the model.

5.32 A subgroup analysis by number of prior lines of treatment (LOT) showed that ibrutinib was more cost effective compared with R-CHOP in patients who received 1 prior LOT (incremental costs £108,398, incremental QALYs 1.67, ICER £64,755) compared with patients who received 2 or more prior LOTs (incremental costs £59,685, incremental QALYs 0.72, ICER £83,256). The company reported that this was consistent with the higher efficacy gains in patients who received 1 prior LOT in the post-hoc analysis of RAY (see section 4.14) and the pooled ibrutinib analyses (see section 4.23).

5.33 The company carried out a threshold analysis on the comparative effectiveness of ibrutinib and R-chemo which showed that the ICER was largely insensitive to increases in the hazard ratio for R-chemo. Similarly, the company reported that reducing the estimate of comparative efficacy of ibrutinib over R-chemo by decreasing the hazard ratio of adding rituximab (which increases the overall PFS hazard ratio of R-chemo), only impacted the ICER substantially when 'unrealistic' hazard ratios for the rituximab effect were tested.

Company scenarios

Table 11 Scenario analyses

Scenario	Total cost	Inc. cost	Inc. QALY	ICER
Base case	[redacted]	£70,522	0.94	£75,317
Comparator efficacy HR for PFS using temsirolimus data	[redacted]	£70,253	0.93	£75,681
Time horizon: 10 years	[redacted]	£70,541	0.94	£75,279
Time horizon: 20 years	[redacted]	£71,847	0.94	£76,732
Comparator: R-CVP	[redacted]	£68,354	0.94	£73,002
Comparator FCR	[redacted]	£69,580	0.94	£74,312
Comparator RC	[redacted]	£70,546	0.94	£75,343
Treatment mix	[redacted]	£70,948	0.94	£75,773
No wastage included	[redacted]	£70,522	0.94	£75,318
Utility decrement for R-chemo based on Schenkel *et al.* 2014	[redacted]	£70,522	0.93	£76,194
No age-adjusted utilities	[redacted]	£70,522	0.95	£74,336
Sequential approach (OS ibrutinib = PFS ibrutinib + PFS R-chemo + PPS)	[redacted]	£82,751	1.08	£76,671
Including FCR as subsequent treatment	[redacted]	£68,940	0.94	£73,628
PFS curve: exponential	[redacted]	£66,914	0.83	£80,296
PFS curve: log-normal	[redacted]	£93,071	1.30	£71,636
PFS curve: log-logistic	[redacted]	£97,926	1.32	£74,194
Risk of death during PFS for R-chemo assumed equal to ibrutinib	[redacted]	£70,275	0.92	£76,605
Response rates of R-chemo equal to temsirolimus response	[redacted]	£70,068	0.94	£74,833
Response rates of R-chemo equal to response in Hess, 2009	[redacted]	£69,607	0.94	£74,341
Response rates of R-chemo equal to ibrutinib	[redacted]	£70,626	0.94	£75,429
No benefit from rituximab in PFS HR (rituximab HR = 1)	[redacted]	£72,309	1.00	£72,311
Rituximab PFS HR applied to Hess, 2009 ITC = 0.75	[redacted]	£70,933	0.95	£74,429
Rituximab PFS HR applied to Hess, 2009 ITC = 0.89	[redacted]	£71,760	0.98	£73,019
Rituximab PFS HR applied to Hess 2009 ITC = 1.6	[redacted]	£74,321	1.05	£70,779
Applying a HR to PPS of R-chemo to adjust survival to be as close as possible to HMRN anticipated survival (8.4 months for patients on	[redacted]	£110,949	1.87	£59,345

2nd line treatment)				
HR: hazard ratio, PFS: progression-free survival, TEM: temsirolimus, R-CVP: rituximab + cyclophosphamide + vincristine + prednisone, FCR: fludarabine + cyclophosphamide + rituximab, RC: rituximab + cytarabine, R-chemo: rituximab-based chemotherapy, OS: overall survival, ITC: indirect treatment comparison, PPS: post-progression survival, HMRN: haematological malignancy research network, QALY: quality-adjusted life year, LY: life year, Inc: incremental				

ERG comments on the company's model results

5.34 Based on a re-run of the company's base case model, the ERG found similar results to the company (probabilistic ICER for ibrutinib versus R-CHOP: £76,014 compared with £75,878 per QALY gained estimated by the company; deterministic ICER £75,317 per QALY gained in both cases).

5.35 The ERG agreed with the company that across all but one of the company's scenario analyses, the ICER for ibrutinib versus R-chemo was greater than £70,000 per QALY gained. The only exception was analysis in which the modelled OS for R-CHOP was "calibrated" against the HMRN OS estimate of 8.4 months by adjusting the post-progression mortality rate in this group only (ICER=£59,345 per QALY gained). The ERG clarified that this analysis was undertaken in the subgroup of patients who had 1 prior LOT rather than the overall base case population. The ERG also highlighted that the choice of comparator regimen did not have a material impact upon the company's deterministic ICER for ibrutinib.

5.36 The ERG considered that the company's subgroup analysis according to number of prior LOTs indicated the potential for an improved cost-effectiveness profile for ibrutinib. However, it was concerned about the post hoc nature of the subgroup analyses and poor fit of the PFS survivor function to the 1 prior LOT subgroup.

ERG exploratory analyses

5.37 The ERG undertook 2 sets of exploratory analyses. The first set of exploratory analyses ("Set A") involved amending the parameter values of the company's model. This included: 1) using the HR for PFS for ibrutinib versus R-CHOP from the ERG's random effects network meta-analysis instead of the company's analysis (ERG's HR = 0.27; company's HR = 0.28); 2) the use of the Kaplan-Meier curve instead of a parametric (Weibull) curve to model TTD/D for ibrutinib; 3) the truncation of the R-chemo QALY loss upon treatment discontinuation rather than for the entire duration of the TTD/D curve). The ERG's exploratory analyses Set A found the following:

- The impact of using the HR for PFS from the ERG's random effects network meta-analysis had a negligible impact upon the cost-effectiveness of ibrutinib (ICER=£75,094 per QALY gained). Use of the Kaplan-Meier curves for TTD/D improved the cost-effectiveness of ibrutinib versus R-chemo; within this analysis the ICER was estimated to be £61,472 per QALY gained. The truncation of the R-chemo disutility upon treatment discontinuation increased the ICER for ibrutinib versus R-CHOP to £77,111 per QALY gained.
- The ERG's preferred analysis within Set A combined all 3 amendments above and this produced a probabilistic ICER for ibrutinib versus R-CHOP of £63,340 per QALY gained. Within this preferred analysis, the use of alternative utility values sourced from the literature for the progression-free (0.805; 0.81) and post-progression (0.618; 0.60) health states produced ICERs for ibrutinib compared with R-CHOP ranging from £59,952 to £60,417 per QALY gained, respectively. In addition, analyses in which rituximab was excluded from the comparator regimen to reflect patients who are resistant to rituximab produced ICERs ranging from £64,727 (cost of rituximab set to zero) to £69,054 ('rituximab effect' removed from the indirect comparison) per QALY gained.

- Using the ERG's preferred analysis, the ICER for ibrutinib compared with R-CHOP for the subgroup of patients who had 1 prior LOT was £44,711 per QALY gained.

5.38 The second set of exploratory analyses ("Set B") explored the impact of using a partitioned survival approach and involved amending the structure of the company's model such that OS data for ibrutinib from the pooled dataset was used as an input. The analysis involved 1) using the hazard ratios for PFS and OS for ibrutinib compared with R-chemo from the ERG's random effects network meta-analysis; 2) the use of the Kaplan-Meier curve instead of a parametric (Weibull) curve to model TTD/D for ibrutinib; 3) the truncation of the R-chemo QALY loss upon treatment discontinuation rather than for the entire duration of the TTD/D curve.The ERG's exploratory analyses set B found the following:

- Irrespective of whether the rituximab effect was estimated using data reported by Forstpointner *et al*., the HRMN audit or both, ibrutinib was dominated by R-CHOP. The ERG noted that this was likely to be a consequence of problems in robustly estimating treatment effects for OS given the evidence.
- Irrespective of the true value of the hazard ratio for PFS and the source of utility values, the hazard ratio for OS for ibrutinib compared with R-CHOP necessary for ibrutinib to have an ICER below £50,000 per QALY gained is around 0.39-0.40.

5.39 Exploratory analyses performed by the ERG suggest that the key uncertainty surrounding the cost-effectiveness of ibrutinib relates to its expected OS gain compared with R-chemo. The ERG highlighted the inherent uncertainty in all the analyses undertaken. Whilst the company's PFS-based model makes a number of restrictive structural assumptions which lead to a poor model fit to the available OS data for ibrutinib, the ERG's partitioned survival analysis (set B) involves using the outputs from a highly uncertain network meta-analysis despite providing a better fit to the OS data.

Table 12 ERG exploratory analyses

Scenario	Total cost	Inc. cost	Inc. QALY	ICER
Company's base case	[redacted]	£70,522	0.94	£75,317
Exploratory Analysis A1 - HR for PFS derived from ERG's random effects NMA	[redacted]	£70,619	0.94	£75,094
Exploratory Analysis A2 - TTD/D for ibrutinib group based on Kaplan-Meier curve	[redacted]	£57,558	0.94	£61,472
Exploratory analysis A3 - Truncation of R-chemo disutility following treatment discontinuation	[redacted]	£70,522	0.91	£77,111
ERG base case: Exploratory analysis A4 - ERG's preferred analysis using the company's model (combining amendments in analysis A1-A3)	[redacted]	£57,656	0.92	£62,697
Exploratory analysis A5 (based on the ERG's preferred analysis)–Use of alternative utility values for progression-free and post-progression states- (i) Utilities for progression-free and post-progression based on Lachaine et al	[redacted]	£57,656	0.95	£60,417
Exploratory analysis A5 – (based on the ERG's preferred analysis)– Use of alternative utility values for progression-free and post-progression states- (ii) Utilities for progression-free and post-progression based on Yoong et al	[redacted]	£57,656	0.96	£59,952
Exploratory analysis A6 – (based on the ERG's preferred analysis)– Cost-effectiveness of ibrutinib versus chemotherapy for rituximab-resistant patients (i) Cost of rituximab set to zero	[redacted]	£63,501	0.92	£69,054
Exploratory analysis A6 – (based on the ERG's preferred analysis)– Cost-effectiveness of ibrutinib versus chemotherapy for rituximab-	[redacted]	£64,182	0.99	£64,727

resistant patients (ii) Cost of rituximab set to zero and PFS HR=0.19				
Exploratory Analysis A7: (based on the ERG's preferred analysis)– Ibrutinib versus R-CHOP in the 1 prior LOT subgroup using the ERG's preferred analysis	[redacted]	£73,069	1.63	£44,711
Exploratory analysis B1 – partitioned survival analysis using alternative NMA-derived hazard ratios for OS, probabilistic model- NMA – rituximab effect informed by Forstpointner et al	[redacted]	£29,999	-1.28	Dominated
Exploratory analysis B1 – partitioned survival analysis using alternative NMA-derived hazard ratios for OS, probabilistic model- NMA – rituximab effect informed by HMRN	[redacted]	£45,909	-0.05	Dominated
Exploratory analysis B1 – partitioned survival analysis using alternative NMA-derived hazard ratios for OS, probabilistic model- NMA rituximab effect informed by Forstpointner et al and HMRN	[redacted]	£42,476	-0.31	Dominated
Abbreviations: Inc., incremental; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio;NMA,network meta-analyses				

Innovation

5.40 The company considers ibrutinib to be innovative because:

- It is a novel treatment option for R/R MCL, an incurable disease with rapid progression, high relapse rates and poor long term prognosis, because it offers opportunity for daily dosing whilst minimising the duration of side effects. Once patients relapse, there is no standard of care and response to second-line treatment is poorer and shorter than for first line treatments. As a result, ibrutinib addresses a significant unmet need within the MCL treatment pathway.

- Its value in addressing this unmet need is highlighted by analysis of Cancer Drug Fund notifications, data from the compassionate use programme (CUP) and of IMS Harmony market research data demonstrating its rapid uptake in clinical practice.

- Its innovative nature was recognised by the EMA and the FDA through their approval based solely upon overall response rate, a surrogate end-point from a phase II study. The oral administration of ibrutinib also reduces the patient, carer and NHS burden associated with current intravenous MCL treatments.

6 End-of-life considerations

6.1 Table 13 summarises the end-of-life criteria in relation to ibrutinib for treatment of R/R MCL:

Table 13 End-of-life considerations

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The company reported that UK data from the HMRN reveals that median OS was 8.4 months in patients with R/R MCL. This is supported by data from 2 additional sources: • Median OS of 9.7 months in patients receiving physician choice (PC) of treatment in the phase III OPTIMAL trial (Hess, 2009), comparing temsirolimus with PC. •Median OS of 5.2 months in a real-world registry of patients treated at the Skåne University Hospital in Sweden between 2000 and 20128. These data provide survival estimates of approximately 5-10 months in current UK clinical practice (see Table 51 in the company submission). The ERG agreed that using treatments currently available on the NHS, the expected OS for the R/R MCL population is typically less than 24 months.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	The pooled analysis of the RAY, SPARK and PCYC1004 trials found a median OS estimate of 25 months for patients receiving ibrutinib. This is considerably greater than the 5-10 month estimate of survival in clinical practice (see above). The company reported that the available literature

<table>
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<td>within MCL indicates that PFS provides a good surrogate for OS and that this approach has been accepted in previous HTAs for MCL. The table below provides a summary of the median OS and PFS estimates for ibrutinib.
Table: PFS and OS to support end-of-life criteria 1 and 2
<table>
<tr><th></th><th>Median PFS (months)</th><th>Median OS (months)</th></tr>
<tr><td>Ibrutinib, RAY (MCL3001)</td><td>14.6</td><td>NR</td></tr>
<tr><td>Ibrutinib, pooled analysis</td><td>12.81</td><td>25.00</td></tr>
<tr><td>HMRN</td><td>NA</td><td>8.4</td></tr>
<tr><td>PC, Hess, 2009</td><td>1.9</td><td>9.7</td></tr>
<tr><td>Skåne registry</td><td>2.8</td><td>5.2</td></tr>
</table>
The ERG notes that whilst comparing the median OS from the pooled analysis against the HMRN data, the OPTIMAL trial and the Skåne registry suggests an incremental gain in median OS of more than 16 months, this form of naïve indirect comparison may be subject to confounding due to differences between the populations recruited into the studies and the design of those studies. In addition, the ERG did not consider the use of PFS data meaningful in supporting the argument that ibrutinib meets the end of life criteria for incremental survival benefits. The ERG noted considerable uncertainty in the incremental survival benefit associated with ibrutinib compared with existing therapies currently used on the NHS. This uncertainty is principally driven by the absence of a direct head-to-head trial against any relevant comparator, the immaturity of the OS data within the pooled ibrutinib dataset and the weaknesses in the studies included in the ERG's network meta-analyses of OS (see section 4.33).</td>
</tr>
<tr>
<td>The treatment is licensed or otherwise indicated for small patient populations</td>
<td>The company estimated that the number of patients with R/R MCL eligible to receive ibrutinib in England, Wales and Northern Ireland in 2017 is 356 (see Section 6 of the company submission). This equates to a patient population smaller than 1 in 50,000.
The ERG agreed that the eligible patient population is expected to be small, but noted that this criterion is no longer considered by NICE.</td>
</tr>
<tr>
<td colspan="2">Abbreviations: HMRN: Haematological Malignancy Research Network, OS: overall survival, NHS: National Health Service, PC: Physician's Choice, NR: not reached, NA: not available
Source: company's submission table 50(page 122)</td>
</tr>
</table>

7 Equality issues

7.1 The company reported that equality issues such as restriction to certain chemotherapy agents known to be less active but better tolerated in older, frailer patients would be alleviated with the use of ibrutinib. Furthermore, the oral administration of ibrutinib allows an effective treatment option to be given to patients that may not have local access or transport to an appropriate infusion unit.

7.2 A submission from a patient group also highlighted that older patients, particularly those with co-morbidities who might not be fit enough for comparator treatments, may benefit more than other patients from ibrutinib due to its reduced toxicity profile. It was noted that if ibrutinib was not approved for use on the NHS, then older people may be disadvantaged, as they will potentially have reduced access to effective treatments with reduced toxicity profiles, compared with younger people.

8 Authors

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with input from the Lead Team (David Thomson, Ellen Rule and Paul Robinson)

Appendix A: Clinical efficacy section of the draft European public assessment report

The positive CHMP opinion can be found at the link below:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/003791/WC500177778.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ibrutinib for treating relapsed or refractory mantle cell lymphoma

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of ibrutinib within its marketing authorisation for treating relapsed or refractory mantle cell lymphoma.

Background

Lymphomas are cancers of the lymphatic system, which is a part of the immune system. Traditionally, lymphomas are divided into Hodgkin's lymphoma and non-Hodgkin's lymphoma. Non-Hodgkin's lymphomas are a diverse group of conditions which are categorised according to the cell type affected (B-cell or T-cell), as well as the clinical features and rate of progression of the disease. Mantle cell lymphoma is a rare and often aggressive type of non-Hodgkin's lymphoma which affects B-cells.

Approximately 10,800 people were diagnosed with non-Hodgkin's lymphoma in England in 2011, including approximately 500 with mantle cell lymphoma. Mantle cell lymphoma is more common in men than women (75% of people with mantle cell lymphoma are men), and it predominantly affects older people (the median age at presentation is 63 years). Most people with mantle cell lymphoma are diagnosed in advanced stages of the disease, with 80–90% of people diagnosed with Ann Arbor stage III or IV lymphoma.

Mantle cell lymphoma has been one of the most difficult types of non-Hodgkin's lymphoma to treat. Although it often responds well to initial chemotherapy, the duration of remission is often short and the median overall survival is 3–5 years. There is no accepted standard treatment for relapsed or refractory mantle cell lymphoma, and the choice of treatment depends on the overall aim of therapy, the grade of disease, age and fitness. The British Committee for Standards in Haematology (BCSH) guidelines recommend that treatment with rituximab (with or without cyclophosphamide and fludarabine), combination chemotherapy, temsirolimus or bortezomib should be considered. However, temsirolimus is not used in clinical practice in England and bortezomib has been removed from the Cancer Drugs Fund (CDF). In NHS clinical practice, treatment for relapsed or refractory mantle cell lymphoma is most commonly rituximab combined with cyclophosphamide, doxorubicin, vincristine and prednisolone, or with bendamustine. However, bendamustine is no longer available on the CDF.

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 the treatment of adult patients with relapsed or refractory mantle cell lymphoma. It is administered orally.

Intervention(s)	Ibrutinib
Population(s)	Adults with relapsed or refractory mantle cell lymphoma.
Comparators	Established clinical management without ibrutinib, including: • Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) • Rituximab,cyclophosphamide, vincristine and prednisolone (R-CVP) • Fludarabine cyclophosphamide and rituximab (FCR) • Rituximab and cytarabine
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • overall response rate • duration of response/remission • time to new anti-lymphoma treatment/time to progression • 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 Technology Appraisals: Appraisals in development 'Bendamustine in combination with rituximab for the first-line treatment of mantle cell lymphoma' NICE technology appraisals guidance [ID609]. Suspended. Publication date to be confirmed. 'Lymphoma (mantle cell, relapsed, refractory) – lenalidomide' NICE technology appraisals guidance [ID739]. Suspended. Publication date to be confirmed. Related Guidelines: 'Improving outcomes in haemato-oncology cancers' Cancer Service Guidance, October 2003 Under review. Guidelines in development 'Non-Hodgkin's lymphoma: diagnosis and management of non-Hodgkin's lymphoma' Publication expected July 2016 Related NICE Pathways: NICE Pathway: Blood and bone marrow cancers, Pathway created: Dec 2013. http://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers/blood-and-bone-marrow-cancers-overview
Related National Policy	Department of Health, Jan 2011, 'Improving Outcomes: A Strategy for Cancer'

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ibrutinib for treating relapsed or refractory mantle cell lymphoma [ID753]

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Manufacturers/sponsors • Janssen (ibrutinib) Patient/carer groups • African Caribbean Leukaemia Trust • Anthony Nolan • Black Health Agency • Bloodwise • Cancer Black Care • Cancer Equality • Cancer52 • Helen Rollason Cancer Charity • HAWC • 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 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 • British Transplantation Society • 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 for Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Comparator manufacturers • Accord Healthcare (doxorubicin) • Actavis UK(fludarabine) • Baxter Healthcare (cyclophosphamide) • Eli Lilly (vincristine) • Genus Pharmaceuticals (vincristine) • Hameln Pharmaceuticals (doxorubicin) • Hospira UK (cytarabine,doxorubicin, fludarabine, vincristine) • Janssen (doxorubicin) • Medac UK (doxorubicin) • Napp Pharmacuticals (cytarabine) • Pfizer (cyclophosphamide, cytarabine doxorubicin,) • Roche Products (rituximab) • Sandoz(cyclophosphamide) • Sanofi (fludarabine) • Teva UK (doxorubicin, fludarabine, vincristine)

Appendix C

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 Radiographers • UK Clinical Pharmacy Association • UK Health Forum • UK Oncology Nursing Society <u>Others</u> • Department of Health • NHS England • NHS Leeds South and East CCG • NHS Salford CCG • Welsh Government	<u>Relevant research groups</u> • Cochrane Haematological Malignancies Group • Elimination of Leukaemia Fund • Health Research Authority • Institute of Cancer Research • Leuka • Leukaemia & Lymphoma Research • 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 experts 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 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;; 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 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 the treatment of relapsed or refractory mantle cell lymphoma

Company evidence submission

April 2016

File name	Version	Contains confidential information	Date
ID753_Janssen_ibrutinib_submission_18Apr16	2.0	Yes	18/04/2016

Foreword

Introduction

Ibrutinib is a first in class Bruton's tyrosine kinase (BTK) inhibitor in a disease area with extremely poor prognosis and unmet need. It represents a clear step-change in the treatment of mantle cell lymphoma (MCL) in patients who did not respond to or relapsed on one or more previous treatments. Ibrutinib is an orphan treatment and meets the end-of-life NICE criteria. At the time of licensing of ibrutinib for relapsed/refractory (R/R) MCL, based upon results from the phase II trial PCYC1104, the CHMP acknowledged (July 2014) that the "*dramatic activity seen in terms of ORR, and DOR is unprecedented historically*"[1]. Since then these impressive results have been further substantiated in the SPARK (MCL2001) and RAY (MCL3001) studies.

Opportunity for further evidence collection to reduce uncertainty

As ibrutinib is a Cancer Drugs Fund (CDF) transition drug, Janssen requests the opportunity to remain on the CDF in order to collect further evidence, to reduce the level of uncertainty that currently exists. The following three reasons outline why we believe that further evidence would decrease the level of uncertainty for the Committee:

- No statistically significant overall survival (OS) benefit has yet been observed in the RAY (MCL3001) trial, at a median of 20 months of follow-up. It should be borne in mind, however, that the study was not statistically powered to show OS difference and was confounded by 32 (23%) patients in the TEM arm who crossed over to ibrutinib treatment. Furthermore, OS may be influenced by the clinical benefit of subsequent anticancer therapies received following progression on ibrutinib or temsirolimus (TEM), as these therapies may affect post-progression survival (PPS). The final data cut of RAY (MCL3001) is expected in the first quarter of 2017, when a statistically significant OS benefit of ibrutinib over TEM is expected.
- No evidence is available to inform any of the comparators listed in the NICE scope within the published literature for R/R MCL. Extensive efforts were made to source evidence to inform any of the comparators and the best sources of evidence found were i) the Hess, 2009 trial that allowed a simple indirect comparison using the TEM arm as a link to the RAY (MCL3001) study and ii) several sources to inform the benefit of combining rituximab with chemotherapy compared to chemotherapy alone. As explained in the submission there is substantial uncertainty around comparative data and, although a scenario analysis was presented assuming the efficacy of comparators to be the same as TEM from RAY (MCL3001), Janssen believe that better options could be explored in the next 12 months:
    - Further data cuts are expected for the Haematological Malignancy Research Network (HMRN) audit. These new analyses are expected to also include data on ibrutinib and, therefore, potentially allow a direct comparison of ibrutinib vs. rituximab in combination with chemotherapy (R-chemo) in UK real-life clinical practice.
    - Other registries are being explored, including registries outside the UK. The Janssen PHEDRA initiative (Platform for Haematology in EMEA: Data for Real World Analysis) is looking to generate R/R MCL data from countries including France, Italy, Germany, Netherlands and Sweden. This will look to describe treatment practices, outcomes and medical resource use.

- The incremental quality of life (QoL) benefit of ibrutinib is a key area of uncertainty. This uncertainty relates to the fact that i) the only EQ-5D data available compares ibrutinib to TEM in the RAY (MCL3001) study, and there is no evidence to support that the QoL of R-chemo (the relevant comparator) is comparable to TEM; and ii) the EQ-5D is not the best instrument to capture changes to patient functioning such as fatigue, where ibrutinib has been demonstrated with other instruments to have a major impact. In particular, the EQ-5D-5L measure contains no explicit fatigue dimension and fatigue has been reported as one of the most important negative QoL impacts associated with MCL[2]. Moreover, the disease-specific FACT-Lym instrument did capture the impressive benefit with ibrutinib, but could not be translated into utility values in the economic analysis. The improvement in QoL observed with ibrutinib using the FACT-Lym instrument was remarkable: nearly twice as many patients in the ibrutinib arm of RAY (MCL3001) achieved a clinically meaningful symptoms improvement compared with TEM, and only approximately half of the number of ibrutinib patients as TEM patients experienced a clinically meaningful worsening of symptoms[3]. In order to capture this benefit appropriately, Janssen is planning a longitudinal study to elicit utility values for ibrutinib and R-chemo in the UK using the EQ-5D instrument and a disease specific instrument. Results will be available in the first quarter of 2017.

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.

Contents

List of tables

List of figures

[redacted]

Abbreviations

AAK	Aurora A Kinase
ACD	Appraisal consultation document
AF	Atrial fibrillation
AIC	Akaike's information criterion
ALLO-SCT	Allogenic stem-cell transplant
ANOVA	Analysis of variance
ASCO	American Society of Clinical Oncology
ASCT	Autologous Stem Cell Transplantation
ASH	American Society of Hematology
ATC	Anatomical Therapeutic Chemical
AWMSG	All Wales Medicines Strategy Group
BCR	B-cell receptor
BCSH	British Committee for Standards in Haematology
BEAM	Bendamustine, etoposide, cytarabine and melphalan
BERT	Bendamustine, rituximab and temsirolimus
BIA	Budget impact analysis
BIC	Bayesian information criterion
BIM	Budget impact model
BMJ	British Medical Journal
BNF	British National Formulary
BR	Bendamustine and rituximab
BSA	Body surface area
BTK	Bruton's kinase
CAN	Canadian
CaRD	Carfilzomib, rituximab and dexamethasone
CC	Critical care
CDA	Cladribine
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CEMP	Cisplatinum, etoposide, mitoxantrone and prednisone
CF	Cyclophosphamide and fludarabine
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLL	Chronic Lymphocytic Leukaemia
CMV	Cytomegalovirus
CNOP	Cyclophosphamide, mitoxantrone, vincristine, prednisolone
CNS	Central nervous system
COP-X	Daunorubicin, cyclophosphamide, vincristine and prednisolone
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CUP	Compassionate Use Programme
CVAD	Cyclophosphamide. Vincristine. Doxorubicin, Dexamethasone
CYP	Cytochrome P450
DAPF	Direct access plain film
DARE	Database of Abstracts of Reviews of Effects
DH	Department of Health
DHAP	Dexamethasone, high-dose cytarabine and cisplatin
DLBCL	Diffuse large B-cell lymphoma

DOR	Duration of response
DSHNHL	German High-Grade Non-Hodgkins Lymphoma Study Group
DSU	Decision Support Unit
EAP	Early Access Programme
ECC	European Cancer Congress
ECCO	European Cancer Organisation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EED	Economic Evaluation Database
EHA	European Hematology Association
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
ENKL	Extranodal NK/T-cell lymphoma
EORTC QLQ-C30	The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EPAR	European Public Assessment Report
ESMO	European Society for Medical Oncology
EU	European Union
EQ-5D-5L	EuroQol - 5 dimensions – 5 levels questionnaire
EVT	Event
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FCL	Follicle centre lymphoma
FCM	Fludarabine, cyclophosphamide and mitoxantrone
FCMR	Fludarabine, cyclophosphamide, mitoxantrone and rituximab
FCR	Fludarabine, cyclophosphamide and rituximab
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FL	Follicular lymphoma
G-CSF	Granulocyte-colony stimulating factor
GIDOX	Gemcitabine, ifosfamide, dexamethasone, and oxaliplatin
GITMO	Gruppo Italiano Trapianto di Midollo Osseo
GLSG	German Low-Grade Lymphoma Study Group
GVHD	Graft-versus-host disease
HCHS	Hospital and Community Health Service
HCT	Haematopoietic cell transplantation
HDACI	Histone deacetylase inhibitor
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
HZ	Herpes Zoster
ICER	Incremental cost-effectiveness ratio
IFETOX	Ifosfamide, etoposide and oxaliplatin
IFN	Interferon
ILROG	International Lymphoma Radiation Oncology Group
InO	Inotuzumab ozogamicin
IQR	Interquartile range
IRC	Independent review committee
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison

ITT	Intention-to-treat
IV	Intravenous
IWRS	Interactive web response system
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LOT	Line of therapy
LYG	Life years gained
LYM	Lymphoma
MCL	Mantle cell lymphoma
MID	Minimally important difference
MIMS	Monthly Index of Medical Specialties
MIPI	Mantle cell lymphoma international prognostic index
MMRM	Mixed model repeated measures
MR	Maintenance rituximab
MRD	Minimum residual disease
MRI	Magnetic resonance imaging
MRU	Medical resource use
N/A	Not applicable
NCI	National Cancer Institute
NE	Not evaluable
NED	No evidence of disease
NF	Nuclear factor
NMB	Net monetary benefit
NHL	Non-Hodgkin's lymphoma
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
OLSG	Osaka Lymphoma Study Group
ONS	Office of National Statistics
ORR	Overall response rate
OS	Overall survival
OSHO	East German Study Group Haematology/Oncology
PAS	Patient access scheme
PASLU	Patient access schemes liaison unit
PC	Physician's choice
PD	Progressive disease
PEP-C	Prednisone, etoposide, procarbazine and cyclophosphamide
PET	Positron emission tomography
PFS	Progression-free survival
PI3K	Phosphoinositide 3-kinase
PICOS	Population, Intervention, Comparator, Outcomes, Study design
PLRG	Polish Lymphoma Research Group
PP	Per-protocol
PPS	Post-progression survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient reported outcomes
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal and social services
PSSRU	Personal and Social Services Research Unit
QALY	Quality-adjusted life year

QoL	Quality of life
R-BAC	Rituximab, bendamustine and cytarabine
R-CBorP	Rituximab, cyclophosphamide, bortezomib and prednisone
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone
R-CVP	Rituximab, cyclophosphamide, vincristine and prednisolone
R-GDP	Rituximab, gemcitabine, cisplatin and dexamethasone
R-ICE	Rituximab, ifosfamide, carboplatin and etoposide
RC	Rituximab and cytarabine
RCT	Randomised controlled trial
RE	Response evaluable
REL	Relapsed
REFR	Refractory
RIC	Reduced-intensity conditioning
RIT	Radioimmunotherapy
RT-PEPC	Rituximab, thalidomide, and prednisone, etoposide, procarbazine, cyclophosphamide
SA	Sensitivity analysis
SAE	Serious adverse event
SAKK	Swiss Group for Clinical Cancer Research
SCH	Stem cell harvest
SD	Standard deviation
SE	Standard error
SLR	Systematic Literature Review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SOC	Standard of Care
STA	Single technology appraisal
TA	Technology appraisal
TEM	Temsirolimus
TOT	Time on treatment
UK	United Kingdom
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
USA	United States of America
VAS	Visual analogue scale
VAT	Value added tax
WM	Waldenström's macroglobulinaemia
WTP	Willingness to pay

1 Executive summary

1.1 *Statement of decision problem*

This submission addresses the clinical and cost-effectiveness of ibrutinib within its marketing authorisation for the treatment for relapsed or refractory mantle cell lymphoma (R/R MCL) in adults, in line with 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 page.

Table 1: Statement of 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 R/R MCL.	Adults with R/R MCL.	N/A – the decision problem matches the final scope.
Intervention	Ibrutinib.	Ibrutinib.	N/A – the decision problem matches the final scope.
Comparator(s)	Established clinical management without ibrutinib, including: • Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) • Rituximab, cyclophosphamide, vincristine and prednisolone (R-CVP) • Fludarabine, cyclophosphamide and rituximab (FCR) • Rituximab and cytarabine (RC).	Established clinical management without ibrutinib, including: • Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) • Rituximab, cyclophosphamide, vincristine and prednisolone (R-CVP) • Fludarabine, cyclophosphamide and rituximab (FCR) • Rituximab and cytarabine (RC).	N/A – the decision problem matches the final scope.
Outcomes	The outcomes to be considered include: • Overall survival (OS) • Progression-free survival (PFS) • Overall response rates (ORR) • Duration of response (DOR)/remission • Time to new anti-lymphoma treatment/time to progression • Adverse effects of treatment • Health-related quality of life (HRQoL).	The outcomes considered in this submission include: • OS • PFS • ORR • DOR/remission • Time to new anti-lymphoma treatment/time to progression • Adverse effects of treatment • HRQoL. Additional outcomes not specified in the scope but presented in this submission are detailed in Table 14.	N/A – the decision problem matches the final scope.
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be	• The economic analysis conforms to the final scope	N/A – the decision problem matches the final scope.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	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 (PSS) perspective	• The outcome measure of the economic analysis is the incremental cost-effectiveness ratio (ICER) • The time horizon considered is 15 years (0% of patients in both model arms are alive at that time) • Costs are considered from an NHS and PSS perspective	
Subgroups to be considered	None detailed	Subgroup analysis provided for: • R/R MCL patients who have received 1 prior line of therapy • R/R MCL patients who have received >1 prior line of therapy	Feedback from clinical experts has indicated that these subgroups are relevant to explore. Evidence supports the increased efficacy of ibrutinib when used at earlier lines of treatment.
Special considerations including issues related to equity or equality	None detailed	N/A	N/A

R/R MCL: relapsed or refractory mantle cell lymphoma, RC: rituximab and cytarabine, R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone, R-CVP: rituximab, cyclophosphamide, vincristine and prednisolone, FCR: fludarabine, cyclophosphamide and rituximab, N/A: not applicable, OS: overall survival, PFS: progression-free survival, ORR: overall response rate, DOR: duration of response, HRQoL: health-related quality of life, NHS: National Health Service, PSS: Personal and Social Services, ICER: incremental cost-effectiveness ratio

1.2 *Description of the technology being appraised*

A summary of the technology being appraised (ibrutinib [Imbruvica®]) is provided in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Ibrutinib (Imbruvica®).
Marketing authorisation/CE mark status	Ibrutinib received a positive opinion from the CHMP on the 24th of July 2014[1]. The marketing authorisation was subsequently granted by the European Medicines Agency (EMA) on the 21st of October 2014.
Indications and any restriction(s) as described in the summary of product characteristics	Ibrutinib is indicated for the treatment of: • Adult patients with R/R MCL • Adult patients with CLL who have received at least one prior therapy, or in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy • 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. 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	R/R MCL: Oral; 4 x 140 mg capsules (560 mg) once daily. Taken until disease progression or the treatment is no longer tolerated by the patient.
CHMP: Committee for Medicinal Products for Human Use, CE: Conformité Européene, EMA: European Medicines Agency, R/R MCL: relapsed or refractory mantle cell lymphoma, CLL: chronic lymphocytic leukaemia	

1.3 *Summary of the clinical effectiveness analysis*

Ibrutinib in R/R MCL

Ibrutinib is a first-in-class Bruton's tyrosine kinase (BTK) inhibitor indicated for the treatment of a number of conditions including R/R MCL, a disease area with extremely poor prognosis and a large unmet medical need. It represents an absolute step-change in the treatment of MCL in patients who did not respond to, or relapsed whilst receiving, one or more previous treatments. Ibrutinib received breakthrough designation through the FDA, has an EMA orphan designation and meets the NICE *end-of-life* criteria in R/R MCL.

Summary of clinical evidence base for ibrutinib

A systematic literature review (SLR) for prospective clinical studies of ibrutinib and potential comparator therapies identified two non-randomised controlled trials (RCTs) and one phase III RCT of ibrutinib in R/R MCL:

- RAY (MCL3001): a phase III RCT comparing ibrutinib (n=139) to temsirolimus (TEM) (n=141) in patients with R/R MCL who had received at least one prior rituximab-containing chemotherapy regimen and had documented relapse or disease progression since their last treatment. This study provides comparative evidence against an active therapy

- The pivotal phase II single-arm PCYC1104 study in 111 patients with R/R MCL
- The SPARK (MCL2001) phase II single-arm study in 120 R/R MCL patients.

Ibrutinib received its European Union (EU) licence based on results from the phase II trial PCYC1104, with the CHMP acknowledging (July 2014) that the "*dramatic activity seen in terms of ORR, and DOR is unprecedented historically*"[1]. Since then, these impressive results have been further substantiated in the SPARK (MCL2001) and RAY (MCL3001) studies. The three clinical trials showed results that have never been observed before in R/R MCL in terms of PFS, OS, ORR and DOR and are consistent across trials.

The three clinical trials of ibrutinib all considered a population of patients with R/R MCL that were sufficiently similar in terms of baseline characteristics to render a pooled analysis appropriate. This provided an estimate of the efficacy of ibrutinib across a total number of patients (n=370) that can be considered large, given the orphan nature of this medicine. Furthermore, this pooled analysis allowed the longer-term follow-up of the PCYC1104 study (median of 26.7 months versus 20.0 months in RAY (MCL3001)) to inform the efficacy estimates for ibrutinib.

This clinical trial evidence base is further supported by two real-world studies: a Compassionate Use Programme (CUP), which recruited 715 patients worldwide, including 154 in the UK (the highest level of enrolment globally), and an Early Access Programme (EAP), which recruited 149 patients in the United States.

RAY (MCL3001)

The RAY (MCL3001) study met its primary endpoint, demonstrating an unparalleled and significant PFS benefit of ibrutinib compared to TEM (14.6 months versus 6.2 months) and providing a 57% reduction in the risk of disease progression or death. In total, 41% of patients treated with ibrutinib remained progression-free at 2 years compared to only 7% of patients treated with TEM. This estimate of median PFS of 14.6 months compares to less than 5 months estimated for rituximab combined with chemotherapy (R-chemo, see Table 4), which represents the comparator in UK clinical practice (see Section 3.4).

These PFS results are supported by outcome measures for tumour response. A substantial and significantly higher proportion of patients receiving ibrutinib achieved a complete response (CR) or partial response (PR) compared to patients receiving TEM: the ORR of 71.9% for patients receiving ibrutinib in RAY (MCL3001) was 31.5% higher than for patients receiving TEM. Furthermore, the odds of achieving a CR were almost 4 times higher for patients receiving ibrutinib than patients receiving TEM. Response rates of this magnitude have never been observed for licensed treatments in R/R MCL, with novel treatments achieving ORRs of 33% (bortezomib) and 28% (lenalidomide) and CRs of 8% (for both treatments)[4].

Median OS has not yet been reached in the ibrutinib arm of RAY (MCL3001, trial ongoing) and was 21.3 months for the TEM arm. The OS hazard ratio (HR) for the analysis on the intention-to-treat (ITT) population was 0.76 after a median follow-up of 20 months, indicating a trend towards improved survival with ibrutinib. This OS improvement was observed despite the fact that 32 patients (23%) in the TEM arm crossed over to the ibrutinib arm, thereby confounding the estimate of OS for TEM. The OS data from the RAY (MCL3001) study is immature and does not reach statistical significance in the comparison to TEM. However, the study was not powered to observe a statistical OS benefit at interim analysis and the final data cut is scheduled for November 2016 and will provide more mature data and greater certainty over OS estimates.

Pooled analysis of RAY (MCL3001), SPARK (MCL2001) and PCYC1104

A pooled analysis of all three trials was conducted for PFS, OS and ORR outcomes. This analysis demonstrates consistency of results across trials and, by making use of the longer-term follow-up of the PCYC1104 study, provides an estimate of median OS. OS and PFS results are summarised in Table 3 for the analysis of the overall pooled population. In addition, results for the pooled analysis of the subgroups of patients who received 1 prior line of therapy (LOT) and >1 prior LOT are presented; these indicate that longer median PFS and median OS were achieved when R/R MCL patients received ibrutinib at an earlier LOT. A pooled ORR estimate of 66.22% was derived for the overall population (n=370). The European Public Assessment Report (EPAR) for ibrutinib in R/R MCL commented that the response rates and DOR observed in the pivotal PCYC1104 phase II study were *"unprecedented"* and the CHMP concluded that they *"must be considered outstanding as responses of this magnitude have not been reported with other available monotherapies for R/R MCL"*. The results from the pooled analysis show a high ORR, consistent with the 68% response rate observed in the PCYC1104 study and to which these statements referred.

Table 3: Summary of ibrutinib OS and PFS results from the pooled analysis

	PFS **Median (95% CI)**	**OS** **Median (95% CI)**
Overall population (n=370)	12.81 (8.48, 16.56)	25.00 (21.59, NE)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		

Results based on IRC-assessed PFS from RAY (MCL3001) and SPARK (MCL2001) and investigator-assessed PFS from PCYC1104 (IRC-assessed PFS not available in PCYC1104)
Source: Rule, 2016[5]; Janssen Research and Development, 2016[6]

Evidence for comparator effectiveness

The RAY (MCL3001) study compared ibrutinib to TEM. The choice of comparator was based on the fact that TEM was the only other therapy for R/R MCL licensed in the European Union (EU) at the time that the trial was conceived. However, TEM is not approved by NICE and clinical experts highlighted that TEM is not used in UK clinical practice for the treatment of R/R MCL. A range of therapies are used in UK practice depending upon patient fitness and, as such, there is no standard of care (SOC). R-chemo regimens are the most prominent therapies used in current clinical practice, as reflected by the NICE scope. Of these, R-CHOP is the most widely used, although other treatments defined in the NICE scope (Table 1) may be used in frailer patients or for historical reasons.

The clinical SLR identified a distinct lack of clinical trial evidence for the relevant comparators, in contrast to the evidence base available for ibrutinib. As a result, further searches were performed after the SLR (as described in Section 4.10) but across all searches no relevant clinical studies were identified for the comparators defined in the NICE scope. The only RCT identified that permitted an indirect treatment comparison (ITC) with the RAY (MCL3001) study was Hess, 2009, which included a physician's choice (PC) comparator arm. This provided a proxy for clinical practice, although this was limited by the fact that the PC arm was comprised of single agent chemotherapy regimens that do not reflect the current use of rituximab in clinical practice. Two other sources of PFS and OS estimates for R/R MCL patients in routine practice settings have been identified. The Haematological Malignancy Research Network (HMRN) provides evidence from a unified clinical network operating across 14 hospitals in Northern England (Yorkshire). The Skåne University Hospital in Sweden provides evidence for patients treated with routine practice, albeit in a different country. The PFS and OS estimates from these three sources are

summarised in Table 4 and suggest median PFS estimates of 2-3 months and median OS estimates of 5-10 months for patients treated with routine treatments.

Table 4: Summary of PFS and OS estimates in current practice

Source	Median PFS (months)	Median OS (months)
HMRN[7] (n=57)	NR	8.4
Hess, 2009[8] (n=54)	1.9	9.7
Skåne University Hospital[9] (n=26)	2.8	5.2
HMRN: Haematological Malignancy Research Network, NR: not reported Patients in the HMRN dataset were R/R MCL patients who had who had initially responded to therapy Patients in Hess, 2009 had received a median of 4 prior lines of therapy Patients from the Skåne University Hospital were 3rd or 4th line R/R MCL patients		

The results of a Bucher ITC with the Hess, 2009 study provided HRs for PFS and OS for ibrutinib vs PC of 0.19 and 0.59, respectively. In order to address the limitation that the therapies comprising the PC arm of Hess, 2009 do not reflect the use of rituximab in clinical practice, the PFS HR from the ITC was adjusted to account for a 'rituximab effect' in exploratory analysis within the cost-effectiveness modelling. A HR comparing chemotherapy + rituximab vs chemotherapy alone was derived from first-line MCL data from the HMRN audit in order to inform this adjustment. The use of this approach provides an estimated PFS HR for ibrutinib vs PC, as a proxy for R-chemo, of 0.28 (from 0.19). Whilst we acknowledge the limitations of this approach, this approach was necessary due to the paucity of data available for R-chemo in a disease area with high unmet need such as R/R MCL. It must be borne in mind that R-chemo regimens are not licensed in R/R MCL (or MCL in general) anywhere globally. Therefore Janssen could not perform a clinical trial comparing to any of these regimens and, instead, planned ibrutinib's phase III comparative RCT versus TEM, which is the only licensed intervention in Europe for R/R MCL. The fact that no R-chemo regimens are licensed in MCL likely explains the paucity of data for these therapies in the literature, as only a few investigator-initiated studies have been run. Given the unlicensed nature of the R-chemo used in practice, there is little that Janssen can do to address the current lack of data associated with the comparator.

Quality of life benefits of ibrutinib

MCL is a rare and aggressive form of lymphoma and the majority (>90%) of patients present with advanced stage disease[10].The quality of life (QoL) in patients who have relapsed or are refractory to previous MCL treatments is extremely poor. Fatigue and loss of mobility commonly impact upon QoL and patients may not be able to perform simple activities of daily living such as preparing meals or housework[11]. Patients receiving R-chemo in current clinical practice tend to feel well initially and then decline; clinical experts describe that the greatest impact on patients of these therapies comes from fatigue and diarrhoea. Patients cannot return to work whilst receiving chemotherapy and frequently require concomitant medications which may also impact their QoL.

The improvement in QoL observed with ibrutinib is extraordinary. In RAY (MCL3001), nearly twice as many patients in the ibrutinib arm of the study achieved a clinically meaningful symptoms improvement compared with TEM (61.9% versus 35.5%), with symptoms improvement achieved significantly more rapidly with ibrutinib (median 6.3 weeks compared to 57.3 weeks with TEM)[3]. Symptom improvement with ibrutinib was accompanied by clinically meaningful improvement from baseline on the Functional Assessment of Cancer Treatment-Lymphoma (FACT-Lym) total score and across physical, functional and emotional well-being sub-scales. In addition, significantly higher EuroQol-5 dimensions-5 levels

questionnaire (EQ-5D-5L) utility for ibrutinib compared to TEM was observed within 4 weeks and maintained through to week 49 of treatment[3]. Overall improvement in QoL from baseline in patients receiving ibrutinib compared to TEM captured by the EuroQoL-Visual Analogue Scale (EQ-VAS) was clinically and statistically significant.

The impact on patients' QoL has been endorsed by expert haematologists and patients as a key benefit of ibrutinib compared to current chemotherapy options. Both the ability for patients to return to normal lives and a 'euphoric effect' of receiving ibrutinib have been highlighted. In addition, testimonials suggest that ibrutinib may allow patients to feel similar to the general population of the same age and to experience potentially rapid improvements such as '*going from a wheelchair to a golf course in 3 weeks*'[12].

Tolerability and side effect profile of ibrutinib

Frequency of all-grade treatment-emergent adverse events (AEs) and serious AEs in RAY (MCL3001) was similar between the ibrutinib arm and the TEM arm, and the number of patients experiencing grade 3 or higher treatment-emergent AEs was lower for ibrutinib (n=94, 68%) than TEM (n=121, 87%). Furthermore, a considerably lower proportion of patients receiving ibrutinib discontinued treatment due to AEs than patients receiving TEM (6.5% versus 25.5%) despite the fact that the median duration of treatment exposure was almost five-fold higher for ibrutinib compared to TEM.

The non-RCT evidence base for ibrutinib supports the tolerability profile observed in RAY (MCL3001). In the PCYC1104 study, only 7% of patients discontinued ibrutinib due to AEs at the primary end-point data cut-off; discontinuation rates due to AEs remained low at only 11% in the long-term extension of the study (median follow-up of 26.7 months). Discontinuation due to AEs was similarly low in SPARK (MCL2001), at 6.7%. The safety profile of ibrutinib reported in the two real-world studies (EAP and CUP) was consistent with that found in the pivotal trials, with low rates of treatment discontinuation due to AEs.

Finally, the EMA have concluded that the safety profile of ibrutinib in R/R MCL is consistent with that observed in the other ibrutinib clinical trials and licensed indications and is considered manageable with dose modifications[1].

End-of-life criteria

Ibrutinib meets the NICE *end-of-life* criteria in R/R MCL (see Section 4.14.3):

- Estimates for median OS of patients treated in routine practice settings are approximately 5-10 months (see Table 4), well below 2 years
- Estimated median OS for patients receiving ibrutinib in the pooled analysis was 25.00 months and therefore above estimates of survival in current clinical practice by considerably greater than 3 months
- The population of R/R MCL patients in England, Wales and Northen Ireland is estimated to be small; approximately 356 patients in 2017 (see Section 6)

1.4 *Summary of the cost-effectiveness analysis*

A *de novo* economic model was constructed to assess the cost-effectiveness of ibrutinib for the treatment of patients with R/R MCL versus R-chemo. Whilst there is no SOC for R/R MCL in the UK, R-CHOP was identified as the main comparator based upon clinical expert advice and the costs associated with R-CHOP were therefore applied in the base case analysis. As a result of the extremely limited data available for these unlicensed R-chemo

comparator therapies, all rituximab-containing regimens requested by the NICE scope were modelled to have equivalent effectiveness.

A standard three health-state model was used (pre-progression, progression and death). In order to be consistent with previous modelling methodology in MCL[13], progression status was used as a surrogate marker for OS, and post-progression survival (PPS) was assumed to be the same for ibrutinib and R-chemo. Available literature within MCL indicates that PFS is a good surrogate for OS and this approach has previously been accepted within front-line MCL[13, 14].

The model was parameterised by PFS, PPS and time on treatment (TOT) data from the pooled dataset for ibrutinib. The model base case derived comparative effectiveness between ibrutinib and R-chemo based on the results of the ITC using PC from Hess 2009, with the added 'rituximab effect' included within the model base case to account for the differences between the Hess data and UK clinical practice (see Section 1.3). A scenario analysis was conducted in which the effectiveness of TEM observed in the RAY (MCL3001) study was used as a proxy for the effectiveness of R-chemo.

Patient QoL was modelled using EQ-5D-5L utilities reported by patients in the RAY (MCL3001) and SPARK (MCL2001) trials, with the impact of R-chemo toxicity on HRQoL taken from expert clinical advice and compared to available published literature. A utility of 0.78 was used for patients who were progression free and 0.68 used for progressed patients. A decrement of 0.20 was applied to patients whilst receiving R-chemo, with utility assumed to return to normal immediately upon stopping treatment. The pattern and magnitude of QoL impact captured by the EQ-5D-5L compared to that observed with the QoL subscales of the FACT-Lym and by clinical experts raises concern that reliance on EQ-5D-5L for economic modelling may risk underestimating the utility gain associated with the meaningful and valuable positive impact of ibrutinib on patients' QoL. In particular, the EQ-5D-5L does not explicitly capture the impact of fatigue, an important aspect of living with R/R MCL, on patient QoL. NICE have recently reviewed ibrutinib for the treatment of CLL and the Committee reported the following conclusions in the draft Appraisal Consultation Document (ACD)[15]: "*clinical experts commented… stating that symptoms improve immediately with ibrutinib and patients have a very good quality of life unless they have an adverse event. Having heard the positive experience of patients with ibrutinib, particularly with regard to energy levels and lack of side effects, the committee was concerned that the quality-of-life benefits may not have been appropriately captured, noting that the EQ-5D-5L does not directly measure fatigue".*

Janssen believe that these same considerations apply to this appraisal, particularly as the modelled EQ-5D-5L utility value for progression free patients represents a utility gain of only 0.05 from the 0.73 baseline EQ-5D-5L utility observed in RAY (MCL3001). This means that the utility gain modelled for ibrutinib is smaller than a published minimally important difference (MID) for UK-index EQ-5D utility scores in cancer (0.08, meaning that any difference equal to or above 0.08 is clinically meaningful) and hence unlikely to be clinically meaningful for patients[16]. By contrast, clinical experts expected utility values for MCL patients on treatment with ibrutinib to be similar to the general population as *"patients feel as good as they have ever felt"*[12].

Costs were obtained from standard UK sources; eMIT and MIMS were used for drug costs and NHS reference costs for resource use costs. As patients progressed through the health states within the model, they incurred costs associated with drug acquisition and administration, healthcare visits and management of AEs. Routine follow-up care costs in the PFS state were assigned according to the distribution of patients' best overall response to treatment.

The SLR conducted to identify evidence for the impact of R/R MCL on resource use indicates a strong link between progression, receipt of chemotherapy and cost to the health care system in R/R MCL. Based on this, ibrutinib is anticipated to lead to a reduction in some of the costs associated with the management of R/R MCL. Firstly, ibrutinib prolongs time to progression. Secondly, use of ibrutinib is associated with a reduction in the requirement for use of chemotherapy. This would be expected to lead to decreases in hospitalisations, emergency visits and supportive care required as a result of toxicity-related events with chemotherapy. It is unlikely that all of these benefits have been adequately captured within the current economic model due to a lack of evidence, and lack of understanding of the full impact of toxicity related to current treatments on either patients or the NHS.

Based upon the economic analysis, ibrutinib was estimated to generate an additional 1.23 life years and 0.94 quality-adjusted life year (QALYs) (2.28 vs 1.04 life years for ibrutinib vs R-chemo and 1.59 vs 0.65 QALYs for ibrutinib vs R-chemo). This represents a substantial improvement to both length and QoL for R/R MCL patients, who currently face an extremely poor prognosis. The mean life years estimated for patients in the ibrutinib arm were more than double than those patients in the R-chemo arm. OS projections for the comparator arm (median OS = 9 months) are in line with the life expectancy of patients receiving treatment for R/R MCL in clinical practice (between 5 and 10 months).

In addition, as demonstrated within the economic model, the use of ibrutinib is expected to offer substantial improvements to patients' QoL. The ICER based upon the list price of ibrutinib was £100,647. However, Janssen have currently agreed a confidential discount with the Patient Access Schemes Liaison Unit (PASLU) and the Department of Health (DH). When this is taken into consideration the ICER falls to £74,256. In scenario analysis where the PPS benefit is reduced to reflect the observed OS of patients within UK clinical practice the ICER falls to £58,757 [redacted]

Key uncertainties within the model related to the parameter estimates for the long-term extrapolation of ibrutinib PFS and TOT data. However, the use of different curve fits only had a minor impact on the overall outcomes of the analysis. The model was also sensitive to the HR assumed for comparative PFS, reflecting the uncertainty in comparative effectiveness due to the paucity of data available.

The majority of uncertainty within the probabilistic analysis related to the estimated QALYs gained (as opposed to the costs encountered from treatment); however, in all cases a substantial QALY improvement was expected for ibrutinib patients compared to those treated with R-chemo (between 0.6 and 1.4 QALYs). [redacted]

Table 5: Incremental cost-effectiveness results in the base case analysis (at list price)

Technology	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER
Ibrutinib	[redacted]	[redacted]	[redacted]	£94,239	1.23	0.94	£100,647
R-CHOP	[redacted]	[redacted]	[redacted]				

ICER: incremental cost-effectiveness ratio, QALY: quality adjusted life year, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

Table 6: Incremental cost-effectiveness results in the base case analysis (discounted price)

Technology	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER
Ibrutinib	[redacted]	[redacted]	[redacted]				
R-CHOP	[redacted]	[redacted]	[redacted]	£69,528	1.23	0.94	£74,256

ICER: incremental cost-effectiveness ratio, QALY: quality adjusted life year, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

2 The technology

2.1 *Description of the technology*

Key details of ibrutinib are presented in Table 7 below.

Table 7: Details of ibrutinib

Approved Name	Ibrutinib
Brand Name	Imbruvica®
Therapeutic Class	Anti-neoplastic agents, protein kinase inhibitors
ATC Code	L01XE27
Pharmaceutical form(s)	Capsule
Strength(s) available	140 mg
Route of administration	Oral
Pack size	90 hard capsules; 120 hard capsules
Manufacturer	Janssen

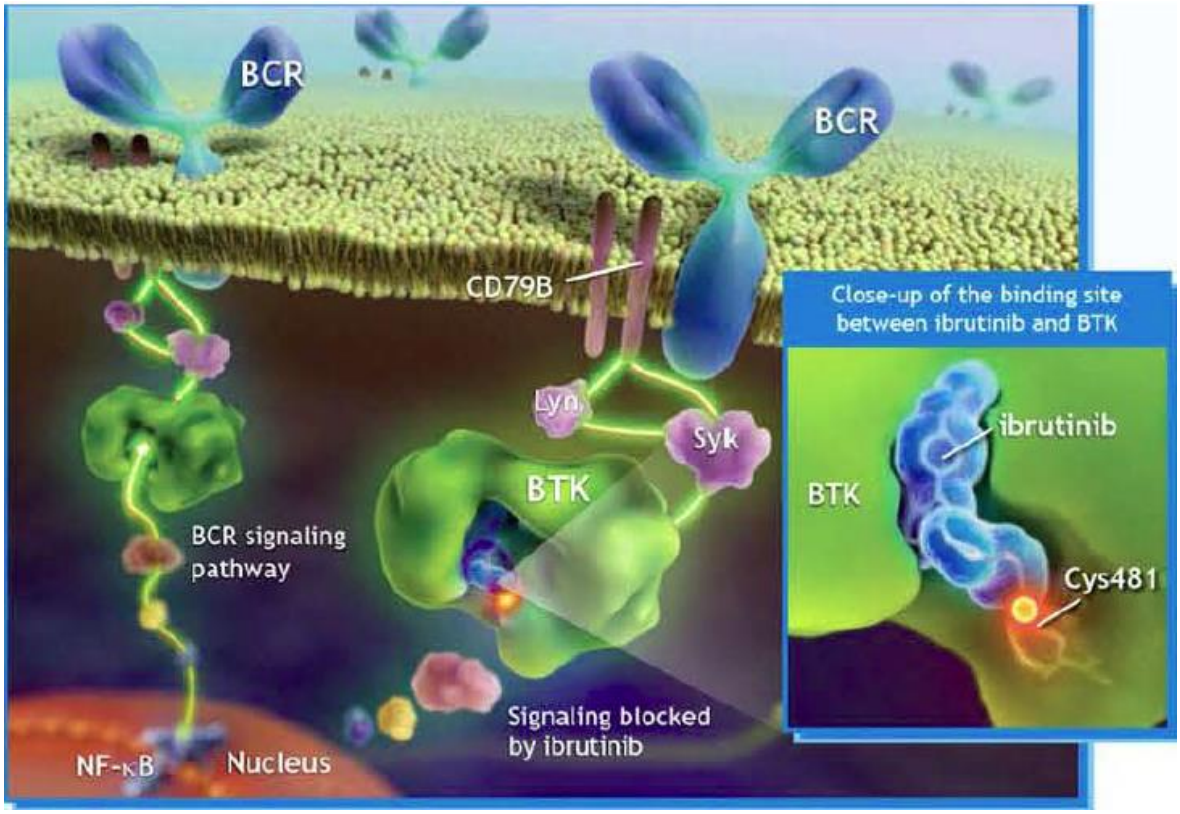
2.1.1 *Mechanism of action*

In MCL, mutation and overexpression of cyclin D1, a cell cycle gene, contributes to the abnormal proliferation of malignant B-cells[17]. Ibrutinib is a first-in-class, orally available, irreversible inhibitor of BTK, a critical signalling molecule in the B-cell receptor (BCR) pathway responsible for malignant B-cell survival and proliferation.

BTK belongs to the “Tec kinase family”, a group of kinases involved in the pathogenesis of several B-cell malignancies, including MCL[18, 19]. Since its identification, BTK has represented an attractive therapeutic target for B-cell malignancies for its proven, prominent role in the development and function, cytoplasmic expression and selective expression of B-cells[18-20].

The BCR plays an important role in normal B-cell development through its regulation of multiple cellular processes, including proliferation, differentiation, apoptosis and cell migration; all of which are essential for the functioning and survival of both normal and malignant B-cells[18, 19, 21, 22]. By irreversibly inhibiting BTK, ibrutinib disrupts the BCR signalling pathway and prevents the proliferation and survival of malignant B-cells in MCL (see Figure 1)[23, 24].

Figure 1: Mechanism of action of ibrutinib



Source: Figure taken from Gayko, 2015[23]

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

2.2.1 *EU marketing authorisation*

2.2.1.1 Mantle cell lymphoma

Ibrutinib is currently licensed in the EU for the treatment of adult patients with R/R MCL[25]. The full summary of product characteristics (SmPC) is provided in the reference pack with this submission[25].

Ibrutinib received orphan status in the treatment of MCL from the EMA on the 26th April 2012. The marketing authorisation application for the use of ibrutinib in R/R MCL was submitted to the EMA on the 30th October 2013 and a positive opinion from the CHMP was received on the 24th July 2014[1]. The marketing authorisation was subsequently obtained from the European Commission on the 21st October 2014.

The EMA approved ibrutinib for the treatment of R/R MCL based upon single-arm data from the pivotal phase II trial PCYC1104, due to the recognition by the EMA of the promise shown by ibrutinib in a disease area with a considerable unmet need.

The following extracts from the CHMP assessment report (provided in the reference pack with this submission) emphasise the regulator's positive opinion of the clinical value of ibrutinib in R/R MCL[1]:

- *"The efficacy evaluation is based on data from the pivotal phase II study 1104 (n=111) and the supportive study 04753 (n=5 with the 520 mg daily dose), both single-arm trials. With the limitations of uncontrolled data acknowledged, the robustness of the 1104 study is not challenged and, looking at the population under study, data should be roughly representative for the general population with R/R MCL"*
- *"From a historical perspective these results must be considered outstanding as responses of this magnitude have not been reported with other available monotherapies for R/R MCL"*
- *"Clinically relevant results were observed in patients with MCL treated with ibrutinib monotherapy. Although the pivotal study is a single-arm study, the dramatic activity seen in terms of ORR, and DOR is unprecedented historically and considered sufficiently important in this heavily pre-treated patient population to support approval".*

2.2.1.2 Other EU indications

Ibrutinib is also licensed in the EU for the treatment of the following:

- Adult patients with CLL who have received at least one prior therapy, or in first-line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy;
- Adult patients with WM who have received at least one prior therapy, or in first-line treatment for patients unsuitable for chemo-immunotherapy[25].

2.2.2 *Non-EU regulatory approval*

Ibrutinib is approved for the treatment of R/R MCL in 46 non EU countries including the US, Mexico, Australia, Canada, most South American countries, Israel, India, Japan, South Korea, Singapore, Philippines, Malaysia, Hong Kong, Indonesia, Thailand and New Zealand (information as of February 2016). In November 2013, the US Food and Drug Administration (FDA) granted breakthrough status and accelerated the approval for ibrutinib to treat R/R MCL based upon the pivotal phase II study (PCYC1104)[26].

2.2.3 *Health technology assessment (UK)*

Table 8 below details the ongoing health technology assessment (HTA) for ibrutinib in the UK.

Table 8: Details of ibrutinib health technology assessment in the UK

HTA body	Indication(s)	Submission date	Anticipated decision date
NICE	CLL	October 2015	June 2016
SMC	R/R MCL, CLL	December 2015	July 2016
AWMSG	R/R MCL, CLL	TBC 2016	TBC 2016

HTA: health technology assessment, NICE: National Institute for Health and Care Excellence, SMC: Scottish Medicines Consortium, AWMSG: All Wales Medicines Strategy Group, CLL: chronic lymphocytic leukaemia, R/R MCL: relapsed or refractory mantle cell lymphoma, TBC: To be confirmed

2.3 *Administration and costs of the technology*

Details of the treatment regimen, including the method of administration and unit costs associated with ibrutinib, are provided in Table 9.

With respect to the acquisition cost of ibrutinib, Janssen have agreed a simple patient access scheme (PAS) with the DH, [redacted]

Table 9: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	140 mg capsule	SmPC[25]
Acquisition cost (excluding VAT)	**List price:** • £4,599.00 for 90 × 140 mg capsules (£51.10 per capsule) • £6,132.00 for 120 × 140 mg capsules (£51.10 per capsule) **Discounted price:** [redacted]	BNF 2016[27]
Method of administration	Oral	SmPC[25]
Dose	Four 140 mg capsules (560 mg) once daily	SmPC[25]
Average length of a course of treatment	Treatment with ibrutinib should be continued until disease progression or unacceptable toxicity. Median PFS from a pooled analysis of the RAY (MCL3001), SPARK (MCL2001) and PCYC1104 studies was 12.81 months[5].	SmPC[25]; Rule, 2016[5]
Average cost of a course of treatment	**List price:** £78,550.92 (based on a 30-day month, therefore assuming a cost of £6,132.00 for a one month supply, and 12.81 months[5] [median PFS from the pooled analysis] of treatment) **Discounted price:** [redacted] (based on a 30-day month, therefore assuming a cost of [redacted] for a one month supply, and 12.81 months[5] [median PFS from the pooled dataset] of treatment)	BNF 2016[27]; Rule, 2016[5]
Anticipated average interval between courses of treatments	N/A - treatment with ibrutinib should be continued until disease progression or unacceptable toxicity; patients will not receive repeat courses	SmPC[25]
Anticipated number of repeat courses of treatments	N/A - treatment with ibrutinib should be continued until disease progression or unacceptable toxicity; patients will not receive repeat courses	SmPC[25]
Dose adjustments	• Ibrutinib dose should be lowered to 140 mg once daily (one capsule) when used concomitantly with moderate CYP3A4 inhibitors.	SmPC[25]

	• Ibrutinib dose should be reduced to 140 mg once daily (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 or greater 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 full dose (four capsules). If the toxicity reoccurs, the once daily dose should be reduced by one capsule (140 mg). A second reduction of dose by 140 mg may be considered as needed. • For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 280 mg daily (two capsules). For patients with moderate liver impairment (Child-Pugh class B), the recommended dose is 140 mg daily (one capsule).	
Anticipated care setting	Treatment should be initiated and supervised in secondary care by a physician experienced in the use of anticancer medicinal products then continued via oral self-administration at home.	SmPC[25]
N/A: not applicable, SmPC: summary of product characteristics, VAT: value added tax, BNF: British National Formulary, CYP: cytochrome P450		

2.4 *Changes in service provision and management*

The pharmacological properties of ibrutinib, together with its efficacy and safety profile, are anticipated to have a noticeable positive impact on the service provision and management of R/R MCL.

Ibrutinib is an oral monotherapy that is self-administered by the patient at home and does not require any pre-medication or associated treatment administration[25]. As such, following initiation by a haematologist in secondary care treatment with ibrutinib has no further associated administration costs. The main resource use to the NHS is anticipated to be the drug acquisition cost.

This is in contrast to the relevant comparators indicated in the NICE final scope for this submission, which are either fully administered as an infusion or are in combination with treatments requiring infusion. It is therefore reasonable to assume a steep reduction in infusion service requirements for patients treated with ibrutinib. The ability for ibrutinib to be self-administered at home will remove the staffing and resource use required for patients to attend hospital to receive their infusions, which can in some cases require a short hospital stay[28].

No additional infrastructure in the NHS is assumed to be required with the use of ibrutinib. Moreover, no further monitoring or tests over and above current clinical practice in R/R MCL is anticipated to be needed. A full evaluation of the resource use and costs associated with treatment can be found in Section 5.5.

With regards to changes in the wider management of the condition, the significant improvements to symptom control and QoL demonstrated by ibrutinib (see Section 4.7.2.4) would be expected to reduce the burden on caregivers in helping patients manage their symptoms, which would again present a change in the management of the condition.

2.5 *Innovation*

Ibrutinib is a first-in-class targeted therapy with a novel mechanism of action

Ibrutinib is a first-in-class, orally available, irreversible inhibitor of BTK; a signalling kinase in the BCR pathway that is critical for malignant B-cell survival and proliferation[18, 19]. BTK plays a crucial role in the pathogenesis of B-cell malignancies such as MCL and the inhibition of BTK represents a truly novel approach in the treatment of the disease. Ibrutinib binds with high affinity to the Cys-481 residue in the BTK active site, providing the opportunity for daily dosing whilst minimising the duration of off-target effects[29]. Following oral administration, ibrutinib is rapidly absorbed, with a time to peak concentration of 1-2 hours[21].

The innovative nature of ibrutinib has been recognised by the EMA and the FDA through their approval of ibrutinib based upon ORR, a surrogate end-point from a phase II study[1, 26]. Furthermore, ibrutinib was awarded the prestigious Prix Galien Award in 2015 for Best Pharmaceutical Agent in both the USA and France[30]. The Prix Galien Award is considered to be the pharmaceutical industry's highest accolade and recognises the vital technical, scientific and clinical research skills necessary to develop medicines.

NICE also recognised the innovative nature of ibrutinib in the draft ACD for ibrutinib in CLL: "*The committee heard from both the patient representatives and clinical experts that ibrutinib is an important new technology in the treatment of CLL and that patients appreciate how well the treatment works and how easy it is to take as an oral treatment… The committee concluded that ibrutinib could be considered an innovative treatmen*t"[15].

A number of reviews by clinical experts in MCL have highlighted the *"impressive efficacy"* and *"excellent tolerability"* of ibrutinib[31, 32]. Furthermore, recent guidelines on the evolving management of R/R MCL by Campo and Rule, 2015 state that the introduction of BTK inhibitors would appear to be a *"step-change in the therapy"* for R/R MCL and, as the evidence base for ibrutinib grows, the treatment paradigm for the disease will fundamentally change, with the *"very real prospect that BTK inhibitors may obviate the need for transplantation in younger patients and even the need for chemotherapy in older patients"*[4].

Ibrutinib addresses a significant unmet need within the MCL treatment pathway

MCL is an incurable disease with rapid progression and the poorest prognosis of all types of NHL[7, 10]. Responses to initial chemotherapy in MCL are temporary, leading to high recurrence rates [33]. As a result, the long-term prognosis for patients with MCL is poor, with a median OS of only 3-4 years from diagnosis[33]. Patients with R/R MCL disease have poorer outcomes still, with a median OS of less than one year[7-9].

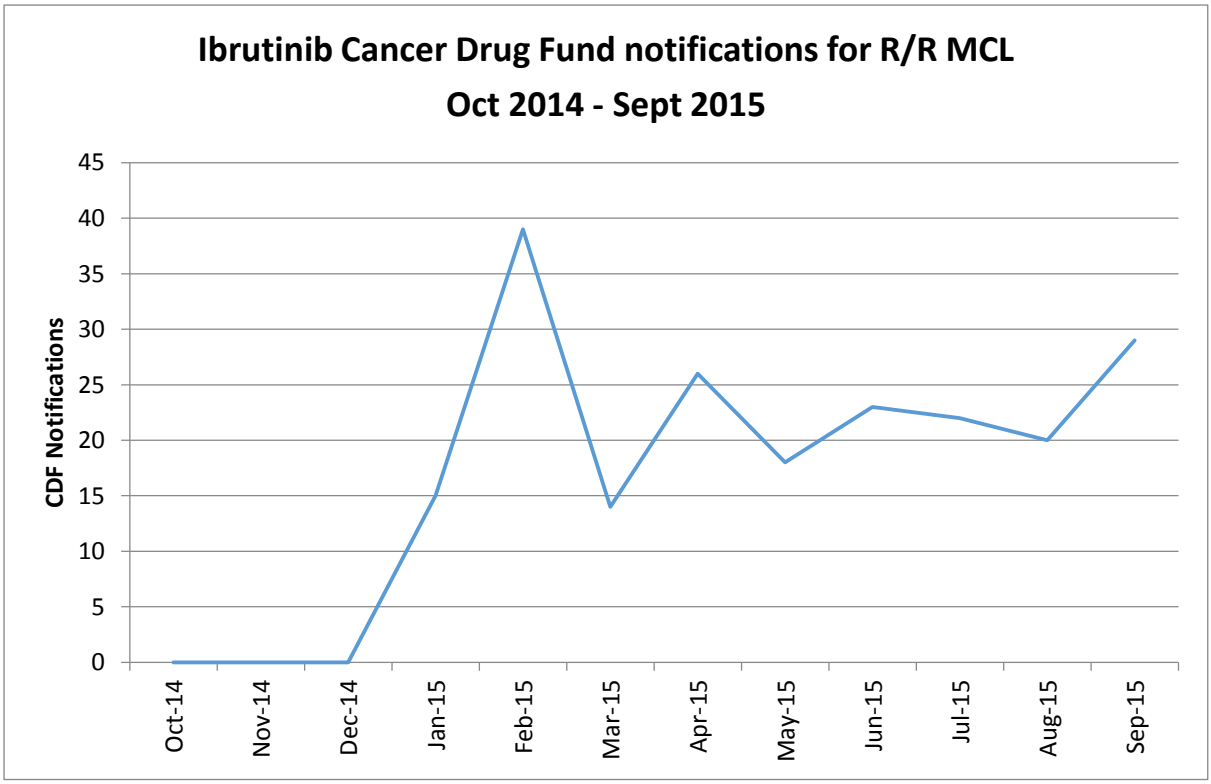
Guidelines from the British Committee for Standards in Haematology (BCSH) published in 2012 and a review of management strategies in MCL published in 2014 recognise that there is a lack of definitive data to guide treatment decisions in MCL and that once patients relapse there is no SOC[4, 10]. Response to second-line treatment is poorer and shorter than for first-line treatment, confirmed by data from HMRN[7]. As such, the introduction of ibrutinib addresses a significant unmet need within the MCL treatment pathway.

The value of ibrutinib as a treatment option to address this unmet need is highlighted by data demonstrating the level of uptake of ibrutinib in clinical practice to date, where ibrutinib has been available via CUPs or, since January 2015, the Cancer Drugs Fund (CDF). An analysis of CDF notifications and of IMS Harmony market research data shows a rapid uptake of ibrutinib in R/R MCL in clinical practice, which reflects the high level of unmet need in this indication and the clear demand for ibrutinib as a treatment option.

Cancer Drugs Fund (CDF) notifications

Figure 2 demonstrates how, following its addition to the CDF in January 2015, notifications for ibrutinib were observed immediately and have been made consistently ever since[34, 35]. There was a gap of 1–2 months between closure of the CUP for ibrutinib and the availability of ibrutinib on the CDF from January 2015. The rapid uptake of ibrutinib observed in the first two months of availability on the CDF (January and February 2015) likely reflects the fact that clinicians were waiting for ibrutinib to become available via the CDF before starting their patients on treatment. Data for the fourth quarter of 2015 are not yet available, but the observed trend is expected to continue.

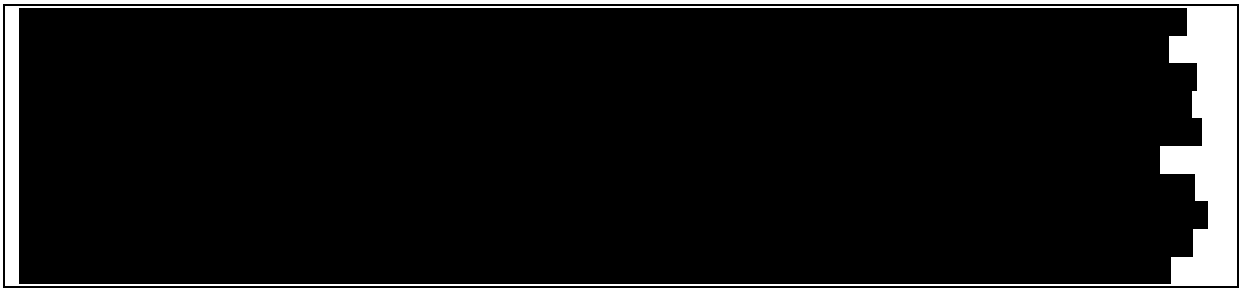
Figure 2: Analysis of ibrutinib CDF notifications for R/R MCL from April 2014 to September 2015



Source: CDF notifications April 2014–September 2015[34, 35]

IMS Harmony market research data

Patient data from IMS Harmony market research, which include treatments that receive baseline funding as well as those funded via the CDF, provide an insight into the market uptake of various therapies for the treatment of MCL at the second or later LOT, including ibrutinib [redacted]



The CDF notifications and IMS Harmony data highlight the clear demand for ibrutinib via currently available funding routes and, therefore, the nature of ibrutinib as an absolute step-change in the treatment of a high unmet need disease area such as R/R MCL.

The evidence base for ibrutinib demonstrates robust clinical efficacy with unprecedented response rates

The clinical efficacy of ibrutinib in R/R MCL has been demonstrated in three clinical trials – one phase III study versus TEM (RAY [MCL3001])[36] and two uncontrolled phase II studies (PCYC1104 and SPARK [MCL2001])[37-39] – in addition to a global CUP in which 715 R/R MCL patients (of which 154 were from the UK) received ibrutinib in a "real-world" setting[40, 41].

As mentioned in Section 1, the clinical trial programme for ibrutinib in R/R MCL demonstrates unprecedented and consistent results in terms of PFS and response rates never observed before for treatments in this disease area. Median OS for ibrutinib has not yet been reached in the RAY (MCL3001) study showing the huge potential in terms of survival. Results from the clinical trial programme were confirmed in two separate real-world studies, including a high number of UK patients.

Section 4 provides details on all the relevant ibrutinib clinical trials separately, the pooled dataset based on the meta-analysis of the three key studies, and the two real-world studies.

The oral administration of ibrutinib reduces the patient, carer and NHS burden associated with current MCL treatments

Ibrutinib is an oral monotherapy administered once daily. This is in contrast to the relevant comparators indicated in the NICE final scope for this submission which, as mentioned previously, are either fully administered as an intravenous (IV) infusion or are in combination with treatments requiring IV infusion. Ibrutinib therefore offers a step-change in the management of MCL with regards to route of administration.

The preference for orally available therapies amongst cancer patients has been demonstrated in a number of studies[42, 43]. Oral administration provides patients with more autonomy and removes the need for both patients and carers to spend lengthy periods of time in secondary care receiving IV chemotherapy. Furthermore, oral administration will free up NHS resources otherwise associated with IV chemotherapy administration and management (as explained in Section 2.4).

In addition, ibrutinib is administered as a monotherapy. No pre- or concomitant medications are specified in the marketing authorisation or were indicated in the principal ibrutinib clinical trials[25, 36-39]. In contrast, the relevant comparators used in R/R MCL involve a combination of IV chemotherapy agents and can require the concomitant administration of a number of additional medications such as paracetamol, anti-emetics, antihistamines and steroids to prevent adverse reactions[28]. This further adds to the administrative convenience of ibrutinib in comparison to IV chemotherapy alternatives, and may provide a psychological benefit to patients in preventing them feeling like they are taking a "cocktail" of different drugs.

Ibrutinib demonstrates a well-tolerated safety profile allowing patients to remain on therapy

The safety profile of ibrutinib has been well characterised in the clinical programme and the drug can be safely administered even in a heavily pre-treated and/or elderly population with baseline comorbidities. AEs are generally predictable, of low grade and can be effectively managed with supportive therapy. The incidence of AEs decreases over time and infrequently results in the need for discontinuation (6.5% in the phase III RAY [MCL3001] study) or dose reduction[36, 44].

Reviews have highlighted how ibrutinib *"appears remarkably well tolerated"* and shows *"excellent tolerability"*[31, 32]. This represents an innovative development in light of the debilitating side-effects of chemotherapy such as nausea and fatigue and the recognised need to improve upon standard therapy by achieving clinical results with less toxicity[4, 11, 45]. As such, the favourable safety profile of ibrutinib may also have the potential to decrease burden on NHS resources from the treatment of chemotherapy-related AEs. A further benefit of ibrutinib's manageable and predictable safety profile is that it allows patients to remain on therapy, which consequently ensures that treatment remains uninterrupted and efficacy is not impacted by tolerability.

Section 4.13 reports the detailed safety data associated with ibrutinib.

Benefits of ibrutinib on QoL may not be fully captured by the QALY metric

The symptoms associated with MCL have a marked effect on patients' QoL, particularly fatigue[2]. Decrements are observed in all areas of QoL, including physical health (mobility and fatigue) and psychological health (anxiety and depression)[11]. Older patients and those with active disease in particular have been reported to have the poorest QoL[2]. Patients' ability to enjoy life – their pastimes/hobbies, relationships, professional and social life – is also impaired, and often patients require the use of carers to undertake normal daily activities[11]. Furthermore, the DOR to treatments for R/R disease is shorter than with initial therapy and life expectancy for R/R MCL patients is less than one year[7, 46]. Coupled with the fact that there is no SOC for the treatment of R/R MCL, patients are faced with significant uncertainty and anxiety regarding their prognosis, which has an additional negative impact on their QoL[10].

Treatment with ibrutinib has been demonstrated to significantly improve symptom control and QoL, as measured by the FACT-Lym and EQ-5D-5L outcome measures (see Section 4.7.2.4 for more details)[36]. These clinical trial data are further supported by patient reports and feedback from clinicians at an Advisory Board, which highlighted a number of anecdotal QoL benefits of ibrutinib[12]:

- Anecdotal reports have described how patients who were confined to bed whilst receiving conventional chemotherapy have shown a rapid response to ibrutinib treatment (within 10 hours in some cases). These reports also highlight that ibrutinib has a 'euphoric effect', with patients' QoL reported as being as good as a healthy individual;
- Clinician feedback was that they can often distinguish patients who are receiving ibrutinib rather than R-chemo by the fact that patients receiving chemotherapy will look sick and be suffering hair loss, whereas patients receiving ibrutinib will often look healthy;
- Anecdotal reports have revealed that patients have been able to return to normal activities such as attending work or playing golf within weeks of receiving treatment. The median PFS observed in the ibrutinib trials (12.81 months, pooled analysis)[5],

when compared with results from the Hess, 2009 study (1.9 months) and from the Skåne University Hospital dataset (2.8 months), supports an extended period in a progression-free state for patients receiving ibrutinib versus treatments in current clinical practice[9, 47]. This is commensurate with the notion that ibrutinib may allow patients to return to their normal activities.

These areas of QoL (lack of energy, ability to work, ability to enjoy life) are well-captured by the physical and functional well-being sub-scales of the FACT-Lym, which are common to the general FACT instrument (FACT-G). These domains showed significant improvement with ibrutinib compared to TEM in RAY (MCL3001), as did the emotional well-being FACT subscale. Whilst a number of the QoL benefits of ibrutinib may be captured using the EQ-5D-5L outcome measure to establish patient QoL preference weights, it is unlikely that this measure fully captures the meaningful and valuable QoL benefit that has been observed in clinical trials and anecdotally as described above. In particular, the EQ-5D-5L measure contains no explicit fatigue dimension and fatigue has been reported as one of the most important negative QoL impacts of the condition[2]. Domain level evaluation of the RAY (MCL3001) EQ-5D-5L data shows that some change from baseline was captured by the usual activities and pain/discomfort domains, but at a level that may not represent a change in EQ-5D health state and hence utility.

In addition to the benefit of ibrutinib on patient QoL, ibrutinib is anticipated to improve the QoL of carers looking after patients with R/R MCL; this is a benefit that is not captured in the QALY calculation presented in Section 5. 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. The burden of MCL on carers in terms of QoL is also likely to increase as the disease progresses and patients relapse. Ibrutinib is an oral treatment and, unlike other treatment options, does not require frequent hospital visits for infusion or monitoring. This is likely to improve carers' QoL as they will no longer be required to provide transport to hospital or help with household activities. In addition, the treatment-free interval after ibrutinib treatment in RAY (MCL3001) was significantly longer than that observed after TEM[36]. The median time to next treatment was not reached in the ibrutinib arm compared with 11.6 months in the TEM arm, at a median follow up of 20 months[36]. This has clear implications for carers who will not be required to attend hospital visits for administration of subsequent treatment during the treatment free period. In addition, there may be a psychological benefit for carers in seeing the patients for whom they provide care experiencing improved QoL on ibrutinib.

Finally, there are further benefits to society that may arise from the introduction of ibrutinib. The marked improvement in QoL from ibrutinib may aid patient self-functioning and allow them to return to work and normal activities faster following treatment with ibrutinib than with conventional chemotherapy. This may result in improved productivity at work and increased engagement with society, and these benefits are not captured under the perspective of the NHS and PSS that represents the NICE reference case.

In summary, ibrutinib is expected to provide a number of benefits that may not be adequately captured by the QALY calculation. These include both patient-centric aspects that may not be fully captured by the EQ-5D-5L utility measure, but also wider societal considerations relating to burden on caregivers and to the wider society that fall outside of the perspective of the health economic analysis presented in Section 5.

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

Summary

MCL is an extremely rare and often aggressive type of NHL. Approximately 13,400 people were diagnosed with NHL in the UK in 2013, including approximately 500 with MCL[48, 49]. The most common signs and symptoms of MCL are lymphadenopathy, splenomegaly, bone marrow infiltration and leukaemic involvement. Extranodal involvement is also frequent, particularly affecting the gut and liver, and involvement of more than two extranodal sites is observed in 30-50% of patients[10].

MCL is an incurable disease with rapid progression and the poorest prognosis of all types of NHL[7, 10]. This is compounded by the fact that the majority of MCL patients are diagnosed in the advanced stages of the disease[10, 49]. Responses to initial chemotherapy in MCL are temporary, leading to a high recurrence rate[33]. Subsequently, there is an ever diminishing response to successive lines of therapy (LOTs) and a shortening duration of remission[7, 46]. As such, patients with MCL have a median OS of only 3-4 years from diagnosis[33] and a median OS of <1 year in R/R disease[7-9].

Patients with stage I-II MCL are considered for radiotherapy. For patients who are asymptomatic but not suitable for radiotherapy, 'watch and wait' should be considered until disease progression[50]. Patients with advanced stage disease require systemic treatment, which tends to be chemotherapy with or without rituximab[50]. For patients with high tumour burden, choice of treatment should be based upon age and fitness.

There is no SOC for R/R MCL[4] and there are no NICE technology appraisals (TA) relating to the treatment of the disease. During a recent advisory board, Janssen was advised that the majority of patients with R/R MCL will receive R-chemo; most commonly R-CHOP, although frail or very frail patients are likely to receive R-CVP or R-chlorambucil, respectively[12]. In cases of early relapse, the European Society for Medical Oncology (ESMO) now strongly recommend newer targeted approaches, including TEM, bortezomib, ibrutinib and lenalidomide[51]. Although licensed for use in R/R MCL in the UK, advice from clinical experts is that TEM is not used in clinical practice. Bortezomib is only recommended for previously untreated MCL patients and lenalidomide is only available via a CUP[12, 13, 52].

3.1 *Disease overview*

MCL is an extremely rare and often aggressive type of NHL, in which mutation and overexpression of cyclin D1, a cell cycle gene, contributes to the abnormal proliferation of malignant B-cells[17]. It is called 'mantle cell' lymphoma because the abnormal B-cells arise from the mantle zone within the lymph node.

3.1.1 *Prevalence*

Approximately 13,400 people were diagnosed with non-Hodgkin's lymphoma (NHL) in the UK in 2013[48]. The prevalence of MCL in the general population is approximately 0.0016% based on data from the HMRN, meaning that ibrutinib is an orphan medicine within MCL. MCL is a disease that occurs more commonly in men than women (75% of patients with MCL are men), and the incidence increases with age; the median age at presentation is 63 years[10, 49]. The number of patients in England, Wales and Northern Ireland with R/R MCL is estimated to be 356 in 2017 (see Section 6) which would equate to an estimate of fewer than 1 in 50,000 of the adult population in the UK.

3.1.2 *Signs and symptoms*

The most common signs and symptoms of MCL are lymphadenopathy (swelling of the lymph nodes, which is usually widespread at diagnosis), splenomegaly (enlargement of the spleen, which can lead to abdominal pain or fullness), bone marrow infiltration (and consequently anaemia, low platelets and low neutrophils) and leukaemic involvement. Extranodal involvement is also frequent, particularly affecting the gut and liver, and involvement of more than two extranodal sites is observed in 30-50% of patients[10]. In addition, about 40% of patients with MCL will also report 'B symptoms', which include fever, night sweats and weight loss, and can have a marked impact on patients' QoL[53].

3.2 *Effect on patients, carers and society*

MCL has the poorest outlook of all subtypes of lymphoma; the duration of remission is short and OS is short[46]. QoL in patients with R/R MCL is poor; fatigue and loss of mobility are commonly observed[11]. As a result, R/R MCL patients may not be able to perform simple activities of daily living such as preparing meals or housework. In such cases assistance will be required from a family member or a professional carer.

Given that R/R MCL is extremely rare, there is a paucity of data on the impact of the disease on carers' QoL. However, the diagnosis in a loved one of a fatal condition with a short survival period is likely to cause carers great concern and have a considerable impact on their QoL. Furthermore, conventional treatment for R/R MCL involves IV chemotherapy infusions and patients are required to attend hospital for treatment administration. Most patients would not be fit enough to drive to hospital and may live in areas without local access or transport to an appropriate infusion unit. In many cases, patients would need a carer to provide transport to the infusion unit, which is also likely to have an impact on carers' QoL (see Section 2.5).

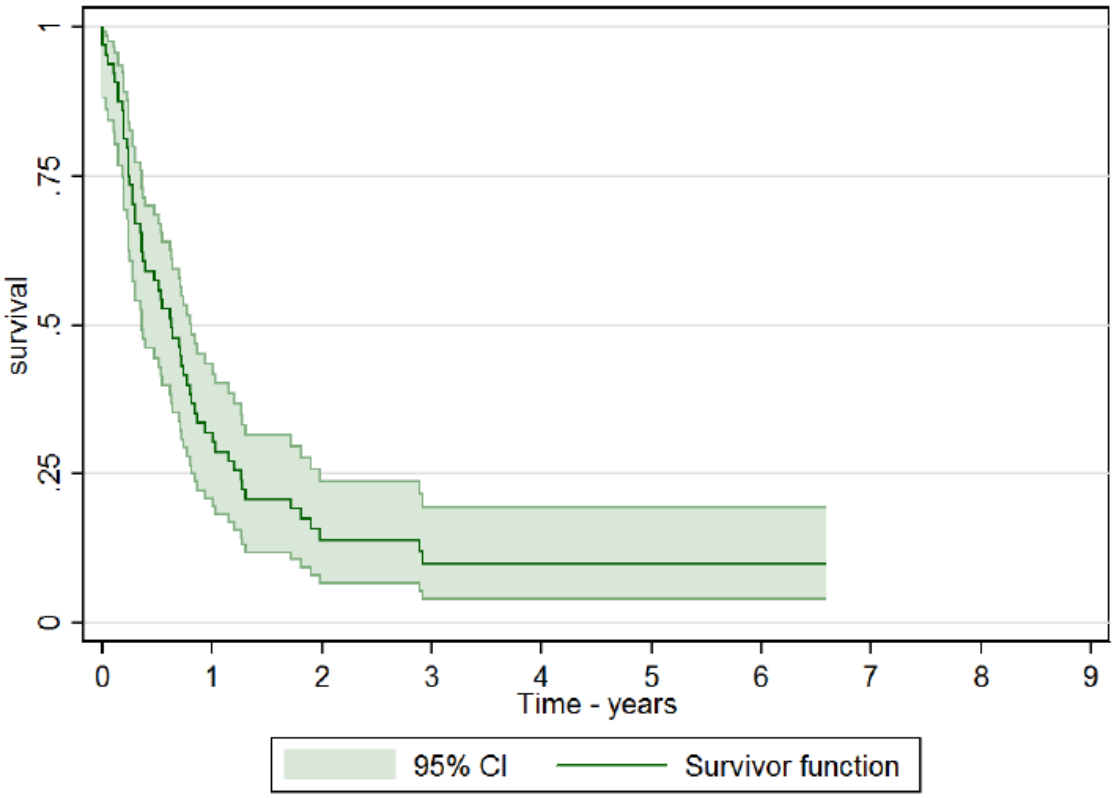
3.3 *Life expectancy*

MCL is an incurable disease with rapid progression and poor outcomes[7]. As stated above, MCL has the poorest prognosis of all types of NHL[10]. This is compounded by the fact that the majority of MCL patients are diagnosed in the advanced stages of the disease, with 80–90% of MCL patients diagnosed with Ann Arbor stage III or IV lymphoma[10, 49].

Responses to initial chemotherapy in MCL are temporary, leading to high recurrence rates[33]. Subsequently, there is an ever diminishing response to subsequent LOTs and a shortening DOR[7, 46]. Data from the HMRN based on a sample of 244 patients diagnosed with MCL between September 2004 and August 2013 revealed that 58% of patients responded to first-line chemotherapy or radiotherapy, 33% responded to second-line therapy and 16% responded to third-line therapy[7]. Furthermore, DOR fell by approximately 60% between each LOT[7].

As such, the long-term prognosis for patients with MCL is poor, with a median OS of only 3-4 years from diagnosis[33] and median OS of <1 year in patients with R/R disease[7-9]. In the HMRN dataset (Figure 4), median OS was 8.4 months in patients with R/R disease who achieved a response to first-line treatment (n=57)[7]. A similar OS estimate of 9.7 months was observed in patients receiving PC in the phase III trial by Hess, 2009[8]. Finally, in the real-world registry of patients treated at the Skåne University Hospital in Sweden between 2000 and 2012, the median OS of 26 patients treated at the 3rd or 4th line of therapy was 5.2 months[9].

Figure 4: OS in patients with R/R disease who achieved a response to first-line treatment (HMRN, n=57)



HMRN: Haematological Malignancy Research Network
Source: HMRN dataset, 2014[7]

3.4 *Treatment pathway*

3.4.1 *First-line treatment pathway*

Clinical guidelines for the diagnosis and management of patients with MCL were published by the BCSH in 2012[10] and, more recently, by the ESMO in 2014[51]. A further review of the evolving management strategies of R/R MCL was published by Campo and Rule in 2015[4].

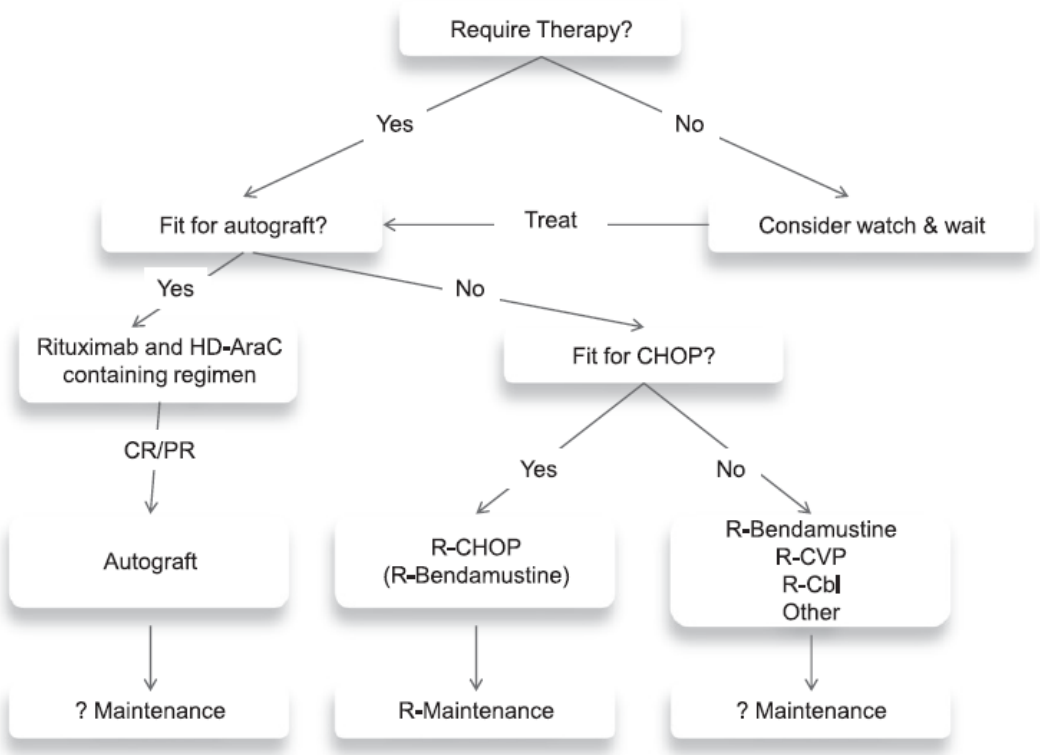
Finally, the draft NICE Clinical Guidelines for diagnosis and management of NHL were published in March 2016 and the final publication is expected in July 2016[50].

The draft NICE Clinical Guidelines note that "*there is no accepted standard of care for patients with MCL. The paucity of randomised control data, the relative infrequency of this lymphoma subtype, historical problems in identifying this entity correctly and finding trials with only MCL patients included have all contributed to this*"[50]. A small number of patients present with limited stage (I or II) disease and are frequently considered for radiotherapy. There is also an 'indolent' form of MCL which may be identified clinically. For people with clinically non-progressive MCL who are asymptomatic and for whom radiotherapy is not suitable, 'watch and wait' (observation without therapy) should be considered until disease progression[50].

The majority of patients have advanced stage disease and require systemic treatment. The regimens that have been studied are mostly similar to those used in other B-cell lymphomas, namely chemotherapy with or without rituximab[50]. For patients with high tumour burden, choice of treatment should be based upon age and fitness. Younger, fitter patients should receive rituximab with a regimen containing high dose cytarabine followed by autologous blood stem cell transplant. For older or less fit patients, a standard dose rituximab-containing chemotherapy regimen such as R-CHOP (rituximab, cyclophosphamide, doxorubicin and vincristine) or R-bendamustine (rituximab and bendamustine) is recommended if patients are fit enough. Alternatively, FCR (rituximab, fludarabine and cyclophosphamide), R-CVP (rituximab, cyclophosphamide, vincristine and prednisolone), or R-chlorambucil (rituximab and chlorambucil) can be used (see Figure 5)[4, 10, 50]. According to the ESMO guidelines, however, R-CVP and FCR are discouraged due to inferior response rates and long-lasting myelosuppression[51].

A current issue with clinical practice is that the use of R-CHOP as a first-line therapy precludes its use as a later stage therapy, where the current alternative chemotherapy regimens are not considered as effective[12].

Figure 5: Current first-line therapy pathway for MCL



Source: Campo, Rule, 2014[4]

3.4.2 ***R/R MCL Treatment Pathway***

Responses to first-line chemotherapy are often temporary and relapse rates are high. Responses to subsequent LOT are then usually poorer and shorter than for first-line treatment[7, 46].There is currently no SOC for R/R MCL as can be observed in the HMRN audit (19 different treatment approaches were used in the 79 patients who received second-line chemotherapy for R/R MCL). Moreover, the IMS Harmony data reveal that [redacted][54].

The choice of treatment in R/R MCL depends on the age of the patient and their fitness. Younger patients who are fit enough for high dose chemotherapy and autologous peripheral blood stem cell transplantation in first remission should receive a high dose cytarabine-containing regimen to achieve an optimal remission, followed by allogeneic transplantation at relapse[4]. The recent advisory board held by Janssen with clinicians who are expert in the treatment of MCL in the UK found that in clinical practice R-CHOP is most commonly used as first relapse treatment for less fit patients. For frail patients R-CVP is the most common treatment and for very frail patients R-chlorambucil is used. For further relapses, patients may receive a variety of salvage therapies as R-CHOP is likely to have already been used in previous LOTs[12]. In cases of early relapse, the ESMO strongly recommends newer targeted approaches, including TEM, bortezomib, ibrutinib and lenalidomide[51]. Other than ibrutinib, TEM is the only agent licensed for use in R/R MCL in the EU; however TEM is not used in clinical practice in the UK. Bortezomib is only recommended for previously untreated MCL patients and lenalidomide is only available via a CUP[12, 13, 52].

3.5 ***Relevant NICE guidance***

Table 10 below provides the details of relevant NICE guidance and technology appraisals (TA) relating to the treatment of R/R MCL.

Table 10. NICE Guidance and TAs relating to the treatment of R/R MCL

Guidance/TA title	Details
NICE clinical guidelines for the diagnosis and management of non-Hodgkin's lymphoma[50].	Draft guidance available; final guidance expected July 2016.
Bortezomib for previously untreated mantle cell lymphoma [TA370][13].	Published in December 2015. Recommendation: Bortezomib is recommended as a possible treatment for adults with mantle cell lymphoma that has not been treated before, if haematopoietic stem cell transplantation is not suitable for them.
Temsirolimus for the treatment of relapsed or refractory mantle cell lymphoma [TA208][55]	Terminated in October 2010. TEM was not recommended for use as no evidence submission was received from the manufacturer.
Lymphoma (mantle cell, relapsed, refractory) – lenalidomide [ID739][52]	Suspended in November 2015. The manufacturer indicated that they would not be making a submission for this appraisal therefore it was suspended by NICE while they consider the next steps.
TA: technology appraisal, NICE: National Institute for Health and Care Excellence, TEM: temsirolimus	

3.6 *Issues relating to current clinical practice*

As highlighted previously, there is currently no SOC for R/R MCL[4, 10]. As explained in Section 2.5 and Section 3.4.2, HMRN and IMS Harmony data show how several different R-chemo regimens are used in the UK. MCL is rare and was only recognised as a specific disease in 1994[56]. Moreover, MCL patients are commonly enrolled in clinical trials together with patients with different NHL, hence there is a lack of definitive data to guide treatment [10].

3.7 *Equity considerations*

Ibrutinib is well tolerated with a consistent survival benefit demonstrated across all patient subgroups[36, 37, 39]. It therefore provides an effective treatment option for all R/R MCL patients including those who cannot receive cytotoxic therapies due to their advanced age, performance status, comorbidities or fitness. Equality issues which may currently exist for older, frailer patients would be alleviated with the use of ibrutinib. Furthermore, the oral administration of ibrutinib allows an effective treatment option to be given to patients that may not have local access or transport to an appropriate infusion unit.

4 Clinical effectiveness

Summary

- Three studies support the use of ibrutinib in R/R MCL: one phase III RCT (RAY [MCL3001]) and two phase II single-arm studies (PCYC1104, the registration study, and SPARK [MCL2001]). A pooled analysis of all three trials provides a robust estimate of ibrutinib efficacy across 370 patients and incorporates the longer-term follow-up of the PCYC1104 study.
- Ibrutinib demonstrated an unparalleled PFS benefit, consistent in all clinical trials. Median PFS in RAY (MCL3001) was 14.6 months for patients receiving ibrutinib, which represented a substantial and significant 57% reduction in the risk of disease progression or death with ibrutinib compared to TEM (hazard ratio (HR) = 0.43, 95% CI: 0.32; 0.58, p<0.0001). Median PFS in the pooled dataset was 12.81 months (95% CI: 8.48, 16.56)[5]. These figures compare to a PFS of less than 5 months estimated for R-chemo.
- The median OS of 25.00 months (95% CI: 21.59, NE)[5] for the 370 patients who received ibrutinib was substantially longer than estimates previously observed in clinical practice from the literature (5-10 months). The pooled median OS was is consistent with median OS in PCYC1104 of 22.5 (95% CI 13.7, NE) at 26.7 months follow-up
- ORRs were 71.9% in RAY (MCL3001) and 66.22% in the pooled dataset[5]. The ORR observed in PCYC1004 at the time of licensing (68%) was considered 'unprecedented' by the CHMP. The pooled analysis also demonstrated that PFS, OS and ORR were higher in patients who had received fewer prior LOTs and supported use of ibrutinib earlier in the treatment of R/R MCL[5]
- The improvement in QoL observed with ibrutinib is extraordinary. In RAY (MCL3001), nearly twice as many patients in the ibrutinib arm achieved a clinically meaningful symptoms improvement compared with TEM (61.9% versus 35.5%), with symptoms improvement achieved significantly quicker with ibrutinib (median 6.3 weeks compared to 57.3 weeks with TEM)[3]. Symptom improvement with ibrutinib was accompanied by clinically meaningful improvement from baseline on the FACT-Lym total score and across physical, functional and emotional well-being sub-scales. In addition, significantly higher EQ-5D-5L utility was observed within 4 weeks and maintained through to week 49 of treatment[3]
- Ibrutinib is well tolerated, with low rates of AEs and treatment discontinuation. In RAY (MCL3001), ibrutinib was better tolerated than TEM, with grade 3 or higher treatment-emergent AEs reported for 94 (68%) patients on ibrutinib versus 121 (87%) patients on TEM. This was despite the fact that the median duration of treatment exposure was almost five-fold higher for ibrutinib compared to TEM in the RAY (MCL3001) study. Furthermore, substantially fewer discontinuations due to AEs were reported for ibrutinib compared with TEM (9 [6%] compared with 36 [26%], respectively)[36]
- A lack of clinical evidence for the R-chemo therapies that represent current clinical practice was identified, reflecting the unlicensed status of these therapies. Comparative effectiveness was therefore estimated based upon a Bucher ITC of the RAY (MCL3001) study and the PC arm of the Hess, 2009 phase III RCT
- This ITC derived a HR for PFS and OS of 0.19 (95% CI: 0.1, 0.36) and 0.59 (0.31, 1.09), respectively. Therapies comprising the PC arm of Hess, 2009, however, do not reflect the current use of rituximab in clinical practice and the PFS HR was therefore adjusted to take account of a 'rituximab effect' in exploratory analyses in the economic model (Section 5). Whilst we acknowledge the limitations of this approach, this is due to the paucity of data available for R-chemo in a disease area with high unmet need such as R/R MCL. This is in contrast to the considerable clinical evidence base which now exists for ibrutinib in R/R MCL. Janssen believe that this is uncertainty that it is not possible for us to fully address, given that R-chemo is unlicensed and does not have a strong evidence base.

4.1 *Identification and selection of relevant studies*

4.1.1 *Systematic literature review*

A SLR of clinical evidence in R/R MCL was conducted to identify relevant RCT and non-RCT studies of ibrutinib. In addition, a number of comparator therapies were considered relevant for inclusion in this review, including those defined in the final scope for this appraisal.

4.1.2 *Search strategy*

The search strategy encompassed searching of electronic databases, hand-searching of relevant bibliographies and grey literature searching, as described below.

Database literature searches were conducted on the 7th of May 2014, updated on the 8th of June 2015, and the search of relevant congress abstracts was updated in February 2016. As the database literature update is now 9 months old, the SLR is in the process of being updated and the results will be available in June 2016. It is not expected, however, that any additional relevant data sources will be identified by this update.

The databases searched were:

- MEDLINE (via PubMed)
- MEDLINE In-Process (via PubMed)
- Embase
- Embase In-Process
- The Cochrane Collaboration Central Register of Clinical Trials (CENTRAL)

Search terms for the searches of electronic databases can be found in Appendix 3. In-Process searches were run through removal of limitation tags and searched using key terms to allow for the inclusion of newer, non-indexed publications (i.e. in-process records), as per the US National Library of Medicine website.

In addition to the electronic database searches described 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 posters presenting any relevant information on the outcomes of interest. Proceedings from 2013-2015 (as available) of the following conferences were screened for relevant abstracts:

- American Society of Clinical Oncology (ASCO) 2013–2015: http://am.asco.org/
- American Society of Hematology (ASH) 2012–2014: http://www.hematology.org/Annual-Meeting/
- European Hematology Association (EHA) 2013–2015: http://www.ehaweb.org/
- European Society for Medical Oncology (ESMO) 2012–2013: http://www.esmo.org/Conferences/ESMO-2014-Congress
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 2013–2015 (International, Europe, and Latin America Meetings): http://www.ispor.org/

An update to the congress searches was performed in February 2016, applying the same methodology as for the original congress searches described above. The only two congresses with updated abstract availability since the original search were the ASH 2015

congress and the European Cancer Congress (ECC) 2015 (an ESMO congress). Updated searches were therefore performed for these two congresses only.

Finally, the bibliographies of any relevant SLR articles identified as part of the electronic database searching described above and published since 2011 were reviewed as a potential supplemental source of relevant studies.

Further details of the full search strategies employed can be found in Appendix 3.

4.1.3 ***Study selection***

The SLR was designed to focus on trials of R/R MCL that reported efficacy and safety outcomes. Prior to study selection, all duplicates of articles identified by the search were removed. The study selection process then consisted of two stages: 1) a review of titles/abstracts; 2) a review of full texts.

At each stage, articles were reviewed against the pre-specified eligibility criteria provided in Table 11, which were based on the PICOS (Population, Intervention, Comparator, Outcomes, Study design) formula. In the initial screening phase (titles and abstracts review), studies were not excluded based on intervention/comparators of interest; these criteria applied to the review of full texts only. No date or language limits were applied to the searches; however, all non-English-language publications that were identified at the abstract level and that would otherwise have met the inclusion criteria for this stage of the review were rejected on the basis of being non-English-language studies. These studies therefore did not progress to full-text review.

The titles/abstracts review was performed by two independent investigators, with any discrepancies between the two investigators reviewed and resolved by a third investigator before proceeding to retrieval of full texts. Full texts were singly reviewed, with all articles rejected during this process then independently verified by a second, senior-level investigator based on the reason for rejection and the accuracy of rejection.

Data extraction was performed for the studies meeting all inclusion and no exclusion criteria. Information from the full-text articles was extracted into a data extraction form by one investigator. Data extraction was then validated by a second investigator and a third investigator was consulted to resolve any discrepancies, as necessary. A number of control measures were put in place to ensure the quality and consistency of data extraction, including pilot testing of the extraction form on several included studies, resolution of potential ambiguities and differences in the interpretation of findings, and provision of written instructions on the outcome measures to be extracted from the full papers.

Table 11: Eligibility criteria for the clinical SLR

	Inclusion criteria	Exclusion criteria
Population	R/R MCL patients	Patients without at least 85% R/R MCL, i.e. studies involving treatment-naïve MCL patients, other lymphoma subtypes, or patients receiving first-/front-line therapies
Intervention	Review of full texts only • Ibrutinib monotherapy • Ibrutinib combination therapy • BR • R-CHOP • Fludarabine + cyclophosphamide ± mitoxantrone (FC ± M) • Fludarabine + (bendamustine or cisplatin or chlorambucil or rituximab or cyclophosphamide) • Chlorambucil + rituximab • Bortezomib monotherapy ± rituximab • Bleomycin monotherapy • Vinblastine monotherapy • Dacarbazine monotherapy • Temsirolimus monotherapy • Doxorubicin monotherapy • Rituximab monotherapy • R-DHAP ± low-dose aracytine • Lenalidomide monotherapy • Rituximab and cytarabine (RC) • Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CVP)	No treatment of interest (for example, radioimmunotherapy, 'watch and wait'/no treatment, prophylactic or palliative care alone)
Comparators	*Review of full texts only* Any of the above interventions	
Outcomes	**Efficacy** • Overall response: number of patients • Complete response: number of patients • Partial response: number of patients • Stable disease: number of patients • Progressive disease: number of patients • Unconfirmed complete response or nodular partial response: number of patients • Minimal residual disease • Response duration: in months • Time to first response: in weeks • Time to progression: in weeks	• Publications that did not report safety outcomes, or efficacy outcomes for R/R MCL • Articles investigating in vitro, animal, foetal, molecular, genetic, pathologic, or pharmacokinetic/pharmacodynamic outcomes without outcomes of interest reported

	Inclusion criteria	Exclusion criteria
	• Progression-free survival: in months • Overall survival: in months • Treatment-related death: number of patients • Overall death: number of patients • Event-free survival: in months • Time to treatment failure: in months **Safety** • Grade 3, 4, or 3/4 safety endpoints (each outcome definition was to be captured as reported; the number of patients was to be captured or calculated from a percent for each outcome unless otherwise specified) • Infusion-related complications • Anaemia/haemoglobin • Febrile neutropenia • Infection-related • Leukopenia • Lymphocytes abnormal • Neurotoxicity • Neutropenia • Pain • Peripheral oedema • Thrombocytopenia	
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 abstract published in English • Comparative studies with fewer than 10 patients per treatment group in at least two treatment arms or single-arm studies with fewer than 10 patients
Language	English language	Non-English-language
R/R MCL: relapsed or refractory mantle cell lymphoma		

4.1.4 ***PRISMA flow diagram***

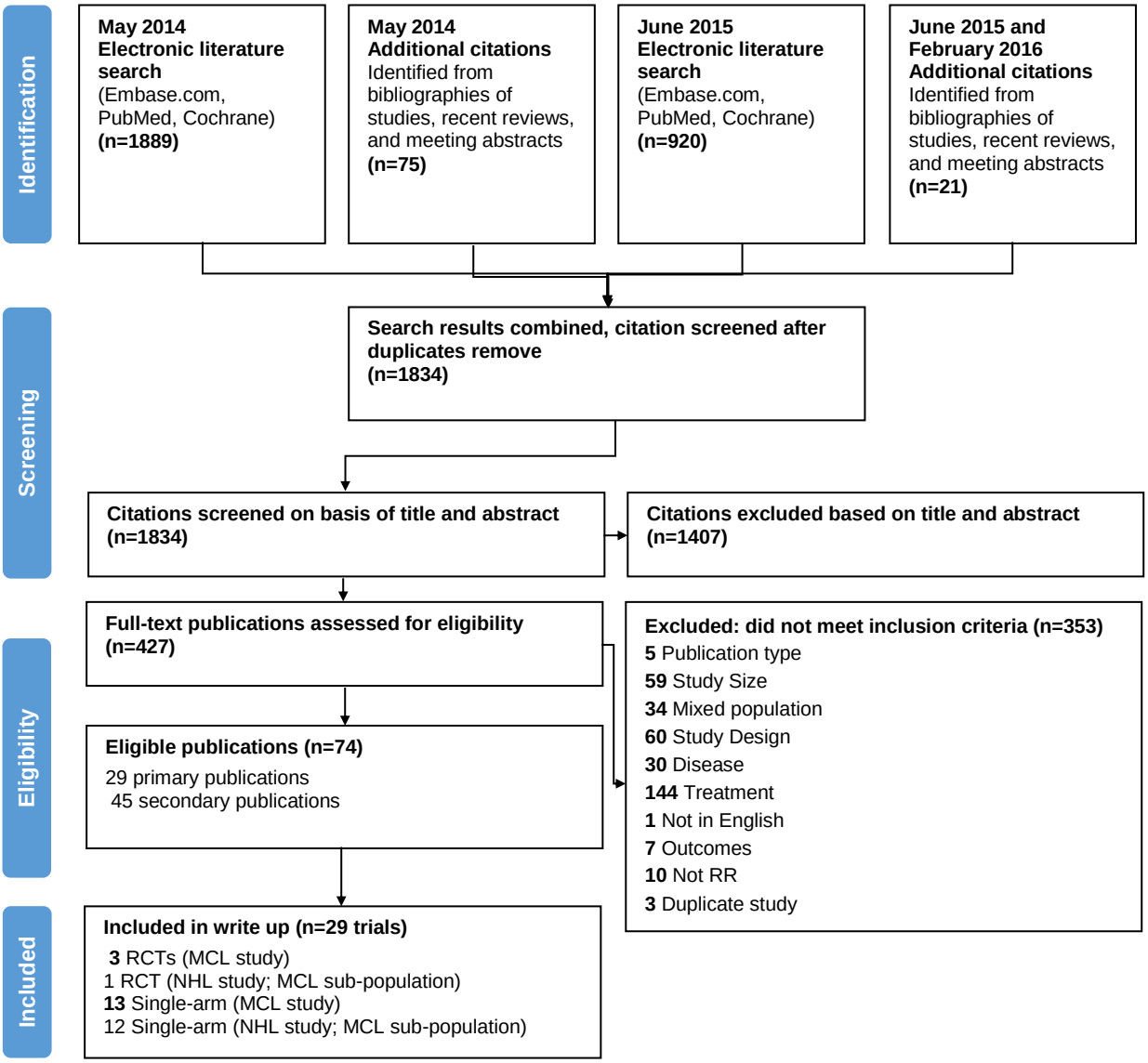
A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram presenting the results of the SLR is provided in Figure 6. This flow diagram takes into account the original searches and the update congress searching.

Overall, a total of 29 studies (4 RCTs and 25 non-RCT studies were identified, corresponding to 29 primary publications and 45 secondary publications). A full list of the 29 identified studies and their linked publications is provided in Appendix 4.

Of the 4 RCTs identified by the clinical SLR, a single RCT evaluated ibrutinib monotherapy: RAY (MCL3001). The three other identified RCTs all evaluated comparator therapies that were included in the eligibility criteria for the SLR but are not relevant to this submission on the basis of the final scope for this appraisal, and understanding of current UK clinical practice. Section 4.2 presents a summary of the four RCTs identified by the SLR and a justification from their subsequent inclusion or exclusion from consideration in this submission.

In total, 4 of the 25 identified non-RCTs evaluated ibrutinib monotherapy and are therefore relevant to this submission. These four non-RCTs are discussed in Section 4.11 whilst the full list of all 25 non-RCTs is provided in Appendix 4.

Figure 6: PRISMA flow diagram for the clinical SLR



4.2 ***List of relevant randomised controlled trials***

As discussed in Section 4.1.4, the clinical SLR identified four published RCTs, of which one was considered relevant to this submission. This was the RAY (MCL3001) study, for which the SLR identified two congress contributions as part of the updated congress search. In addition, a full-text journal publication for this study (Dreyling *et al.* 2015) was identified outside of the SLR, as it was published after the date of database searching[36].

All four RCTs are summarised in Table 12. The RAY (MCL3001) study is considered the most relevant RCT to this submission as it is the only comparative study of ibrutinib in R/R MCL. This study is therefore presented in detail in the subsequent sections.

RAY (MCL3001) was a phase III open-label RCT comparing ibrutinib to TEM in patients with R/R MCL who had received at least one prior rituximab-containing chemotherapy regimen[36]. TEM was chosen as the comparator for the phase III RCT for a number of reasons:

- It was the only agent licensed for R/R MCL by the EMA at the time of study conception;
- It was also approved for this indication in several countries outside the EU in which there were study centres for RAY (MCL3001) (see Section 4.3.1.1)
- It is recommended by international treatment guidelines for R/R MCL[10, 57, 58].

A summary of RAY (MCL3001) is presented in Section 4.3.

Table 12: Summary of RAY (MCL3001) and the non-ibrutinib RCTs identified by the SLR

Trial	Population	Intervention	Comparator	Primary study reference	Relevance to the decision problem
Phase III (comparative)					
RAY (MCL3001)	R/R MCL who have received at least one prior rituximab-containing chemotherapy regimen	Ibrutinib (n=139)	TEM (n=141)	Dreyling, 2015[36]	Highly relevant to the decision problem. Investigates the intervention under consideration (ibrutinib).
OPTIMAL	R/R MCL who have received two to seven prior therapies	TEM	Investigator's choice	Hess, 2009[8]	Provides an estimate of PFS and OS on PC therapy. The interventions comprising the PC arm were single-agent chemotherapy options that are not used in current UK clinical practice. However, as the only identified RCT that permitted an ITC with the RAY (MCL3001) study via the common TEM comparator, this study was used for the ITC presented in Section 4.10 and therefore informed the cost-effectiveness modelling.
MCL002 (SPRINT)	MCL patients with up to 3 relapses or who failed prior therapy and were ineligible for intensified treatment or stem cell transplantation	LEN	Investigator's choice	Trneny, 2014[59]	Not relevant. Although this study contained an investigator's choice arm, similarly to Hess, 2009 these interventions were single-agent chemotherapy options that are not used in current UK clinical practice. However, unlike Hess, 2009, the lenalidomide comparator in this study does not permit an ITC with the RAY (MCL3001) study. Therefore, this study could not be used to inform the submission. See Appendix 9 for further discussion.
German	R/R follicular, mantle cell or	FCM	FCMR	Forstpointner 2004[60]	Not relevant. Interventions

Low-Grade Lymphoma Study Group	lymphoplasmocytoid lymphoma*				considered are not relevant to the decision problem. See Appendix 9 for further discussion.

ASH: American Society of Hematology, CSR: clinical study report, FCM: fludarabine, cyclophosphamide and mitoxantrone, FCMR: fludarabine, cyclophosphamide, mitoxantrone and rituximab, LEN: lenalidomide, MCL: mantle cell lymphoma, TEM: temsirolimus, PFS: progression-free survival, R/R: relapsed or refractory.
*MCL population a subgroup of larger study population

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

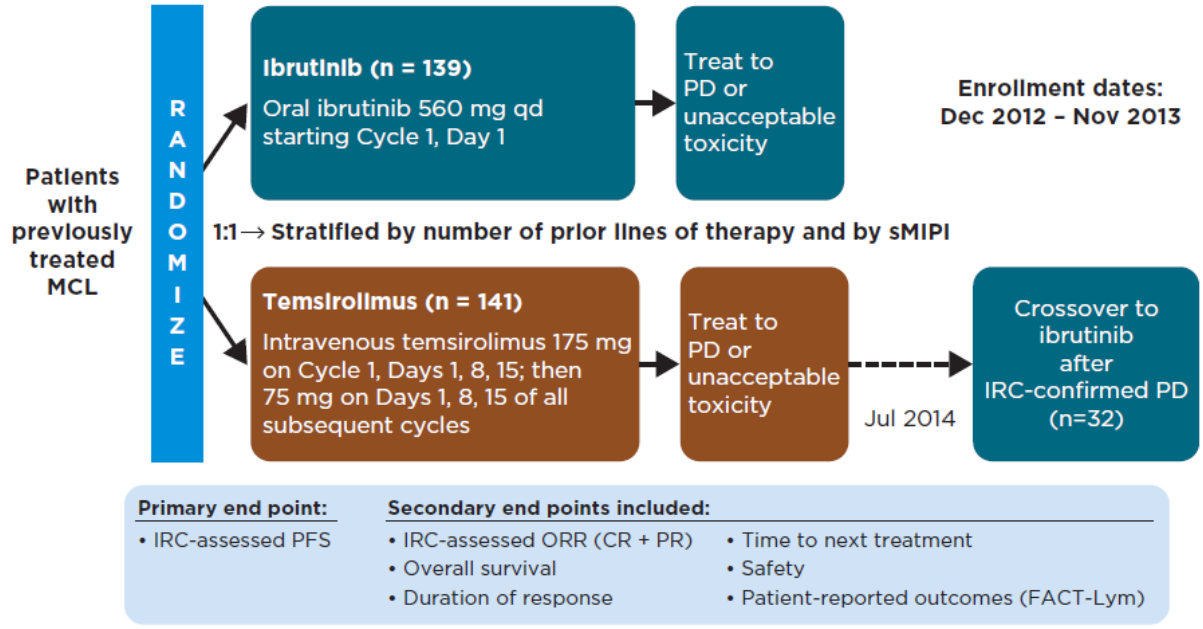
4.3.1 *RAY (MCL3001)*

Data from this section are drawn from the published paper by Dreyling, 2015 (Dreyling M, Jurczak W, Jerkeman M *et al.* Ibrutinib versus TEM in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. Lancet. 2015. http://dx.doi.org/10.1016/S0140-6736(15)00667-4), the Clinical Study Report (CSR)[36, 61], a poster presented at the ASH 2015 conference focusing on QoL[3] and an oral presentation also presented at the ASH 2015 conference[62].

4.3.1.1 Study design

RAY (MCL3001) was a randomised, controlled, open-label, multicentre, phase III study which compared the efficacy and safety of ibrutinib versus TEM in patients with R/R MCL (see schematic in Figure 7).

Figure 7: Study design of RAY (MCL3001)



MCL: mantle cell lymphoma, IRC: Independent Review Committee, CR: complete response, PR: partial response, ORR: overall response rate, PD: progressive disease, sMIPI: simplified mantle cell lymphoma international prognostic index, FACT-Lym: Functional Assessment of Cancer Therapy-Lymphoma

Source: Hess, 2015 ASH Conference Poster[3]

Patients were eligible for the trial if they had received at least one prior rituximab-containing chemotherapy regimen and had documented relapse or disease progression after the last anti-MCL treatment, measurable disease by Revised Response Criteria for Malignant Lymphoma and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Between the 10th December 2012 and the 26th November 2013 a total of 337 patients were assessed for eligibility, of which 280 patients were selected for inclusion in the trial. Patients

were stratified by previous therapy and simplified MCL international prognostic index (MIPI) score, and were randomly assigned in a 1:1 ratio to receive either:

- ibrutinib 560 mg orally once daily (n=139), or
- TEM 175 mg (IV) on days 1, 8 and 15 of the first cycle, followed by 75 mg IV on days 1, 8 and 15 of each subsequent 21-day cycle (n=141).

Both groups continued treatment until disease progression or unacceptable toxic effects. On the 30th July 2014 the trial protocol was amended to allow patients from the TEM group who had IRC-confirmed progression of disease to formally crossover to receive treatment with ibrutinib 560 mg once daily, on a 21-day cycle until disease progression, unacceptable toxicity or the end of the study.

The primary end-point of RAY (MCL3001) was PFS, defined as the interval between the date of randomisation and the date of disease progression (as assessed by an IRC) or date of death, whichever occurred first, irrespective of the use of subsequent antineoplastic therapy. The clinical cut-off for the primary analysis of PFS was defined as the time at which approximately 178 PFS events were observed. The end of the study was to occur when 80% of the randomised patients died, or 3 years after the last subject was randomised, whichever occurred first.

Secondary end-points of the trial included ORR, OS, one-year survival rate, duration of response (DOR), time to next treatment, safety, pre-specified patient-reported outcomes (PROs), biomarkers and pharmacokinetics, and medical resource use (MRU).

Full details of the methodology of RAY (MCL3001) are presented in Table 13 below.

Table 13: Summary of methodology of RAY (MCL3001)

	RAY (MCL3001)
Location	Belgium, Brazil, Canada, Colombia, Czech Republic, France, Germany, Hungary, Ireland, Italy, Mexico, Netherlands, Poland, Portugal, Russian Federation, South Korea, Spain, Sweden, Taiwan, UK (27/280 patients) and Ukraine
UK patients	27 patients from nine sites, 11 randomised to ibrutinib and 16 randomised to TEM
Trial design	Multicentre, randomised, controlled open-label phase III study
Enrolment	From December 10th 2012 to November 26th 2013, 337 patients were assessed for eligibility into the study and 280 randomised into the study
Randomisation and blinding	Randomisation was performed using an interactive web response system (IWRS). Randomisation was in a 1:1 ratio and stratified by prior LOTs (1 or 2 versus ≥3), and simplified MIPI index (low risk [0-3] versus intermediate risk [4-5] versus high risk [6-11]). The MIPI is derived from four prognostic factors: age, ECOG score, lactate dehydrogenase level and baseline white blood cell count. The index classifies patients as having low-risk, intermediate-risk, or high-risk disease. The study was not blinded since patients received either an oral (ibrutinib) or IV (TEM) treatment; however, efficacy evaluations were performed by an IRC that was blinded to study treatment.
Inclusion criteria	• Men and women aged ≥18 years • Confirmed diagnosis of MCL with cyclin D1 overexpression or translocation breakpoints at t(11:14) and measurable disease • Had received at least one prior rituximab-containing treatment for MCL • Relapse or disease progression after the most recent regimen • ECOG performance status score of 0 or 1 • Adequate organ function • Absolute neutrophil count of at least 1,000/mm^3 independent of growth factor support • Platelet count ≥75,000/mm^3 or ≥50,000/mm^3 if marrow involvement independent of transfusion support • Haemoglobin ≥ 80 g/l independent of transfusion support • Use of contraception for patients of child-bearing age
Exclusion criteria	• Prior chemotherapy within 3 weeks, prior anticancer antibodies within 4 weeks, radiotherapy within 3 weeks, radio- or toxin-immunoconjugates within 10 weeks or major surgery within 4 weeks of randomisation • Prior treatment with TEM or ibrutinib, or agents from the same class • Known central nervous system lymphoma • History of stroke or intracranial haemorrhage within 6 months • Requirement for anti-coagulation with warfarin or a strong CYP3A4/5 inhibitor • Clinically significant cardiovascular disease • Infection with HIV, hepatitis C, hepatitis B or any uncontrolled active systemic infection • Pregnant or breast feeding women • Serum aspartate transaminase or alanine transaminase ≥3-times the ULN • Creatinine ≥2 times ULN • Total bilirubin ≥1.5 times ULN • Fasting serum cholesterol ≥9 mmol/l (350 mg/dl) and serum triglyceride ≥10.3 mmol/l (400 mg/dl)
Trial drugs	Patients were randomised to oral ibrutinib (self-administered 560 mg once daily (od) continuously for 21-day cycles) or IV TEM (175 mg on days 1, 8, 15 of the

	first cycle followed by 75 mg on days 1, 8, 15 of each subsequent 21-day cycle). Both groups continued treatment until disease progression or unacceptable toxic effects. Patients who were randomised to treatment with TEM and had disease progression confirmed by IRC prior to study end were eligible to crossover to ibrutinib until disease progression or unacceptable toxicity.
Concomitant medications	Standard supportive care therapies (e.g. anti-emetics, loperamide) other than anticancer treatment required for the management of symptoms were permitted, as clinically indicated. Haematopoietic growth factors were allowed. Prohibited medications included: any chemotherapy, anticancer immunotherapy, experimental therapy and radiotherapy. Systemic use of corticosteroids (i.e. any systemic corticosteroids ≥20 mg/day prednisone or its equivalent per day for more than 10 days) was prohibited.
Monitoring	Whilst patients were on treatment, assessments were made on day 1 of the 21-day cycle until 15 months after randomisation and every 42 days (2 cycles) thereafter until progressive disease (PD). Assessments included physical examination, ECOG score, B-symptoms, haematology and serum chemistry, coagulation and PROs. Assessments of efficacy included: • CT/MRI scans were carried out every 9 weeks up to 15 months, then every 24 weeks until PD or the clinical cut off • PET scans were carried out at the time of maximal tumour reduction (e.g. CR or PR with two consecutive CT scans showing no further tumour reduction) and at suspected disease progression, if a new lesion was detected on CT • Endoscopy was carried out to confirm CR for patients with known baseline GI involvement • Bone marrow aspirate and biopsy was carried out to confirm CR. If feasible an additional aspirate sample was collected for biomarker evaluation at the time of PD
Primary outcome	Duration of PFS as per the revised Cheson criteria[63] (the time from entry onto a study until lymphoma progression or death as a result of any cause) performed by an IRC blinded to study treatment. The clinical cut off for the primary outcome was defined as the time at which approximately 178 PFS events were observed. PFS was defined as duration in days from the date of randomisation to the date of disease progression or relapse from CR or death, whichever was first reported.
Secondary outcomes	• ORR, defined as the proportion of patients who achieve CR or PR (see Section 4.3.1.2) • DOR • OS, measured from the date of randomisation to the date of death • 1-year survival rate • Time to next treatment • Pre-specified PROs (FACT-Lym, EQ-5D-5L) • Safety • MRU* • Biomarkers and pharmacokinetics* Please see Section 4.3.1.2 for further details of secondary outcomes
PRO outcomes	• Time to worsening in the Lym subscale of the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) • Mean change from baseline in EQ-5D-5L scores for each post baseline assessment
Adherence	Adherence to ibrutinib was assessed by the investigator or designated study

	research staff at each visit using direct questioning, examination of patient diaries and capsule counts. TEM was administered at the clinical site and details of each administration were recorded in the case report form.
Pre-planned subgroups for PFS	• Age (<65 versus ≥65) • Gender (Male, Female) • Race (Caucasian, Non-Caucasian) • Geographical region (Europe, Non-Europe) • ECOG at randomisation (0, 1) • Bulky disease (<5 cm, ≥5 cm) • Number of prior treatment lines (<3, ≥3) • Baseline extranodal disease (Yes, No) • Simplified MIPI (low risk, intermediate risk, high risk) • Stage of disease (I-III, IV) • Prior bortezomib (Yes, No) • Histology (Blastoid, Non-blastoid) • Refractory disease (Yes, No)
IWRS: interactive web response system, MIPI: MCL International Prognostic Index, ECOG: Eastern Cooperative Oncology Group, IV: intravenous, IRC: Independent Review Committee, MCL: mantle cell lymphoma, HIV: human immunodeficiency virus, ULN: upper limit of normal, od: once daily, PD: progressive disease, PRO: patient reported outcome, CT: computed tomography, MRI: magnetic resonance imaging, PET: positron emission tomography, CR: complete response, GI: gastro-intestinal, ORR: overall response rate, PFS: progression-free survival, OS: overall survival, DOR: duration of response, MRU: medical resource use, FACT-Lym: Functional Assessment of Cancer Therapy-Lymphoma, VAS: visual analogue scale. *These outcomes were collected as part of the trial protocol but results for these outcomes are not considered relevant to this submission and are therefore not presented. Source: Dreyling, 2015[36] RAY (MCL3001) CSR[61].	

4.3.1.2 Study outcomes: definitions

The definitions of the outcomes used in RAY (MCL3001) are presented in Table 14.

Table 14: Validity and clinical use of outcomes used in RAY (MCL3001)

Outcome	Definition	Reliability/validity/current use in clinical practice
Primary outcome		
PFS	The interval from date of randomisation to the date of disease progression (as assessed by the IRC) or date of death, whichever occurred first, irrespective of the use of subsequent antineoplastic therapy. Progressive disease was determined according to the revised International Working Group Criteria for NHL* [63].	PFS is a common primary end-point in oncology clinical trials, and is therefore commonly presented both to the regulatory authorities and NICE as evidence of clinical efficacy in delaying disease progression or death. The revised Cheson criteria consider that PFS is often considered the preferred end point in lymphoma clinical trials, especially those involving incurable histologic subtypes (e.g. follicular, other low-grade lymphoma, or MCL). PFS reflects tumour growth, and therefore is interpretable earlier than the end-point of OS[63]. PFS is used in clinical practice to determine treatment decisions. Furthermore, PFS represents a benefit in itself; patients are likely to experience worsening QoL upon progression of disease and hence value a delay to disease progression or death. Unlike OS, PFS estimates are not confounded by crossover or by treatment with subsequent treatments. PFS is affected by the timing of assessments, however, and can be prone to investigator bias unless strict criteria for response evaluation are used. The RAY (MCL3001) study applied strict criteria, based on the revised International Working Group criteria for NHL[63].
Secondary/exploratory outcomes		
PFS2	The time interval between the date of randomisation to the date of an event, where event is defined as progressive disease as assessed by the investigator after the next line of therapy, death from any cause, or start of subsequent therapy if no disease progression is noted.	The drug resistance profile of a tumour might be expected to be influenced by therapy (due to the therapy applying a selection pressure, so that resistant tumour cell populations with advantageous mutations are selected for). As noted in the EMA Guideline on Evaluation of Anticancer Medicinal Products in Man, the development of resistant tumour mutations has potential relevance for the activity of next-line therapies[64]. PFS2 aims to capture PFS on next-line therapy and therefore account for the potential downstream impact of subsequent therapy on progression or death.
OS	The duration (months) from the date of randomisation to the date of the subject's death from any cause. Survival time of living subjects was censored on the last date a subject was known to be alive or lost to follow-	Death is definitive, is easily comparable and is not subject to investigator bias. An extension to survival is a highly valued outcome, as reflected by NICE's end-of-life criteria that account for an increased value placed on therapies able to extend life near to the end of

	up. The estimate of OS included all patients in the ITT analyses, including patients in the TEM arm who crossed over to ibrutinib as part of the amended protocol. A post hoc sensitivity analysis of OS was performed in which data from patients who crossed over from the TEM arm to receive ibrutinib during the study or who had received ibrutinib as subsequent therapy were censored at the date of the first dose of next-line ibrutinib treatment. The result was consistent with that recorded using the ITT analysis set (data not shown).	life. Limitations of the OS outcome are that results may be diluted by crossover and contaminated by subsequent agents, unlike with PFS estimates.
One-year survival rate	Proportion of patients who are still alive one year after randomisation	See above for a description of the relevance of the OS outcome.
ORR	The proportion of subjects who achieved either CR or PR as best overall response, as assessed by IRC at or prior to initiation of subsequent antineoplastic therapy, according to the revised International Working Group Criteria for NHL*[63].	Response rate provides an indication of the patients who will benefit from treatment. Not all patients who respond to treatment will benefit, but in order to benefit, an initial response must be seen. Response rate can deepen from a PR to a CR over time, demonstrating an improvement in response.
DOR (CR or PR)	The duration in days from the date of initial response to the date of first documented evidence of PD (or relapse for subjects who experience CR during the study) or death. Subjects who were progression-free and alive could have been censored at the time of last disease assessment.	DOR provides an indicator of the length of the effect provided by the treatment. The longer the DOR, the longer the effect provided from the treatment until progression.
Time-to-next treatment	Measured from the date of randomisation to the start date of any anti-lymphoma treatment subsequent to the study treatment. Subjects without subsequent treatment were censored at the date of their last site visit.	Subsequent treatments may be associated with greater toxicity and side-effects that negatively impact on QoL. Furthermore, use of subsequent treatment regimens may be associated with differing resource requirements. It is therefore informative to understand the extent to which requirement for subsequent treatment may be delayed.
EQ-5D-5L	Mean change from baseline in EQ-5D-5L scores for each post baseline assessment.	As an incurable aggressive cancer with a R/R nature, MCL is associated with poor QoL as described in Section 3.2. The EQ-5D-5L is a 5-item questionnaire with a visual analogue scale (VAS) ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The scores from the five dimensions are used to compute a single utility score ranging from below zero to one representing the general health status of the patient. The EQ-5D-5L is a validated generic preference-based measure of health and is

		the preferred measure of QoL in adults according to the NICE reference case. Although originally developed with three levels (EQ-5D-3L), an EQ-5D measure composed of 5 levels (EQ-5D-5L) has subsequently been developed with the aim of expanding the range of responses and hence providing further discriminatory power[65]. The EQ-5D-5L is used in the RAY (MCL3001) study.
FACT-Lym	Time to worsening in the Lym subscale of the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) as measured from the date of randomisation to the start date of worsening. Worsening was defined by a 5-point decrease from baseline.	FACT-Lym is a validated questionnaire for lymphoma patients which assesses physical, social/family, emotional and functional well-being together with leukaemia-specific concerns. The respondent answers each question as it applies to the past 7 days on a scale of 0 (not at all) to 4 (very much). FACT-Lym was originally developed to assess functional status and well-being of patients with NHL[66]. Reliability and validity have been assessed in NHL[67] and more recently construct validity has been supported in subjects with R/R MCL[68].
Safety	Assessments were based on reported AEs, clinical laboratory tests, physical examinations, ECOG criteria for performance status, and concomitant medication usage. AEs that occurred between the signing of informed consent through 30 days following the last dose of study drug, or until the start of subsequent anti-MCL therapy were collected. Severity of AEs was assessed using National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE), Version 4.03.	Safety and toxicity of therapies are important to understand both for patients and for clinical decision-makers.
PFS: progression-free survival, OS: overall survival, FACT-Lym: Functional Assessment of Cancer Therapy-Lymphoma, R/R MCL: relapsed or refractory MCL: mantle cell lymphoma, NCI: National Cancer Institute, NICE: National Institute for Health and Care Excellence, ITT: intention-to-treat, QoL: quality of life, CR: complete response, PR: partial response, AEs: adverse events, CTCAE: Common Terminology Criteria for Adverse Events. *Revised International Working Group Criteria for NHL: CR: disappearance of all evidence of disease, PR: regression of measurable disease and no new sites; stable disease (SD), failure to attain CR/PR or progressive disease (PD), relapsed disease or PD: any new lesion or increase by 50% of previously involved sites from nadir[63]. Source: Dreyling, 2015[36] RAY (MCL3001) CSR[61].		

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

A summary of the statistical analyses in the RAY (MCL3001) study, including study hypothesis and sample size calculation, is provided in Table 15.

Table 15: Summary of statistical analyses in RAY (MCL3001)

Primary hypothesis	The primary hypothesis was that ibrutinib significantly prolongs PFS compared with TEM in patients with R/R MCL who had received at least one prior rituximab-containing chemotherapy regimen.
Calculation of study sample size	The study planned to enrol approximately 280 patients in a 1:1 ratio. The data cut-off date for the primary analysis was planned to be after approximately 178 PFS events had occurred. Assuming 57% improvement in median PFS of the ibrutinib arm over the TEM arm (a HR of 0.64 for the ibrutinib relative to TEM group, under the exponential distribution assumption, or an improvement in median PFS from 7 months to 11 months), with 178 events the study had at least 85% power to achieve a statistical significance level of 2.5% (1-sided).
Primary analysis	The stratified log-rank test was used to compare PFS curves between the two treatment groups, stratified by prior LOTs and simplified MIPI. Pre-specified pooling was implemented when some strata had fewer PFS events. The KM method was used to estimate the proportion of progression-free patients for each treatment group at different points in time. Median PFS was provided for each treatment group and the HR for ibrutinib relative to TEM and its associated 95% CI were calculated based on the Cox Proportional Hazards model by prior LOTs and simplified MIPI. Pre-planned PFS subgroup analyses were performed for potential prognostic variables at screening or baseline. Additionally, the following sensitivity analyses were planned to be performed: • Assessment of PFS by the investigator (where the primary analysis was performed by an IRC) • Investigating the influence of subsequent therapy by alternatively: 1. considering patients to have had a PFS event at the initiation of change of therapy; 2. Censoring patient data at the last disease assessment showing no evidence of progressive disease, prior to the change of therapy • Assessment of PFS based on the ITT and per protocol (PP) populations, provided that analysis of the PP population was conducted (as noted in Table 16 the PP population was ultimately not analysed). Further exploratory analyses, such as sensitivity analyses to address the potential impact of an unequal number of subject visits that could result in unscheduled tumour assessments due to the different treatment schedules in the two groups, were performed as appropriate.
Data management, patient withdrawals	If a patient withdrew from the study prior to completion, the reason for withdrawal was documented. Patients who withdrew after randomisation were not replaced.
PFS: progression-free survival, R/R MCL: relapsed or refractory mantle cell lymphoma, MIPI: MCL International Prognostic Index, HR: hazard ratio, CI: confidence interval, ITT: intention-to-treat, PP: per protocol, IRC: Independent Review Committee, PRO: patient reported outcomes, TEM: temsirolimus Source: RAY (MCL3001) CSR[61].	

The analysis populations considered for the RAY (MCL3001) study are detailed in Table 16. All efficacy analyses were ultimately conducted on the intention-to-treat (ITT) population. All safety analyses were conducted on the safety analysis population.

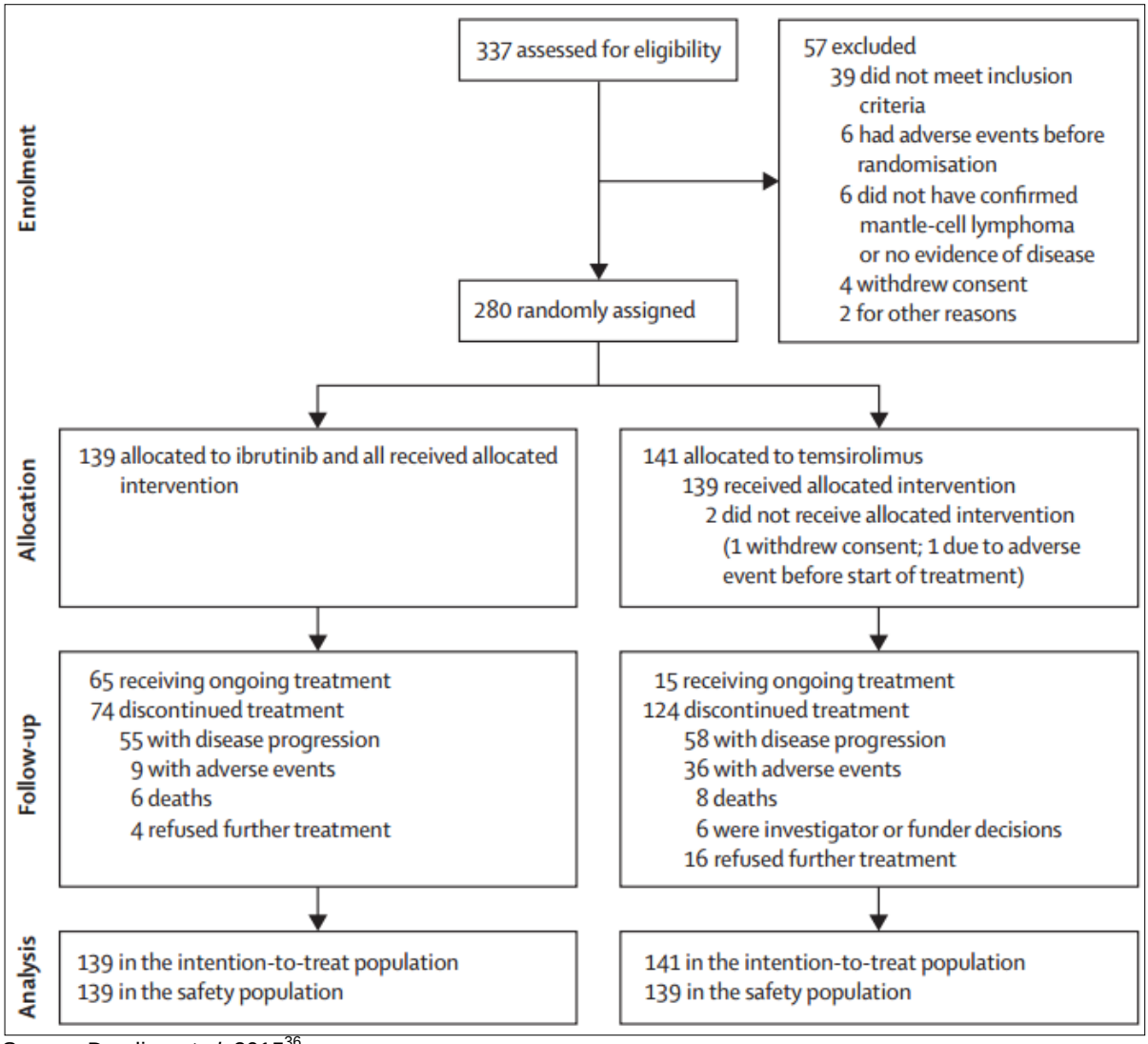
Table 16: Summary of analysis populations considered in the RAY (MCL3001) study

Analysis set	Description
Intention-to-treat (ITT) population	The ITT population consisted of all randomised patients and was used to summarise the study population and characteristics, efficacy, PRO data, and health economic data.
Per-protocol (PP) population	The PP population consisted of all randomised patients who underwent at least one adequate post-baseline disease assessment and did not have major protocol violations. The statistical analysis plan dictated that no analyses would be performed on the PP population if ≥95% of patients in the ITT population were included in the PP population. In total, 134 (96.4%) of patients in the ibrutinib arm and 133 (94.3%) of patients in the TEM arm of the ITT population were included in the PP population. In total (taking into account both study arms), ≥95% of patients in the ITT population were included in the PP population and therefore no analysis of the PP population was performed.
Safety analysis population	The safety population was defined as all randomised patients who received at least one dose of study drug and was used to summarise the safety data. Safety data were analysed according to the actual treatment received.
Crossover ibrutinib population	The crossover population consisted of all TEM patients who crossed over to ibrutinib, as part of the amended protocol, and received at least one dose of ibrutinib
ITT: intention-to-treat, PP: per-protocol, PRO: patient-reported outcomes, TEM: temsirolimus Source: RAY (MCL3001) CSR[61].	

4.5 *Participant flow in the relevant randomised controlled trials*

As of the clinical cut-off date (22nd April 2015; defined as the time at which approximately 178 PFS events were observed), 280 patients were enrolled with a median follow-up of 20.0 months. Overall, 139 patients were randomised to ibrutinib and 141 to TEM; two patients randomised to TEM did not receive any study drug (see Figure 8).

Figure 8: RAY (MCL3001) – participant flow



Source: Dreyling *et al.* 2015[36]

4.5.1 ***Treatment discontinuation and crossover***

At clinical cut-off, 74 patients (53.2%) in the ibrutinib arm and 124 (87.9%) in the TEM arm had discontinued treatment, see Figure 8.

At the study cut-off date (defined as the time at which approximately 178 PFS events were observed, which was 22nd of April 2015), 32 patients (22.7%) in the TEM arm had received next-line ibrutinib treatment after IRC confirmation of disease progression. [redacted][61].

The median duration of treatment exposure was significantly longer (nearly 5-fold) for ibrutinib compared to TEM (14.4 months versus 3.0 months, respectively)[36]. This is due to the fact that PFS with ibrutinib was longer than with TEM and, therefore, patients remained on ibrutinib treatment for longer (both drugs are 'treat-to-progression'). The median relative dose intensity was also higher for ibrutinib compared to TEM (99.9% versus 81.8%, respectively). Additionally, discontinuation rates were lower with ibrutinib compared to TEM, particularly with regards to the number of patients discontinuing due to AEs, investigator decision and patient refusal (see Figure 8), even though the duration of exposure was nearly 5-fold for ibrutinib compared to TEM. Most patients discontinued treatment because of

disease progression or relapse (39.6% ibrutinib versus 41.1% TEM) and AEs (mainly in the TEM arm, 6.5% ibrutinib versus 25.5% TEM). It should be noted that 11.3% of patients refused further treatment with TEM compared to 2.9% with ibrutinib.

Subsequent anti-neoplastic systemic therapy was received by 31.7% (n=44) of patients in the ibrutinib arm and by 58.2% (n=82) in the TEM arm. A lower proportion of patients in the ibrutinib arm had progressed or died at the time of the PFS analysis (53% [73/139] for ibrutinib versus 79% [111/141] for TEM), which explains the lower proportion of ibrutinib patients receiving subsequent antineoplastic therapy. As a proportion of the number of patients in each arm who had progressed or died, the proportion receiving anti-neoplastic systemic therapy was 60% (44/73) for the ibrutinib arm and 74% (82/111) for the TEM arm.

4.5.2 *Baseline characteristics*

The baseline characteristics of the patients in RAY (MCL3001) were well balanced between the two arms. Most patients were men (74.3%) and white (87.1%). Median age was 68 years (range: 34 to 88), with 61.8% of patients aged 65 years or older. Most patients (82.9%) had stage IV disease at study entry. The median number of prior lines of systemic therapy for MCL was two (range: 1 to 9 lines) in both arms. Table 17 shows the patient characteristics at baseline.

Table 17: Patient characteristics at baseline in RAY (MCL3001)

	Ibrutinib (n=139)	**TEM (n=141)**
Median age (range)	67.0 (39-84)	68.0 (34-88)
Age < 65	53 (38.1%)	54 (38.3%)
Age ≥ 65	86 (61.9%)	87 (61.7%)
Male sex, no (%)	100 (71.9%)	108 (76.6%)
Race, no (%)		
White	115 (82.7%)	129 (91.5%)
Asian	16 (11.5%)	5 (3.5%)
Other	3 (2.2%)	4 (2.8%)
Unknown/ not reported	5 (3.6%)	3 (2.1%)
ECOG performance status, no (%)		
0	67 (48.2%)	67 (47.5%)
1	71 (51.1%)	72 (51.1%)
2	1 (0.7%)	3 (1.4%)
Median time from initial diagnosis to randomisation (months)	38.90	46.23
Median time from end of last prior therapy to randomisation (months)	8.25	7.03
Stage of MCL at study entry, no (%)		
I	3 (2.2%)	2 (1.4%)
II	7 (5.0%)	5 (3.5%)
III	17 (12.2%)	14 (9.9%)
IV	112 (80.6%)	120 (85.1%)
Simplified MIPI, no (%)		

Low risk (1-3)	44 (31.7%)	42 (29.8%)
Intermediate risk (4-5)	65 (46.8%)	69 (48.9%)
High risk (6-11)	30 (21.6%)	30 (21.3%)
Prior LOTs		
Median (range)	2 (1-9)	2 (1-9)
Relapsed disease, no (%)	103 (74.1%)	94 (66.7%)
Refractory disease, no (%)	36 (25.9%)	47 (33.3%)
ECOG: Eastern Cooperative Oncology Group, MCL: mantle cell lymphoma, MIPI: Mantle Cell Lymphoma International Prognostic Index, LOTs: lines of therapy. Source: Dreyling *et al.*, 2015[36]		

4.6 *Quality assessment of the relevant randomised controlled trials*

A summary of the quality assessment of the RAY (MCL3001) study is provided in Table 18. A full quality assessment with explanation for the responses given in Table 18 is provided in Appendix 5.

Table 18: Quality assessment results for RAY (MCL3001)

	RAY (MCL3001)
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	No
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	No
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

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

All clinical effectiveness results presented in sections 4.7 and 4.8 are based on the clinical cut-off on the 22nd of April 2015, representing the primary analysis at median follow-up of 20 months, and the latest available data cut-off for the RAY (MCL3001) study at the time of writing this submission. As detailed in Table 16, all presented analyses were performed on the ITT population.

4.7.1 *Primary end-point: progression-free survival*

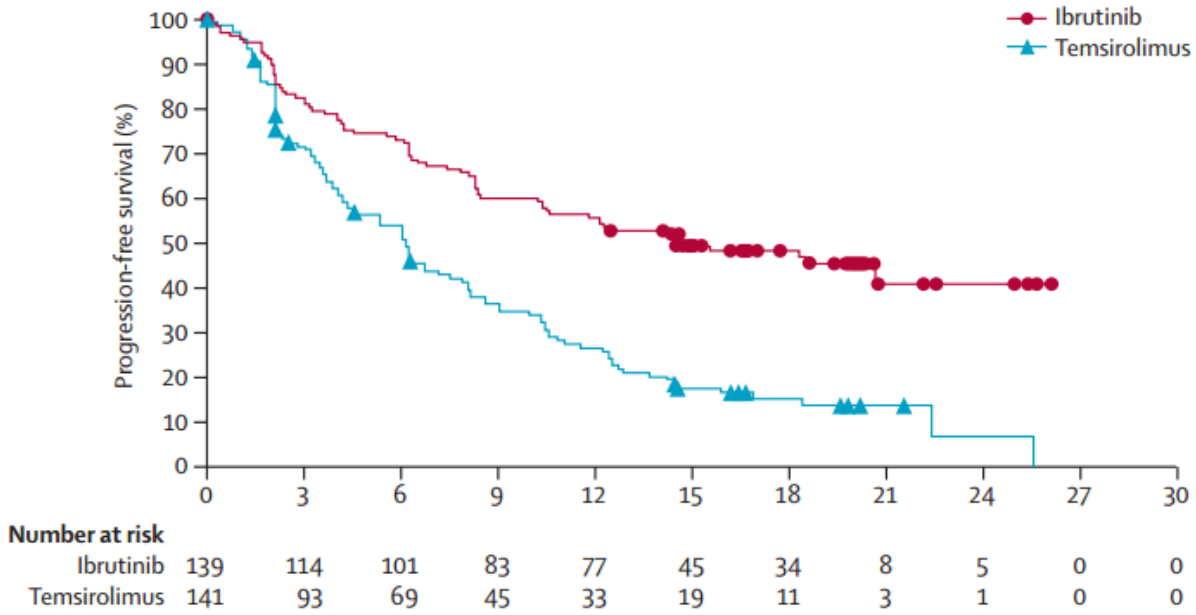
The primary analysis of PFS by IRC assessment showed a statistically significant advantage ($p<0.0001$) for ibrutinib over TEM (HR = 0.43, 95% CI: 0.32; 0.58), corresponding to a 57% reduction in the risk of disease progression or death with ibrutinib. Median PFS was 14.6 months for the ibrutinib arm versus 6.2 months for the TEM arm. The results for the two treatment arms in terms of PFS outcomes are summarised in Table 19. The Kaplan-Meier (KM) plot for PFS at the primary analysis is presented in Figure 9.

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

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

ITT: intention-to-treat, CI: Confidence interval, HR: Hazard ratio, NE: Not estimable, PFS: Progression-free survival, TEM: temsirolimus
Source: Dreyling *et al.*, 2015[36] RAY (MCL3001)

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



Source: Dreyling *et al.*, 2015[36]

4.7.2 *Results of relevant secondary analyses of the primary outcome and analyses of relevant secondary outcomes*

4.7.2.1 Secondary analyses of PFS

Sensitivity analyses on PFS

A sensitivity analysis on the PFS outcome was performed in which the investigator-determined PFS was considered (as opposed to PFS determined by IRC). The results of this sensitivity analysis were consistent with the primary analysis results presented in Table 19, with ibrutinib found to be associated with a HR (95% CI) versus TEM of 0.43 (95% CI: 0.32, 0.58, p<0.0001)[69]. Other sensitivity analyses on the PFS outcome investigating the influence of subsequent therapy on PFS estimates and considering the use of an unstratified (rather than stratified) log-rank test also demonstrated robustness of the results of the primary analysis [69].

Subgroup analyses on PFS

Pre-planned subgroup analyses of the PFS outcome showed internal consistency of the primary end-point across all subgroups. In addition to these pre-specified subgroup analyses, a *post-hoc* analysis of PFS by number of prior LOTs (1 versus ≥2) was conducted. Results of these subgroup analyses are presented in detail in Section 4.8.

PFS2

In addition to the primary analysis of PFS, an exploratory analysis of progression or death was also conducted. This was an analysis of PFS2, defined as the time interval between the date of randomisation to the date of an event, where the event was defined as progressive disease as assessed by the investigator after the next line of subsequent therapy, death from any cause, or start of the second line of subsequent therapy if no disease progression was noted (definitions of PFS and PFS2 can be compared in Table 14).

PFS2 aims to capture the potential impact of the therapy in question on the risk of progression or death (i.e. the PFS achieved) on subsequent-line therapy. PFS2 therefore recognises that treatment with a therapy has the potential to exert a selection pressure for the development of tumour mutations that confer resistance to subsequent anticancer therapy, thereby influencing the potential for patients to derive clinical benefit further down the treatment pathway. As a result, PFS2 is a useful measure in providing an indication of the overall benefit of the therapy under investigation in terms of risk or progression or death in the context of the treatment pathway. The European Medicines Agency Guideline on the Evaluation of Anticancer Medicinal Products in Man defines PFS2 as the time from randomisation to objective tumour progression on next-line treatment or death from any cause (a similar definition to that employed in the RAY (MCL3001) study), and discusses this measure as a proxy for OS where OS cannot be measured[64, 70]. Although RAY (MCL3001) did also assess OS, the study was not statistically powered to show OS difference and median OS has not yet been reached in the ibrutinib arm (also due to crossover confounding). Results of the PFS2 analysis are considered useful to present here in order to provide an indication of how treatment with ibrutinib or TEM might differentially impact clinical benefit of subsequent-line therapy, thereby providing an additional measure of overall treatment effect with regards to risk of progression or death.

A summary of the anticancer therapies received subsequent to ibrutinib or TEM, respectively, is provided in Table 20, in order to aid in interpretation of the PFS2 analysis. A full list of the subsequent anticancer therapies used in at least 2% of patients is provided in Appendix 7.

Table 20: Summary of subsequent anticancer therapy in RAY (MCL3001), ITT analysis set

	Ibrutinib (n=139)	**TEM (n=141)**
Number progressed or died	73	111
Overall number of patients receiving subsequent anticancer therapy (as percentage of overall population/as percentage of those who progressed or died)	44 (32%/60%)	82 (58%/74%)
Most common subsequent anticancer therapies, n (% of ITT population)*	Rituximab: 21 (15%) Bendamustine: 15 (11%) Cyclophosphamide: 12 (9%)	Rituximab: 36 (26%) Ibrutinib: 32 (23%) Bendamustine: 22 (16%) Cyclophosphamide: 19 (13%)
*Note: Some patients received multiple subsequent therapies (also as part of combination therapies) and hence n numbers in this row may total more than the number of patients who received subsequent anticancer therapy. Percentages given in this row use the intention-to-treat population as the denominator.		

TEM: temsirolimus, ITT: intention-to-treat
Source: Dreyling *et al.* 2015 Appendix[69]

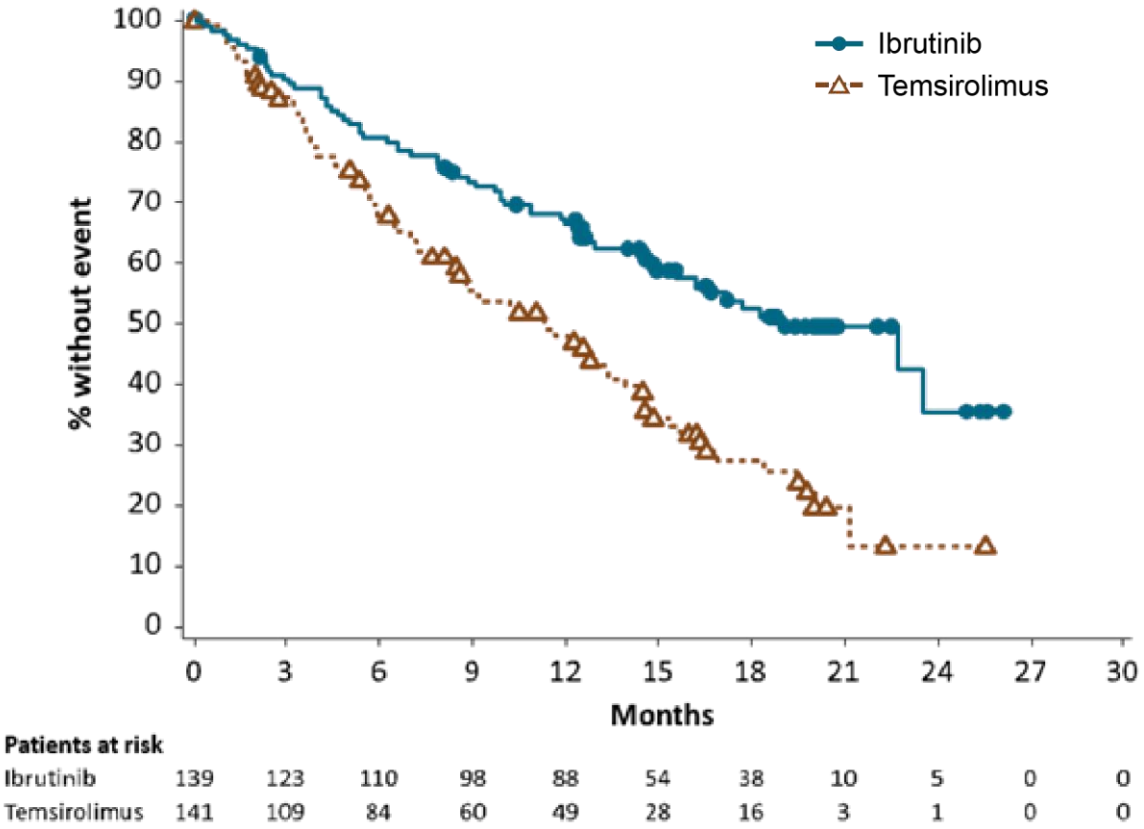
The results of the analysis found PFS2 to be statistically significantly longer for ibrutinib than for TEM, as detailed in Table 21 and in the KM plot presented in Figure 10. These PFS2 results provide supportive evidence to the OS results presented in Section 4.7.2.2, indicating that the overall benefit of ibrutinib is maintained on patients receiving subsequent line anticancer therapy.

Table 21: Summary of PFS2 results in RAY (MCL3001), ITT analysis set

	Ibrutinib (n=139)	TEM (n=141)
Median PFS2, months	19.1	11.3
HR (95% CI) ibrutinib versus TEM	0.49 (0.36; 0.69), p<0.0001	

CI: Confidence interval, HR: Hazard ratio, PFS: Progression-free survival, TEM: temsirolimus
Source: Dreyling *et al.* 2015[36]

Figure 10: KM plot of PFS2 in RAY (MCL3001), ITT analysis set



Source: Dreyling *et al.*, 2015 Appendix[69]

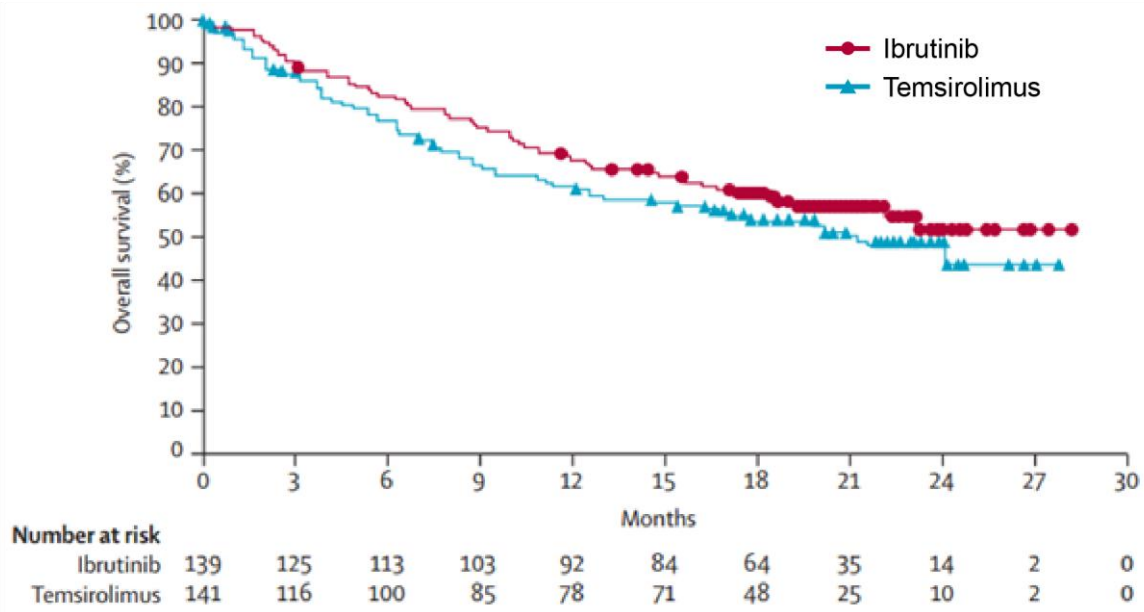
4.7.2.2 Overall survival

After a median follow-up of 20.0 months, the HR for the stratified analysis of OS was 0.76 (95% CI: 0.53; 1.09, p=0.1324), which represents a 24% reduction in the risk of death with ibrutinib. Median OS was not reached in the ibrutinib arm, indicating that more than 50% of

patients remained alive at study cut-off. In contrast, median OS was reached at 21.3 months in the TEM arm. The KM plot for OS is presented in Figure 11.

Survival rates at 12 months for the ibrutinib and TEM treatment groups were 68% (95% CI: 59%, 75%) and 61% (95% CI: 52%, 69%), respectively.

Figure 11 KM plot of OS by IRC assessment in RAY (MCL3001); ITT analysis set



Source: Dreyling *et al.*, 2015[36]

The OS data showed a tendency towards survival improvement with ibrutinib. Although the HR for OS was not statistically significant, Janssen would not expect to see a statistically significant difference at this stage in the trial for a number of reasons. Firstly, following a protocol amendment (30th July 2014), formal crossover of patients from the TEM group to the ibrutinib group was permitted within the study; indeed, 22.3% of patients in the TEM arm crossed over to ibrutinib in RAY (MCL3001). Inclusion of crossover into clinical study design has become a necessary condition to recruit patients into clinical trials, but has the effect of confounding estimates of survival. Furthermore, R/R MCL is an extremely rare disease and the study size necessary to show a statistically significant difference in OS after 20 months would have meant an extremely prolonged recruitment period with the attendant risk that the results would be outdated, even if it was possible to recruit and retain patients in the study; therefore the study was not powered to detect an OS difference.

It should be noted that OS might be influenced by the clinical benefit of subsequent anticancer therapies received following progression on ibrutinib or TEM, as these therapies may affect PPS. More patients in the TEM arm received subsequent anticancer systemic treatment compared to ibrutinib (see Table 20). Given the significant benefit in terms of PFS observed for ibrutinib over TEM, the lack of a significant difference in the OS benefit might be interpreted as representing a lower PPS for ibrutinib-treated patients due to compromised efficacy of subsequent line anticancer therapy. However, the results of the PFS2 analysis presented in 4.7.2.1 indicate that efficacy of subsequent-line anticancer therapy following ibrutinib is not compromised, and support the overall benefit of ibrutinib. The non-significant OS estimates may be a result of the fact that some TEM patients crossed over to effective salvage therapy with ibrutinib and the fact that TEM patients who crossed over had a

substantially poorer prognosis compared the ones who did not. In addition, a substantial proportion of patients receiving ibrutinib have not yet progressed at the current data cut-off for the RAY (MCL3001) study. Therefore, it may be that the death events observed to date in the ibrutinib arm represent the deaths of those patients with a poorer prognosis (i.e. "*rapid progressors*") and for whom treatment is unlikely to be able to offer a survival benefit. It is conceivable that, in the next data cut for OS (expected in early 2017), a statistical OS benefit might be observed as a result of the longer follow-up time capturing events that have occurred at later time points in those patients receiving ibrutinib who have better prognosis.

Recent retrospective studies conducted by Martin *et al.* (2016) and Cheah *et al.* (2015) report quick progression following ibrutinib failure[71, 72]. Martin *et al.* also stress that this is not a unique situation to lymphoma patients, the same having been observed when rituximab was added to CHOP in diffuse large B-cell lymphoma. These patients are heavily pre-treated, likely refractory to their last treatment and will have exhausted most standard therapies. The prognosis of patients included in this study was poor, with almost half of patients (46%) classified as having a high MIPI score at baseline. It is therefore not surprising that the PPS is short in this study. Martin *et al.* also report that patients with less aggressive disease or a better response (duration) to ibrutinib experienced better outcomes following ibrutinib failure. In the literature (Martin *et al.* (2016) and Tucker and Rule (2015)) it is acknowledged that mechanisms of resistance to ibrutinib are presently poorly understood [32, 71]. Proposed mechanisms have included mutations of the BTK binding site such that ibrutinib inhibition is reversible and not irreversible, and known and novel mutations of signalling molecules downstream of BTK, such as Nuclear Factor (NF) kappa B; however, further research is required[32, 73].

4.7.2.3 Response rates

Overall response rate

The IRC-determined ORR was significantly higher (p<0.0001) for the ibrutinib arm (71.9%) than the TEM arm (40.4%). The ORR determined by the investigator was also significantly higher (p<0.0001) in the ibrutinib arm (77.0% versus 46.1%, respectively).

Table 22: ORR by IRC assessment in RAY (MCL3001), ITT analysis set

	Ibrutinib (n=139)	**TEM (n=141)**
ORR (CR or PR), n (%)	100 (71.9%)	57 (40.4%)
Difference in ORR (95% CI), p-value	31.5% (20.5, 42.5), p<0.0001	
Odds ratio (95% CI)	3.98 (2.38, 6.65)	
Best response		
CR	26 (18.7%)	2 (1.4%)
PR	74 (53.2%)	55 (39.0%)
SD	15 (10.8%)	43 (30.5%)
PD	15 (10.8%)	23 (16.3%)
Not evaluable (NE)	[redacted]	[redacted]
No evidence of disease (NED)	[redacted]	[redacted]

ORR: overall response rate, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, NE: not evaluable, NED: no evidence of disease.
Source: Dreyling *et al.* 2015[36] and RAY (MCL3001) CSR[61, 62]

Duration of response

The median DOR for patients in the TEM arm was 7.0 months (95% CI: 4.2, 9.9) and was not reached, at the time of the clinical cut-off, for patients who received ibrutinib. Median DORs at the 25% quartile were longer for the ibrutinib group than the TEM group (Table 23).

Table 23: Duration of response by IRC assessment in RAY (MCL3001), ITT analysis set

	Ibrutinib (n=100)[a]	**TEM (n=57)[a]**
Duration of response		
25% quantile (95% CI)	7.9 (4.7, 12.4)	4.0 (2.1, 5.1)
Median (95% CI)	NE (16.2, NE)	7.0 (4.2, 9.9)
75% quantile (95% CI)	NE (NE, NE)	14.9 (9.5, 23.5)
6-month DOR rate (95% CI)	0.83 (0.74–0.89)	0.60 (0.46–0.72)
12-month DOR rate (95% CI)	0.69 (0.59–0.77)	0.26 (0.15–0.38)
18-month DOR rate (95% CI)	0.58 (0.46–0.68)	0.20 (0.09–0.35)
24-month DOR rate (95% CI)	0.51 (0.35–0.65)	0.00 (NE–NE)

[a] Duration of response was derived for patients who achieved complete response or partial response.
Source: Dreyling *et al.*, 2015, Appendix[69]

Median time to next treatment

At the time of the clinical cut-off, the median time to next treatment was not reached with ibrutinib, compared to 11.6 months with TEM (p<0.0001), perhaps reflecting the higher response rate and better DOR achieved with ibrutinib. [redacted][61].

4.7.2.4 Quality of life assessment

QoL was assessed using FACT-Lym, a cancer-specific, non-preference based measure of QoL with a lymphoma-specific subscale, and EQ-5D-5L, a generic preference-based measure (see Table 14).

Both scales demonstrated a significant improvement in QoL with ibrutinib versus TEM. QoL results from RAY (MCL3001) were presented at the ASH 2015 conference in the form of a poster[3].

FACT-Lym

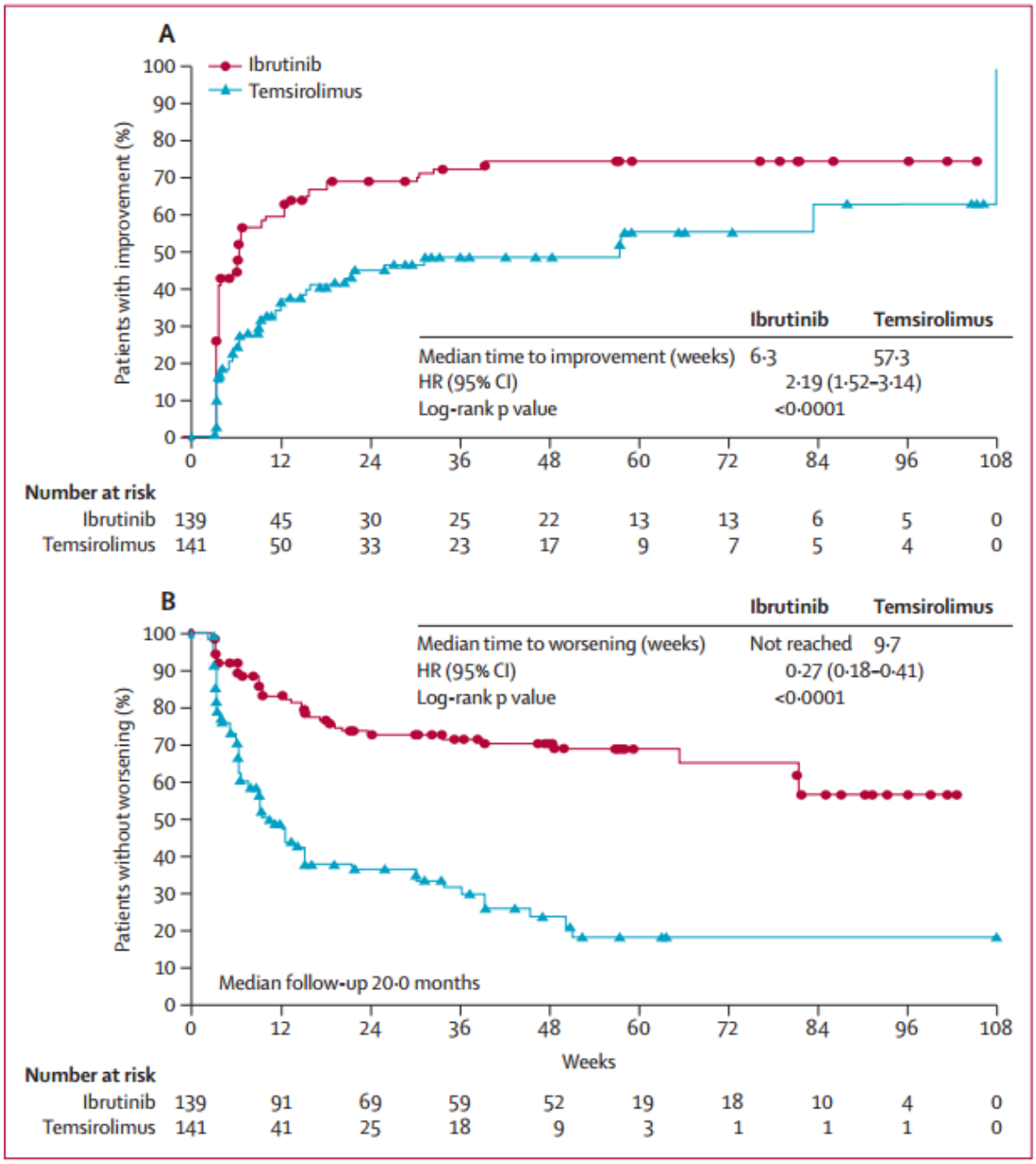
FACT-Lym comprises the four general cancer-related QoL sub-scales of the original Functional Assessment of Cancer Therapy outcome measure (FACT-G: physical, social/family, emotional and functional well-being) and a lymphoma-specific sub-scale which measures lymphoma symptoms. The FACT-Lym total score combines scores across all sub-scales. Higher scores indicate better QoL and fewer lymphoma-specific symptoms. Scores on the 15-item lymphoma subscale range from 0 to 60. Scores on the FACT-Lym lymphoma sub-scale were assessed in terms of the proportion of patients achieving a clinically meaningful (≥5-point change from baseline) increase or decrease in lymphoma symptoms, and in terms of the median time to a clinically meaningful improvement/worsening of lymphoma symptoms[74].

Of 280 randomised patients, 253 completed the FACT-Lym at baseline (ibrutinib, n=130/139; TEM, n=123/141). PRO compliance rates were generally acceptable, with less than 20% missing at most time points[3].

Significantly more patients treated with ibrutinib achieved a clinically meaningful improvement in lymphoma symptoms compared with TEM (61.9% versus 35.5%, p<0.0001). Median time to improvement was reached in 6.3 weeks (95 % CI: 3.6, 9.7 weeks) with ibrutinib versus 57.3 weeks (95% CI: 15.3, 107.7 weeks) with TEM (HR 2.19; 95% CI: 1.52, 3.14, p<0.0001) as presented in Figure 12[36].

Conversely, significantly fewer patients treated with ibrutinib experienced a clinically meaningful worsening of lymphoma symptoms compared with TEM (26.6% versus 51.8%, p<0.0001). Symptom worsening occurred significantly more slowly with ibrutinib than TEM (median time to worsening not reached versus 9.7 weeks, respectively (HR 0.27; 95% CI: 0.18, 0.41, p<0.0001), as presented in Figure 12[3, 36].

Figure 12: Time to clinically meaningful improvement (A) and worsening (B) on the FACT-Lym lymphoma subscale in RAY (MCL3001), ITT analysis set



Source: Dreyling, 2015[36]

The FACT-Lym total score also showed clinically meaningful improvement from baseline in patients treated with ibrutinib in RAY (MCL3001), whilst patients treated with TEM showed clinically meaningful worsening (mean change from baseline 5.13 vs -5.32, mixed model repeated measures (MMRM) estimate of mean difference in change from baseline 10.44, p<0.0001).

Across the broader HRQoL domains that contribute to the FACT-Lym total score, patients treated with ibrutinib showed improvement in physical, functional and emotional well-being that was significantly better than change in HRQoL from baseline in patients treated with TEM (MMRM mean difference in change from baseline 2.68 (p<0.0001), 1.64 (0.0009), 0.95 (p=0.0009) respectively).

EQ-5D-5L

The EQ-5D-5L, a generic, preference-based measure, assesses QoL across 5 domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and overall current health with the EQ-5D-5L Visual Analogue Scale (VAS). Preference-weighted utility values are calculated from the EQ-5D-5L domain scores and the VAS ranges from 0 (worst imaginable health) to 100 (best imaginable health). At baseline, EQ-5D-5L mean utility values were 0.73 (SD: 0.2) for both treatment arms and VAS mean values were 66.6 (SD: 19.3) and 64.5 (SD: 21.9) for patients in the ibrutinib group and TEM group, respectively. Improvements from baseline over time in VAS scores were observed in the ibrutinib arm, while patients treated with TEM experienced reduced QoL relative to baseline.

A statistically significant difference in EQ-5D-5L utility score favouring ibrutinib over TEM was observed within 4 weeks and maintained through to week 49 (Table 24). EQ-5D-5L utility values for ibrutinib did not return to baseline level (i.e. change from baseline remained positive) at all time points up to week 40; in contrast mean change from baseline values with TEM were negative at all time points up to week 106, the longest available time point at the clinical data cut-off.

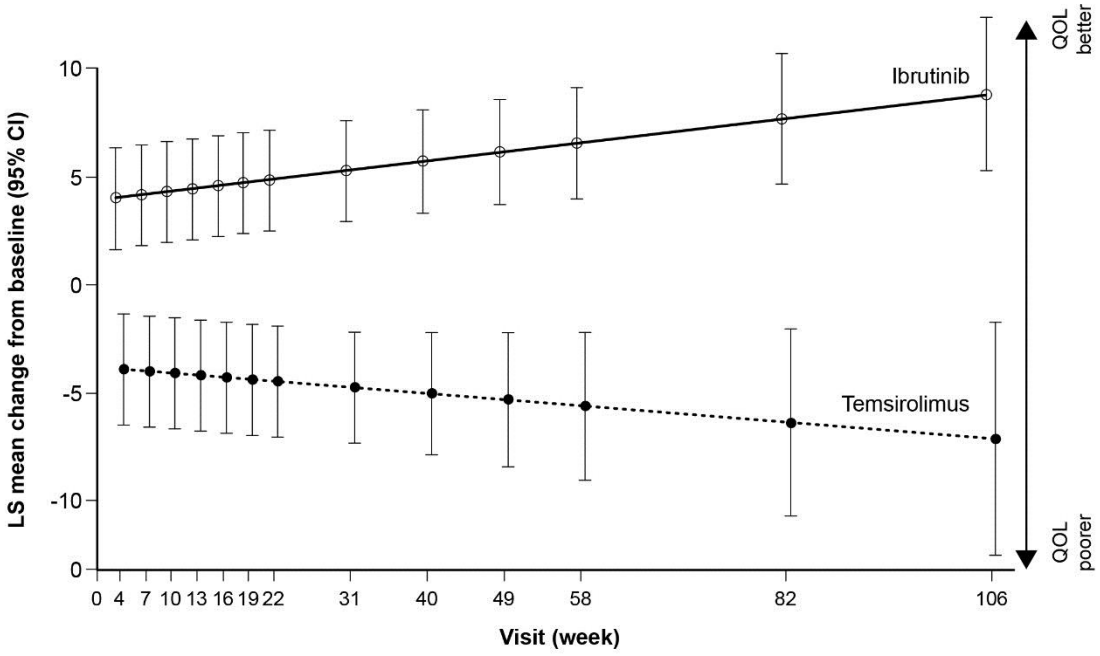
Table 24: Least square mean (95% CI) change from baseline in EQ-5D-5L utility score over time in RAY (MCL3001), ITT analysis set

	Ibrutinib		TEM		TEM vs Ibrutinib	P value
Analysis set (ITT)	139		141		-	-
Baseline score, mean (SD)	130	0.73 (0.2)	120	0.73 (0.2)	-	-
	n	**LS mean change from baseline (95% CI)**	**n**	**LS mean change from baseline (95% CI)**		
Week 4	108	0.03 (-0.00, 0.05)	84	-0.07 (-0.10, -0.05)	-0.09 (-0.13, -0.05)	<0.0001
Week 7	101	0.02 (-0.00, 0.05)	71	-0.07 (-0.09, -0.04)	-0.09 (-0.13, -0.05)	<0.0001
Week 10	94	0.02 (-0.00, 0.05)	59	-0.06 (-0.09, -0.03)	-0.09 (-0.12, -0.05)	<0.0001
Week 13	93	0.02 (-0.01, 0.05)	48	-0.06 (-0.09, -0.03)	-0.08 (-0.12, -0.05)	<0.0001
Week 16	88	0.02 (-0.01, 0.05)	41	-0.06 (-0.09, -0.03)	-0.08 (-0.12, -0.04)	<0.0001
Week 19	79	0.02 (-0.01, 0.04)	40	-0.06 (-0.09, -0.03)	-0.08 (-0.11, -0.04)	<0.0001
Week 22	78	0.02 (-0.01, 0.04)	30	-0.06 (-0.09, -0.03)	-0.07 (-0.11, -0.04)	0.0001
Week 31	64	0.01 (-0.01, 0.04)	23	-0.05 (-0.08, -0.02)	-0.06 (-0.10, -0.03)	0.0010
Week 40	53	0.01 (-0.02, 0.04)	21	-0.05 (-0.08, -0.02)	-0.05 (-0.09, -0.01)	0.0073
Week 49	52	0.00 (-0.03, 0.03)	17	-0.04 (-0.08, -0.01)	-0.05 (-0.09, -0.00)	0.0387
Week 58	45	-0.00 (-0.03, 0.03)	13	-0.04 (-0.07, 0.00)	-0.04 (-0.08, 0.01)	0.1327
Week 82	12	-0.01 (-0.05, 0.03)	1	-0.02 (-0.07, 0.03)	-0.01 (-0.07, 0.05)	0.7340
Week 106	3	-0.02 (-0.07, 0.02)	2	-0.01 (-0.07, 0.05)	0.02 (-0.06, 0.09)	0.6857

LS: least squares, CI: confidence interval, TEM: temsirolimus.
Source: RAY (MCL3001) CSR[61]

With regards to EQ-5D-5L VAS, statistically significant improvements in least square mean changes from baseline were observed for ibrutinib versus TEM at each assessment point for VAS scores (see Figure 13). This is due to an improvement in QoL in patients receiving ibrutinib (positive mean change from baseline) versus a worsening of QoL (negative mean change from baseline) in patients receiving TEM. Overall improvement in the EQ-5L-VAS in patients receiving ibrutinib compared to TEM was clinically and statistically significant [redacted], MID for EQ-VAS scores in cancer >7 points considered to be clinically meaningful)[16].

Figure 13: Least square mean (95% CI) change from baseline in EQ-5D-5L VAS over time in RAY (MCL3001), ITT analysis set



Source: Hess, 2015 ASH Conference Poster[3]

[redacted]

4.7.3 ***Conclusion of RAY (MCL3001)***

RAY (MCL3001) provides high quality evidence confirming the unprecedented benefit of ibrutinib in terms of response rates, PFS and QoL of ibrutinib compared to TEM. In addition, it provides initial evidence of an OS improvement (median OS has not yet been reached in the ibrutinib arm at the end of the final data cut [study ongoing]).

- This study demonstrated a highly significant reduction in the risk of disease progression of ibrutinib compared to TEM (PFS 14.6 months versus 6.2 months, p<0.0001, HR=0.43, 95% CI 0.32 to 0.58, p<0.0001) with benefits maintained across all patient types. ORR (IRC-determined) was significantly higher (p<0.0001) for the ibrutinib arm (71.9%) than the TEM arm (40.4%). PFS and response rates observed

in RAY (MCL3001) are unparalleled and (at least) twice as higher compared to any other intervention in R/R MCL

- The QoL improvement while receiving ibrutinib is extraordinary. Whilst on treatment, patients receiving ibrutinib showed significant improvements in QoL and in symptom control compared with TEM. This was maintained throughout treatment; indeed, a significant difference in EQ-5D-5L favouring ibrutinib was observed within 4 weeks and maintained through to week 106, $p<0.0001$

- After a median follow-up of 20.0 months, median OS has not yet been reached (study ongoing) in the ibrutinib arm versus 21.3 months in the TEM arm[36]. More mature OS ibrutinib data are expected at final data cut in early 2017

When considering the results from RAY (MCL3001), Janssen assert that the immediate benefit of improvement in QoL and symptom control in patients receiving ibrutinib, in addition to the ORR, CR, DOR, PFS and PFS2 results, provide supporting evidence for longer-term benefits. The value of this improvement in QoL and symptom control with ibrutinib should not be underestimated given the detrimental effect on QoL that R/R MCL has as a result of its impact on physical health, mobility, fatigue and loss of vitality and the fact that standard practice in the UK is comprised of combinations of chemotherapy agents with associated toxicities. However, the pattern and magnitude of QoL impact captured by the EQ-5D-5L compared to that observed with the QoL subscales of the FACT-Lym and reported anecdotally by clinical experts raises concern that reliance on EQ-5D-5L for economic modelling risks underestimating the utility gain associated with the meaningful and valuable positive impact of ibrutinib on patients' QoL.

4.8 ***Subgroup analysis***

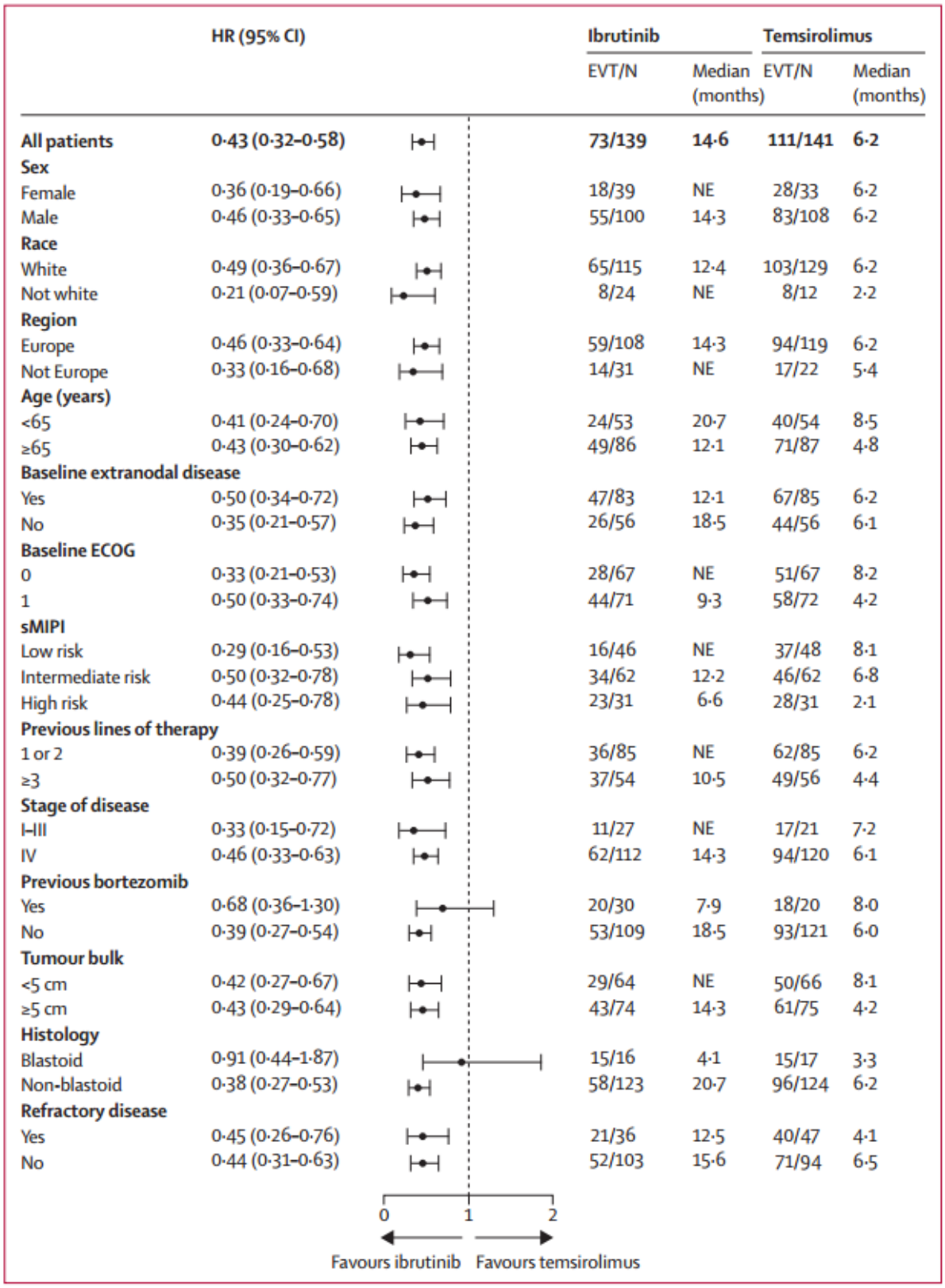
4.8.1 ***Pre-planned subgroup analysis of PFS***

Pre-planned subgroup analysis of the primary end-point of PFS by IRC was conducted across subgroups defined based upon potential prognostic variables at baseline or screening.

Results of these pre-planned subgroup analyses (Figure 14) showed consistency with the primary analysis across almost all subgroups. Patients with blastoid histology appeared to have derived no statistically significant benefit to PFS; however, the small number of patients with blastoid histology (n=33) means that this result should be interpreted with caution. Similarly, although no statistically significant benefit to PFS was observed for patients treated with prior bortezomib, this should be interpreted in light of the small patient numbers in this subgroup (n=30). The efficacy of ibrutinib in the post-bortezomib setting is supported by the SPARK (MCL2001) study presented in Section 4.11.2, which only enrolled patients who had progressed after bortezomib therapy, and demonstrated a median PFS of 10.5 months (95% CI: 4.4; 15)[39].

Imbalances in important prognostic factors may affect the estimate of the treatment effect. Therefore, a multivariate cox regression analysis was conducted to evaluate the treatment effect when controlling for pre-specified potential prognostic factors. The HR for the treatment effect of ibrutinib versus TEM, after adjustment for important prognostic factors, was 0.41 (95% CI: 0.30, 0.57). The model also identified significant prognostic factors ($p<0.05$) as baseline ECOG performance status, sMIPI, blastoid histology and previous LOTs (see Appendix 8).

Figure 14: Subgroup analysis of PFS in RAY (MCL3001) by IRC assessment



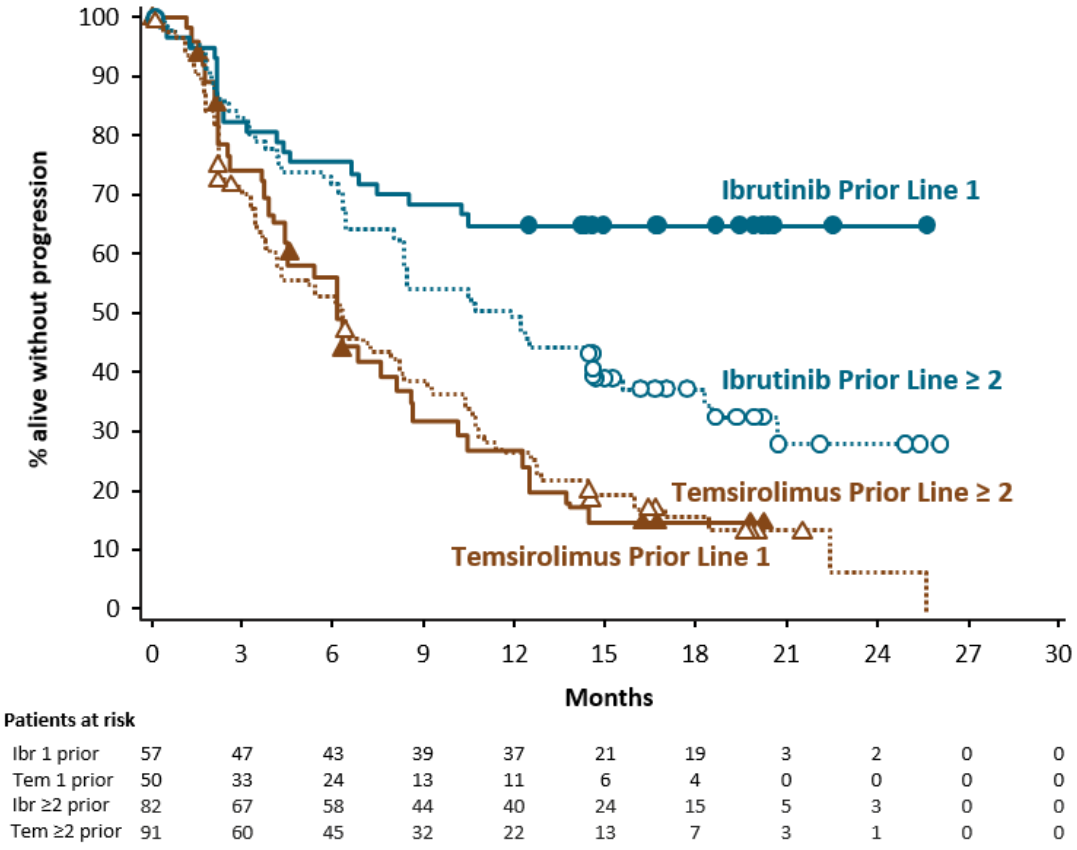
EVT: event (progressed or died), ECOG: Eastern Cooperative Oncology Group, HR: hazard ratio, NE: not estimable, sMIPI: simplified mantle cell lymphoma international prognostic index, IWRS: interactive web response system.
Source: Dreyling, 2015[36]

4.8.2 *Analysis of PFS and ORR by number of prior lines of therapy*

In addition to the pre-planned subgroup analyses described in Section 4.8.1, a *post-hoc* analysis of PFS and ORR by number of prior LOTs was also conducted for the RAY (MCL3001) study.

The results of the analysis of PFS are presented in the KM plot in Figure 15. This analysis demonstrates that, whilst the KM plots for patients with TEM are similar for patients treated with 1 or 2 prior LOTs, there is a substantial PFS benefit for patients who receive ibrutinib following 1 prior therapy, as opposed to 2.

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



Source: Rule *et al.*, 2015[62]

This benefit of earlier treatment with ibrutinib is further supported by the analysis of response rates of patients who received 1, 2 or ≥3 LOTs. Table 25 shows that the proportion of patients achieving a CR as opposed to a PR with ibrutinib is markedly higher the earlier the line of treatment at which ibrutinib is used.

Table 25: Results of *post-hoc* subgroup analysis of ORR by number of prior LOTs in RAY (MCL3001)

		Ibrutinib	TEM
1 prior LOT	ORR (%)	71.9%	48.0%
	CR (%)	24.6%	2.0%
	PR (%)	47.4%	46.0%
	CR as a proportion of ORR (%)	**34.2%**	**4.2%**
2 prior LOTs	ORR (%)	68.4%	39.5%
	CR (%)	18.4%	2.3%
	PR (%)	50.0%	37.2%
	CR as a proportion of ORR (%)	**26.9%**	**5.8%**
≥3 prior LOTs	ORR (%)	75.0%	33.3%
	CR (%)	11.4%	0.0%
	PR (%)	63.6%	33.3%
	CR as a proportion of ORR (%)	**15.2%**	**0.0%**

LOT: line of therapy, ORR: overall response rate, CR: complete response, PR: partial response, TEM: temsirolimus.
Source: Rule *et al.*, 2015[62]

Results of this *post-hoc* analysis were presented at the ASH 2015 congress[62]. Following presentation of these results at this congress, feedback from clinical experts at a recent advisory board held by Janssen was that these results were considered compelling, and provided clear evidence that ibrutinib should not be left for later LOTs[12].

4.9 *Meta-analysis*

A pooled analysis of the ibrutinib RCT (RAY [MCL3001]) and non-RCTs (PCYC1104; SPARK [MCL2001]) was performed. The methodology and results of this pooled analysis are logically presented after consideration of the non-RCTs, in Section 4.12.

4.10 *Indirect and mixed treatment comparisons*

As noted in Section 4.1, no direct head-to-head trial evidence for ibrutinib against a comparator reflective of current UK clinical practice was identified and therefore an ITC approach was considered. The only study identified by the SLR that contained a potentially relevant comparator and permitted an ITC to ibrutinib via a shared TEM comparator with the RAY (MCL3001) trial was the Hess, 2009 study. As previously noted, the Hess, 2009 study contained a PC arm in which patients received a range of single-agent chemotherapy regimens (primarily gemcitabine IV [42%] and fludarabine IV [23%]) that do not reflect current UK clinical practice.

Since this limitation was highlighted by clinicians during the advisory board, extensive efforts were undertaken to identify any other potential sources of evidence that might yield a comparison of ibrutinib to current SOC in UK clinical practice. The steps taken included:

1. Reconsider those studies that were identified by the SLR but had been subsequently dismissed as not relevant to the decision problem (see Section 4.2).

2. Returning to review studies (RCTs and single-arm studies) that had been excluded from the clinical SLR described in Section 4.1 at the full text-stage on the basis of:

- Not assessing a relevant treatment (n=143)
- Not being of sufficient study size (n=59)
- Representing a mixed population (n=34)
- Not being in a R/R population (i.e. studies in a 1st line population)

3. Reviewing the literature review performed as part of the draft NICE clinical guideline on NHL and assessing the 22 included studies and 90 articles excluded at full text review
4. Attempting to receive further data from HMRN.

Following this process, a total of four studies were identified that merited consideration for providing an estimate of the efficacy of current SOC in UK clinical practice. However, upon further assessment, all four studies were considered less suitable than the Hess, 2009 study for a number of reasons. The criteria applied to identify these four studies, a summary description and the reason for their inappropriateness as a source of effectiveness for R-chemo are summarised in Appendix 9.

Therefore, following this process, the Hess, 2009 study remained the most appropriate option for generating an estimate of the comparative effectiveness of ibrutinib versus R-chemo. The notable paucity of clinical evidence for R-chemo such as R-CHOP in R/R MCL reflects the fact that current SOC in UK clinical practice is mostly based upon the off-label use of therapies.

In an effort to address the limitation of Hess, 2009 in terms of not fully reflecting UK clinical practice, the results of the ITC were adjusted to take into account an estimated "rituximab effect" – that is, additional efficacy resulting from the addition of rituximab to the therapies used in the PC arm of Hess, 2009. The results of the ITC between RAY (MCL3001) and Hess, 2009 are presented in this section; the details of the application of the "rituximab effect" and the results following this are reserved for the write-up of the cost-effectiveness model (CEM) (see Section 5.3.2).

4.10.1 *ITC methods*

The ITC was conducted using the Bucher, 1997 method[75]. As with other methods of indirect comparison, Bucher ITCs adjust estimates according to the results of direct comparisons with a common comparator (e.g. placebo). For example, studies A vs C and B vs C can be used to obtain the adjusted indirect comparison of A vs B with a common intervention C. ITCs rely on an underlying assumption that the relative effectiveness of a treatment is the same across all trials used in the comparison.

Traditional indirect comparisons, based on the comparison of relative treatment effects across trials, 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. Differences in trial populations may impact relative treatment efficacy estimates, which could introduce bias. Therefore, Bucher analyses require comparable populations where common treatment techniques were applied.

4.10.2 *Data inputs and results*

Two phase III, RCTs included TEM 175/75 mg as a treatment arm, which presented the opportunity to conduct an ITC:

- RAY (MCL3001) study: Phase III, open-label, RCT comparing ibrutinib with TEM in patients with R/R MCL who received at least one prior therapy

- Hess, 2009 (OPTIMAL study, NCT00117598): Phase III, open-label, RCT comparing TEM with single agent treatment as per Physician's choice (PC) in patients with R/R MCL after two to seven prior therapies. The single-agent treatment in the PC therapy group was chosen based on an extensive review of the literature and discussions with a large number of investigators, comprised of: gemcitabine IV (42%), fludarabine IV (23%), fludarabine oral (4%), chlorambucil oral (6%), cladribine IV (6%), etoposide IV (6%), cyclophosphamide oral (4%), thalidomide oral (4%), vinblastine IV (4%), alemtuzumab IV (2%), and lenalidomide oral (2%).

The RAY (MCL3001) study has been described in detail in Section 4.7. The Hess, 2009 study has been referred to previously but a fuller description is presented below.

Hess, 2009 was a multicentre, phase III RCT (in Canada, France, Germany, Sweden and the US) evaluating two dose regimens of TEM monotherapy in comparison with a single-agent therapy chosen by the investigator for patients with R/R MCL (PC)[8]. The study included two TEM treatment arms with different dosing (175/75 mg and 175/25 mg). PC in Hess, 2009 was defined as a single-agent treatment that had to be widely available for R/R MCL at the time of the study. The most commonly used single-agent treatments as part of the PC arm were gemcitabine IV (42%) and fludarabine IV (23%). A study overview is provided below in Table 26. A comparison of the RAY (MCL3001) and Hess, 2009 studies under PICOS criteria is provided in Appendix 11.

Table 26: Summary of the Hess, 2009 study

Aim	• To compare the efficacy and safety of TEM with established treatment options (PC) in patients with R/R MCL
Trial design	• Multicentre, open-label, phase III study of 162 patients ≥18 years of age with R/R MCL • Eligible patients with R/R MCL after two to seven prior therapies. Pre-treatment must have included an alkylating agent, an anthracycline and rituximab, and could have included haematopoietic stem cell transplantation • Patients were randomised to TEM 175/75 mg (n=54), TEM 175/25 mg (n=54) and PC (n=53) • The PC therapy group received single-agent treatment as chosen by the investigator – the most common treatments were gemcitabine (42%), fludarabine (IV) (23%)
Patient characteristics	• Median age: 67 years (range 39-88 years), time from diagnosis to randomisation: 48.5 months (range 5-216 months), stage III-IV disease at baseline: 97% • Median number of prior therapies: 3 in the TEM arms and 4 in the PC arm, median number of prior rituximab and other anti-CD20 immunotherapy regimens: 2 in all arms, prior haematopoietic stem cell transplantation: 32%
Primary end-point results	• Primary end-point IRC assessed median PFS was 4.8 months, 3.4 months and 1.9 months for TEM 175/75 mg arm, TEM 175/25 mg and PC • Patients treated with TEM 175/75-mg had significantly longer PFS than those treated with PC (p<0.0009). • No significant differences in efficacy with respect to PFS with TEM 175/75-mg or 175/25-mg and PC therapies were observed based on age, sex, baseline Karnofsky performance score, stage of disease at diagnosis, bone marrow involvement, number of extranodal sites and number of prior regimens of anticancer therapy
Secondary end-point results	• ORR: 22%, 6% and 2% for TEM 175/75 mg arm, TEM 175/25 mg and PC • Duration of response: 5 months, 6 months and 0 months • OS (at July 19 2007): 11.1 months, 8.8 months and 9.5 months • OS (at February 1 2008): 12.8 months, 10.0 months and 9.7 months

Safety findings	• The most common AEs in all three arms were thrombocytopenia, asthenia, anaemia, diarrhoea, fever, chills, nausea, neutropenia, dyspnoea, weight loss, peripheral oedema • The most common AEs that occurred in the TEM groups were thrombocytopenia, asthenia, anaemia, diarrhoea, and fever • Leukopenia occurred more commonly in the PC arm • Grade 3 or 4 AEs occurred in 89% of patients in the TEM175/75 mg group, 80% of patients in the 175/25 mg group and 68% of patients in the PC group
PC: Physician's choice, RR: relapsed or refractory, MCL: mantle cell lymphoma, IRC: independent review committee, PFS: progression free survival, ORR: overall response rate, OS: overall survival, AE: adverse event	

The data presented in Hess, 2009 was used in the ITC: i.e. IRC-assessed ORR odds ratio (OR), IRC-assessed PFS HR, and OS HR. For OS, two HRs were available for TEM 175/75 mg vs PC, representing the HRs at a 2007 data cut and a later 2008 data cut, respectively[8]. Both HRs were analysed as part of the ITC. The results of the TEM 175/25 mg arm from the Hess, 2009 study were not considered as the TEM dose used in RAY (MCL3001) was different (175/75 mg, see Section 4.3.1). The IRC-assessed ORR OR, IRC-assessed PFS HR, and OS HR of ibrutinib compared to TEM from the CSR were used[61]. A diagram showing how the ITC was conducted is presented in Figure 16.

Figure 16: Diagram of the ITC between ibrutinib (RAY [MCL3001]) and PC (Hess, 2009) via TEM

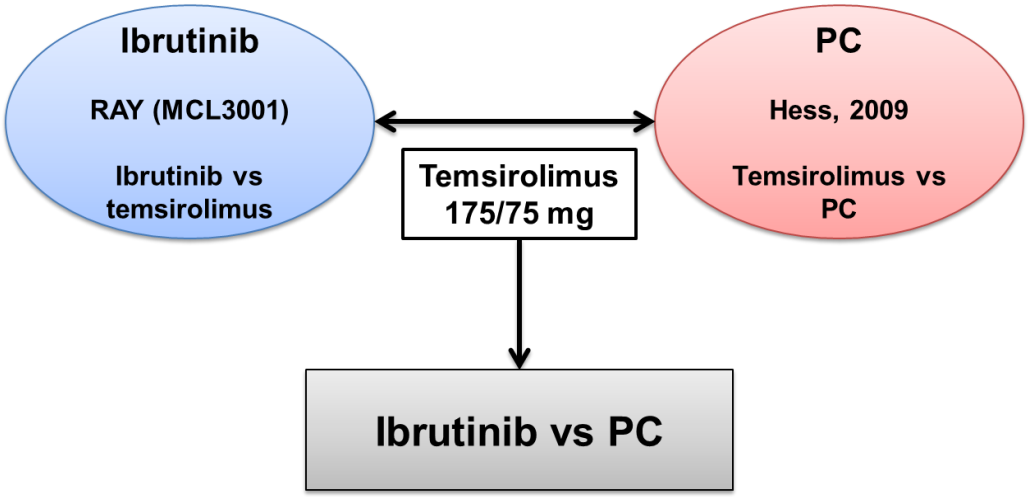


Table 27 presents the ORs and HRs comparing ibrutinib vs TEM and TEM vs PC which were used in the ITC without adjustment for baseline characteristics.

Table 27: ORs and HRs used in ITC analyses

	Ibrutinib vs TEM 175/75 mg			**Temsirolimus 175/75 mg vs PC**		
Outcome	**ORR**	**PFS**	**OS**	**ORR**	**PFS**	**OS***
Assessor	IRC	IRC	N/A	IRC	IRC	N/A
Source	CSR[61]			Hess, 2009[8]		
ITC inputs	3.98 [2.38, 6.65]	0.43 [0.32, 0.58]	0.76 [0.53; 1.09]**	15.14 [1.89,121.19]^	0.44 [0.25, 0.78]	July 19th 2007: 0.77 [0.46, 1.28] February 1st 2008: 0.80 [0.50, 1.28]
PC: Physician's choice, ORR: overall response rate, PFS: progression-free survival, OS: overall survival, IRC: independent review committee, N/A: not applicable, ITC: indirect treatment comparison						

Binary outcomes are presented as odds ratios (95% confidence intervals); Continuous outcomes presented as hazard ratios (95% confidence intervals)
* Two estimates for median OS are available for the Hess, 2009 study, representing analyses at different data cuts
** Cox regression model with MIPI and prior lines of therapy from IWRS as stratification factors. ITT population censored at Initiation of Subsequent Ibrutinib Therapy
^ The OR is calculated with # of patients per arm and % of patients achieved ORR: TEM 175/75 mg 22% ORR; PC: 2% ORR from Table 3 in the Hess, 2009 publication.

Table 28 presents the results of the ITC. The ITC found a HR for ibrutinib vs. PC of 0.19 (95% CI: 0.1, 0.36). The ITC HRs for ibrutinib vs. PC for the OS outcome were similar when using the two time points for OS presented in the Hess, 2009 study: 0.59 and 0.61, respectively.

Table 28: ITC results

	Ibrutinib vs PC		
Outcome	**ORR**	**PFS**	**OS**
Result	60.26 [7.07, 513.4]	0.19 [0.1, 0.36]	July 19th 2007: 0.59 [0.31, 1.09] February 1st 2008: 0.61 [0.34, 1.1]
PC: Physician's choice, ORR: overall response rate, PFS: progression-free survival, OS: overall survival			

4.11 *Non-randomised and non-controlled evidence*

Table 29: List of relevant non-RCTs

Trial no. (acronym)	Objective	Intervention	Population	Primary study ref.	Justification for inclusion
PCYC1104	Efficacy and safety	Ibrutinib	R/R MCL who have received at least one prior treatment	Wang, 2013[38] Wang, 2015*[37]	Phase II studies have longer follow-up than the phase III study. Phase II studies are in a wider population (for example: ECOG 0-2 versus 0-1 in the phase III study)
SPARK (MCL2001)	Efficacy and safety	Ibrutinib	R/R MCL who have received prior bortezomib	CSR[76] Wang, 2014. ASH 2014 Congress Poster [39]	

R/R MCL: relapsed or refractory mantle cell lymphoma, ASH: American Society of Hematology, ECOG: Eastern Cooperative Oncology Group, CSR: clinical study report
* Wang, 2015[37] was not identified by the SLR as it was published after the search date

4.11.1 *PCYC1104*

PCYC1104 is the registration, pivotal trial of ibrutinib in R/R MCL.

Data in this section are drawn from two published manuscripts (Wang, 2013[38] and Wang, 2015[37]) which presented data with a median follow-up time of 15.3 months (interim analysis) and 26.7 months (final analysis), respectively. The published studies are used wherever possible, with additional information drawn from the PCYC1104 CSR[77].

4.11.1.1 PCYC1104: methodology

The methodology of the PCYC1104 study is summarised in Table 30.

Table 30: Methodology of PCYC1104

Study type	PCYC1104 was an international open label phase II study conducted in the US (nine sites), Germany (two sites), Poland (three sites) and UK (four sites).
UK patients	21 patients from four sites
Eligible patients	Confirmed diagnosis of MCL with cyclin D1 overexpression or translocation breakpoints at t(11:14) and measurable disease and had received at least one prior treatment for MCL with a poor response or disease progression after the most recent regimen.
Inclusion criteria	• Men and women aged ≥18 years • Confirmed diagnosis of MCL with cyclin D1 overexpression or translocation breakpoints at t(11:14) and measurable disease • Had received at least one prior treatment for MCL, but no more than five previous lines of treatment • Poor response (defined as no partial or better) or disease progression after the most recent regimen • ECOG performance status score of 2 or less • Adequate organ function • Absolute neutrophil count of at least 0.75 x 10^9 per litre and platelet count of at least 50 x 10^9 per litre, unless the patient had bone marrow involvement by lymphoma • Use of contraception for patients of child-bearing age.
Exclusion criteria	• Prior chemotherapy within 3 weeks, prior anticancer antibodies within 4 weeks, radiotherapy within 3 weeks, radio- or toxin-immunoconjugates within 10 weeks or major surgery within 2 weeks of the first dose of study drug • History of malignancies within 1 year (except for treated basal cell or squamous skin cancer or in situ cervical cancer) • Clinically significant cardiovascular disease or ECG abnormalities • Any condition which would impact on absorption of ibrutinib • Infection with HIV, hepatitis C or hepatitis B or any uncontrolled active systemic infection • Pregnant or breast feeding women • Serum aspartate transaminase or alanine transaminase ≥3-times the ULN • Creatinine ≥2-time ULN.
Study design	Patients were enrolled without randomisation and were classified as either receiving prior bortezomib treatment (≥2 cycles) or not receiving bortezomib treatment (<2 complete cycles or no treatment).
Treatment	Patients received 560 mg oral ibrutinib od continuously on a 21 day cycle until disease progression or unacceptable toxicity
Number of patients	111
Primary end-point	ORR, defined as either a PR or a CR, according to the Revised International Working Group Criteria for NHL as assessed by the investigator. In addition, a response evaluation was also carried out by an IRC (CT and PET scans, bone marrow biopsy, GI biopsy, if required, and clinical data).
Secondary end-	Secondary end-points included DOR (measured from the day when criteria for

points	response were met to the first date on which progressive or recurrent disease was documented), PFS and OS. Safety end-points were also assessed. The study also measured peripheral blood lymphocytes after treatment with ibrutinib, as there is evidence in the related indication of CLL that ibrutinib can cause a transient increase in blood lymphocytes.
Assessments	Tumour assessment was carried out at screening, and CT scans were repeated at cycles 3, 5 and 7 and then every three cycles until disease progression. A PET scan was required to confirm a CR.
MCL: mantle cell lymphoma, ECOG: Eastern Cooperative Oncology Group, HIV: human immunodeficiency virus, ULN: upper limit of normal, od: once daily, od: once daily, ORR: overall response rate, PR: partial response, CR: complete response, NHL: non-Hodgkin lymphoma, IRC: Independent Review Committee, CT: computed tomography, PET: positron emission tomography, CR: complete response, GI: gastro-intestinal, DOR: duration of response, PFS: progression-free survival, OS: overall survival, CLL: chronic lymphocytic leukaemia Source: Wang, 2013;[38] Wang, 2015;[37] PCYC1104 CSR[77]	

4.11.1.2 PCYC1104: statistical analysis

The study was designed to assess the efficacy of ibrutinib in a small group of patients before enrolling the entire planned study population. Enrolment would only continue if an appropriate number of patients had a response in the first stage. All enrolled patients who received at least one dose of the study drug were used for primary analysis of the primary outcome. The last known data assessment was used in the case of missing data.

The response rate was provided and the corresponding 95% 2-sided CI was calculated using normal approximation to the binomial distribution. Response was assessed in pre-specified subgroups of patients, that is, those who had received prior bortezomib therapy and those who had not, by baseline characteristics and the presence of risk factors associated with chemotherapy failure.

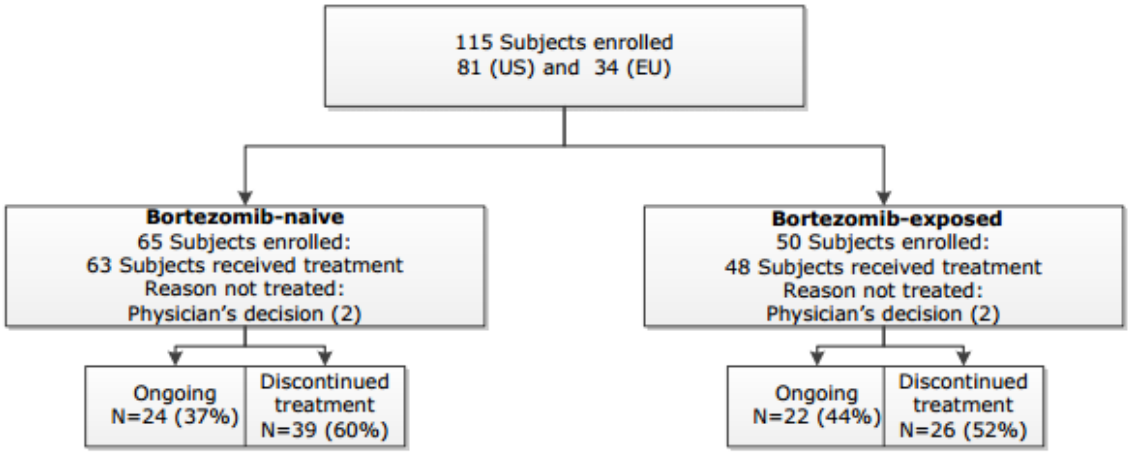
For the cohort of patients without prior treatment with bortezomib, a two-stage design was planned to test the null hypothesis that the response rate would be ≤ 20%. It was estimated that a sample of 65 patients would provide 91% power to test a difference in the response rate of 20% versus 40% at a one-sided alpha level of 0.01. For the cohort of patients with prior bortezomib treatment, a two-stage design was also planned to test the null hypothesis that the response rate would be 15% or less. It was calculated that a sample of 50 patients would provide 80% power to test a difference in the response rate of 15% versus 35% at a one-sided alpha level of 0.01.

The final analysis was planned to be carried out eight months after the last patient was enrolled in the study. KM curves were used to estimate distribution of time to event end-points (DOR, PFS and OS). All statistical tests were based on a two-sided alpha level of 0.05.

4.11.1.3 PCYC1104: participant flow

From February 2011 to March 2012, 115 patients were enrolled (50 with prior bortezomib treatment and 65 without, Figure 17). Of the 115 patients, four did not receive the study drug due to rapid disease progression (n=3) or administrative reasons (n=1).

Figure 17: Randomisation of patients to treatment arms



Source: PCYC1104 CSR[77]

The median number of cycles administered was nine (range 1-24). With an estimated median follow-up of 15.3 months (range 19.9-23.3), 46 (41%) of patients were still receiving treatment.

After a median follow-up of 26.7 months, 46% of patients remained on treatment for >1 year and 20% for >2 years.[37].

4.11.1.4 PCYC1104: baseline characteristics

Patients were elderly (median age 68 years) and had received a median of three prior therapies. The majority (86%) had intermediate or high-risk disease, as presented in Table 31 below.

In PCYC1104, the subgroup of patients with prior treatment with bortezomib was slightly older and had undergone a slightly higher median number of previous lines of therapy than those patients who had not received prior bortezomib. Additionally, more patients in the no prior treatment with bortezomib subgroup had advanced disease than in the prior treatment subgroup. However, the subgroups of patients with and without prior treatment with bortezomib were well matched with regards to prognosis and prior rituximab-containing regimens and overall there were no major differences between the subgroups. A pre-specified analysis revealed that response did not vary according to baseline characteristics (see Section 4.11.1.7).

Table 31: Patient characteristics at baseline in PCYC1104

Characteristic	No prior treatment with bortezomib (n=63)	Prior treatment with bortezomib (n=48)	All patients (n=111)
Age, year, median (range)	66 (46-83)	69 (40-84)	68 (40-84)
Male sex, no (%)	46 (73%)	39 (81%)	85 (77%)
ECOG performance status, no (%)			
0 or 1	53 (84%)	46 (96%)	99 (89%)
2	9 (14%)	2 (4%)	11 (10%)
>2	1 (2%)	0	1 (1%)
Number of prior regimens			
Median (range)	2 (1-5)	3 (1-5)	3 (1-5)
≥3, no (%)	31 (49%)	30 (62%)	61 (55%)
Previous therapy, no (%)			
Hyper-CVAD	18 (29%)	15 (31%)	33 (30%)
Stem-cell transplantation	8 (13%)	4 (8%)	12 (11%)
Lenalidomide	9 (14%)	18 (38%)	27 (24%)
Rituximab or rituximab-containing regimen	56 (89%)	43 (90%)	99 (89%)
Simplified MIPI, no (%)			
Low risk	9 (14%)	6 (12%)	15 (14%)
Intermediate risk	24 (38%)	18 (38%)	42 (38%)
High risk	30 (48%)	24 (50%)	54 (49%)
Bulky mass, no (%)	6 (10%)	3 (6%)	9 (8%)
At least one node ≥5 cm, no (%)	26 (41%)	17 (35%)	43 (39%)
Refractory disease, no (%)	27 (43%)	23 (48%)	50 (45%)
Advanced disease, no (%)	49 (78%)	31 (65%)	80 (72%)

ECOG: Eastern Cooperative Oncology Group, CVAD: Cyclophosphamide. Vincristine. Doxorubicin, Dexamethasone, MIPI: Mantle Cell Lymphoma International Prognostic Index.
Source: Wang, 2015[37]

4.11.1.5 PCYC1104: quality assessment

A quality assessment of PCYC1104 has been performed based on the Downs and Black checklist for the methodological quality of randomised and non-randomised studies of health care interventions[78]. This quality assessment is presented in Appendix 6.

4.11.1.6 PCYC1104: primary end-point

At the interim analysis with median follow-up of 15.3 months, the investigator assessed ORR was 68% in the total patient cohort (67% in prior bortezomib patients and 68% in bortezomib-naive patients). Results of the response assessment are presented in Table 32[38].

Table 32: PCYC1104 Best responses to therapy at median follow-up of 15.3 months

Variable	No prior treatment with bortezomib (n=63)	Prior treatment with bortezomib (n=48)	All patients (n=111)
Response, no (%)			
ORR	43 (68%)	32 (67%)	75 (68%)
CR	12 (19%)	11 (23%)	23 (21%)
PR	31 (49%)	21 (44%)	52 (47%)
None	20 (32%)	15 (31%)	35 (32%)
ORR: overall response rate, CR: complete response, PR: partial response Source: Wang, 2013[38]			

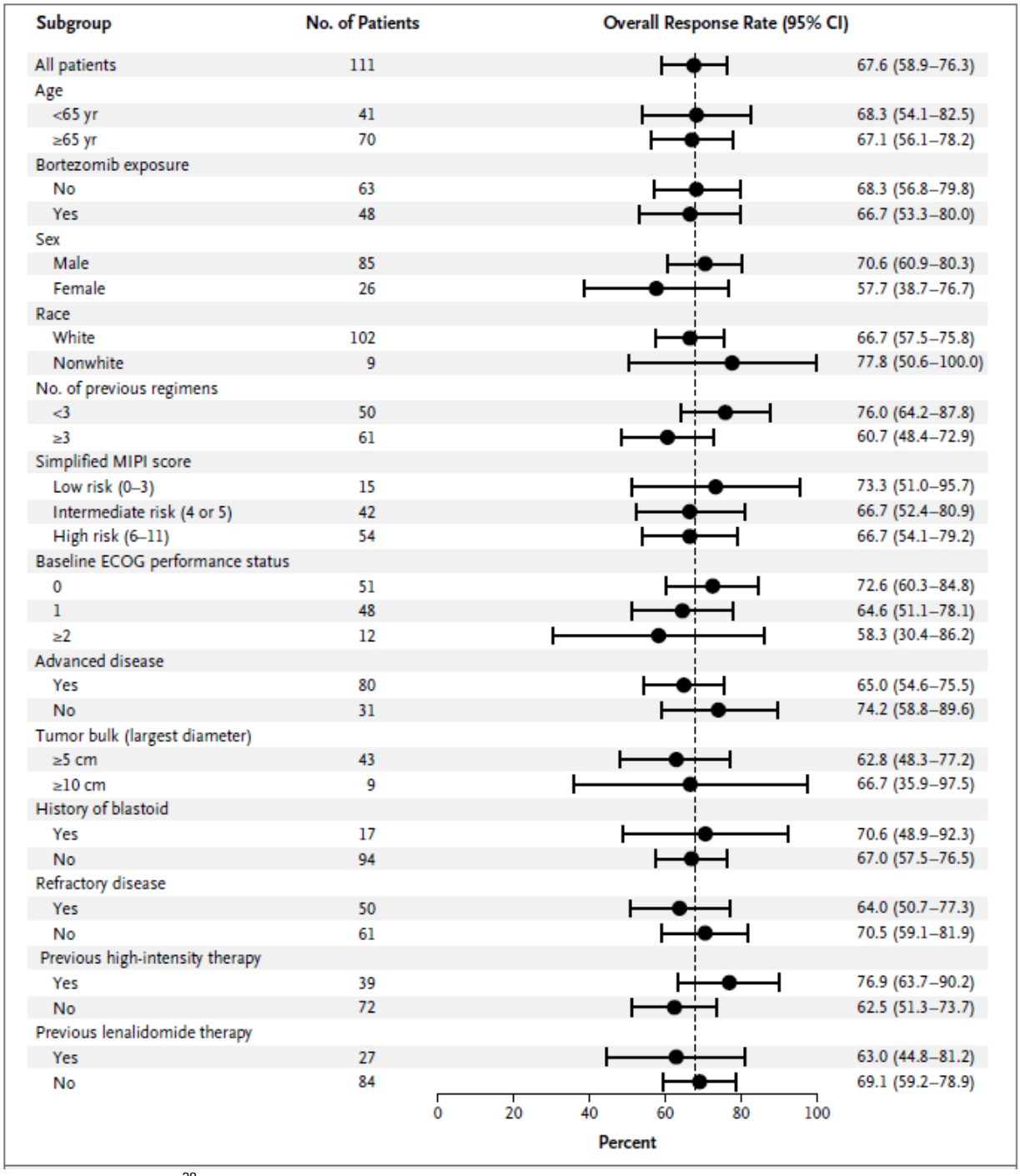
At the final analysis performed at median follow-up of 26.7 months, the response rates were maintained, with an ORR of 67% (95% CI: 57.1%, 75.3%) and a CR of 23% (95% CI: 15.1%, 31.4%)[37].

4.11.1.7 PCYC1104: secondary analyses of the primary outcome

Response rates were also assessed by the IRC and rates were very similar to those observed by the investigators, ORR of 69%, CR 21% and PR 48% at 15.3 months of follow-up. Indeed, for 95% of patients with an investigator-assessed response, the response was confirmed by the IRC.

A pre-specified analysis revealed that response did not vary according to baseline characteristics or the presence of risk factors associated with chemotherapy failure (Figure 18). Response rates were also similar across patients who had received prior bortezomib and bortezomib-naive patients.

Figure 18: Subgroup analyses of ORR in PCYC1104



Source: Wang, 2013[38]

4.11.1.8 PCYC1104: secondary end-points

The results of the secondary outcomes for the interim analysis (15.3 months follow-up) and the final analysis (26.7 months follow-up) are reported in Table 33. PFS KM plots for the two analyses of ibrutinib are shown in Figure 19. The KM OS plot for the final analysis of ibrutinib is shown in Figure 20.

The results observed correspond to a long follow-up period and demonstrate the impressive sustained response, prolonged PFS and extended OS that can be achieved with ibrutinib. Median PFS is consistent with that observed in RAY (MCL3001) and the long-term follow-up

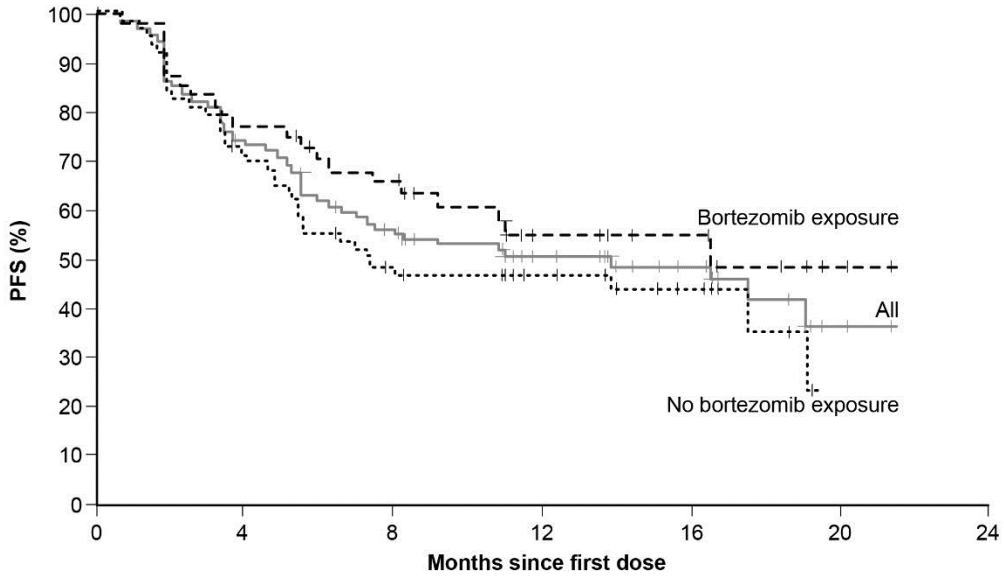
of PCYC1104 means that this study can provide an estimate of median OS, which is just below 2 years.

Table 33: PCYC1104 secondary end-points

Variable	No prior treatment with bortezomib (n=63)	Prior treatment with bortezomib (n=48)	All patients (n=111)
Median DOR (95% CI), months			
At 15.3 month follow-up	15.8 (5.6, NE)	NE	17.5 (15.8, NE)
At 26.7 month follow-up	NR	NR	17.5 (14.9, NE)
Median PFS (95% CI), months			
At 15.3 month follow-up	7.4 (5.3, 19.2)	16.6 (8.3, NE)	13.9 (7.0, NE)
At 26.7 month follow-up	NR	NR	13.0 (7.0, 17.5)
Median OS (95% CI), months			
At 15.3 month follow-up	NE (10.0-NE)	NE (11.9-NE)	NE (13.2, NE)
At 26.7 month follow-up	NR	NR	22.5 (13.7, NE)

NE: Non evaluable, PFS: progression-free survival, OS: overall survival, NR: not reported.
Source: Wang, 2013[38]; Wang 2015[37]

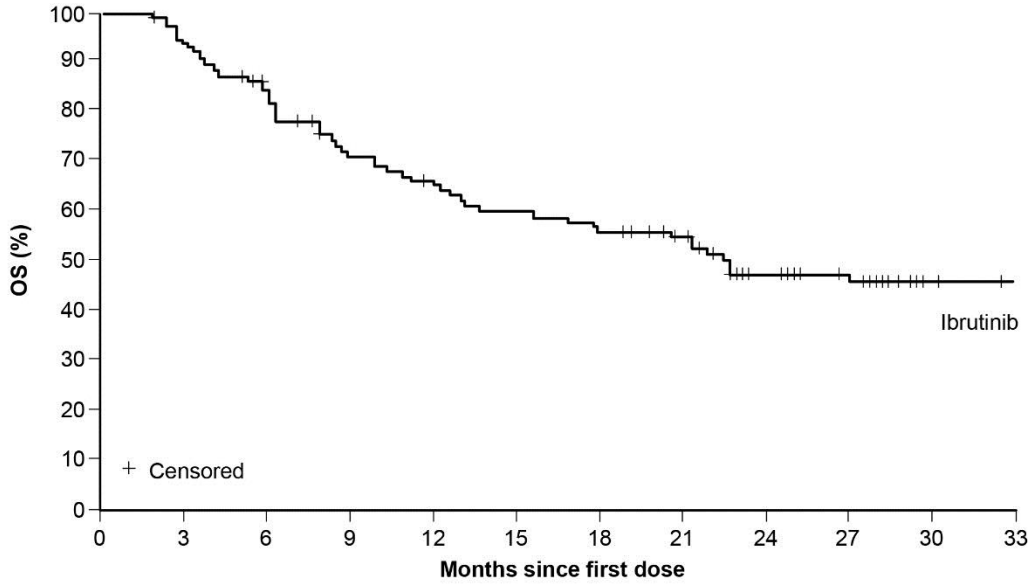
Figure 19: KM plot of PFS for ibrutinib in PCYC1104 after 15.3 months follow-up (top) and after 26.7 months of follow-up (bottom)



Number at risk							
No bortezomib exposure	63	44	28	19	12	0	0
Bortezomib exposure	48	37	29	14	10	2	0
All	111	81	57	33	22	2	0

Source: Wang, 2013[38]; Wang 2015[37]

Figure 20: KM plot for ibrutinib of OS in PCYC1104, 26.7 months of follow-up



Source: Wang, 2015[37]

4.11.2 ***SPARK (MCL2001)***

SPARK was a phase II, multicentre single-arm study evaluating the efficacy and safety of ibrutinib in patients with R/R MCL who progressed after bortezomib therapy. Given that this trial only included patients receiving prior bortezomib and therefore reflects a subset of the ibrutinib licensed indication, the study might be considered less relevant than that of RAY (MCL3001) and PCYC1104. Nonetheless, this study is presented in full here.

Data to inform this section were derived from the SPARK (MCL2001) CSR[79] and a poster presented at the ASH 2014 conference, 2014[39].

4.11.2.1 SPARK (MCL2001): methodology

The methodology of the SPARK (MCL2001) study is summarised in Table 34.

Table 34: Methodology of SPARK (MCL2001)

Study type	SPARK (MCL2001) was an international phase II single-arm study conducted at 38 sites in 7 countries (Belgium, France, Israel, Poland, Russia, UK and US)
UK patients	6 patients from 2 centres in the UK
Eligible patients	Patients with MCL who had received at least one prior rituximab-containing chemotherapy regimen and who progressed after bortezomib therapy were enrolled without randomisation.
Inclusion criteria	• Men and women aged ≥18 years • Confirmed diagnosis of MCL and measurable disease • Had received at least one prior rituximab-containing treatment for MCL • Had received at least two cycles of bortezomib treatment (monotherapy or combination) and had documented PD during or after bortezomib • Absolute neutrophil count of ≥750/mm^3 and platelet count of ≥50,000/mm^3
Exclusion criteria	• Prior treatment with ibrutinib or other BTK inhibitor • More than 5 prior lines of therapy
Permitted and disallowed concomitant medicines	Standard supportive care therapies (e.g. anti-emetics, loperamide) required for the management of symptoms were permitted, as clinically indicated, other than anticancer treatment. Hematopoietic growth factors were allowed. Prohibited medications included: any chemotherapy, anticancer immunotherapy, experimental therapy and radiotherapy. Systemic use of corticosteroids (i.e. any systemic corticosteroids ≥20 mg/day prednisone or its equivalent per day) was prohibited. Patients were excluded if it was known that they would require concomitant treatment with strong CYP3A4/5 inhibitors or anticoagulation with warfarin or equivalent vitamin K antagonists.
Study design	Single-arm.
Treatment	Patients received 560 mg oral ibrutinib od continuously on a 21 day cycle until disease progression or unacceptable toxicity.
Number of patients	120
Primary end-point	ORR, defined as either a PR or a CR, according to the Revised International Working Group Criteria for NHL as assessed by the investigator.
Secondary end-points	Secondary end-points included time to initial response, DOR, PFS and OS. PROs measured were the mean change from baseline in FACT-Lym and mean change from baseline in EQ-5D-5L for each post-baseline assessment.
Assessments	Response assessment was carried out every 9 weeks for the first 15 months and then every 24 weeks until disease progression. Tumour assessment was performed during screening with the use of CT scans of the chest, abdomen, pelvis and any other disease sites (e.g. neck); PET scans; and bone marrow biopsy. A PET scan was mandatory for confirmation of a CR. For those patients with PET-negative tumours at baseline response was based on the CT scan.

Od: once daily, CR: complete response, NHL: Non-Hodgkin's lymphoma, DOR: duration of response, EQ-5D-5L:EuroQoL 5 dimensions, FACT-Lym: Functional Assessment of Cancer Therapy-Lymphoma, ORR: overall response rate, MCL: mantle cell lymphoma, OS: overall survival, PFS: progression-free survival, PRO: patient-reported outcome
Source: Wang, 2014[39], SPARK (MCL2001) CSR[76]

4.11.2.2 SPARK (MCL2001): statistical analysis

The primary analysis of ORR was carried out using the response-evaluable population (n=110), which included all enrolled subjects who received at least one dose of study drug, had measurable disease at baseline and underwent at least one post-baseline tumour/response assessment.

The last known data assessment was used in the case of missing data.

The response rate was provided and the corresponding 95% 2-sided CI was calculated using normal approximation to the binomial distribution. The null hypothesis was tested at the overall significance level of 0.025 and rejected if the lower bound of the CI exceeded 40%.

The sample size was based on the assumption that the ORR for ibrutinib would be 56% in the study population, which gives a sample size of 101 patients. With 101 evaluable patients, the study was designed to have 90% power to declare the ORR is 40% or higher at the 1-sided significance level of 0.025.

The end of the study was planned to occur 2 years after enrolment of the last patient. The study was initiated on the 17th July 2012; clinical cut-off was the 29th April 2014 and database lock was the 20th June 2014.

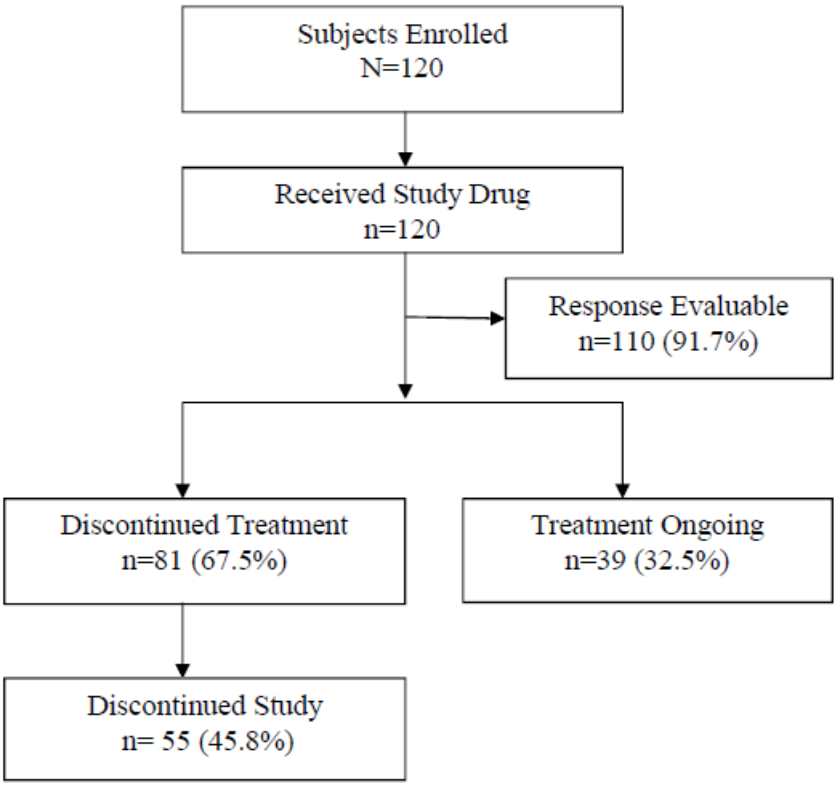
4.11.2.3 SPARK (MCL2001): participant flow

The flow of participants in the SPARK (MCL2001) study is shown in Figure 21 below.

A total of 120 patients were enrolled at 38 centres worldwide. All 120 patients received one or more dose of ibrutinib and 39 (32.5%) continued treatment. Eighty-one (67.5%) patients discontinued treatment, with the main reasons for discontinuation being progressive disease or relapse (44.2%) or AEs (6.7%). The response evaluable (RE) population was 110 patients (91.7%).

The median number of 21-day cycles of ibrutinib administered was 12 (range 1-31) over a median treatment duration of 8.0 months (range 0.5-20.9).

Figure 21: Participant flow in SPARK (MCL2001)



Source: SPARK (MCL2001) CSR[76]

4.11.2.4 SPARK (MCL2001): baseline characteristics

Patients had a median age of 67.5 years and had received a median of two prior therapies; the majority (72%) had intermediate or high-risk disease, as presented in Table 35.

Table 35: Patient demographic and baseline disease characteristics in SPARK (MCL2001)

Characteristic	SPARK (MCL2001) (n=120)
Age, year, median (range)	67.5 (35-85)
< 65 no (%)	45 (37.5)
Male sex, no (%)	104 (86.7%)
Time from initial diagnosis to first dose, median (range), months	43.9 (6.8-189.6)
Stage of MCL at entry, no (%)	
I and II	7 (9.2)
III	16 (13.3)
IV	93 (77.5)
Histology, no (%)	
Blastoid	11 (9.2)
Diffuse	62 (51.7)
Nodular	29 (24.2)
Other	18 (15.0)
Simplified MIPI, no (%)	

Characteristic	SPARK (MCL2001) (n=120)
Low risk (1-3)	28 (23.7)
Intermediate risk (4-5)	57 (48.3)
High risk (6-11)	33 (28.0)
Extent of disease	
Number of lesions, median (range)	5.0 (1.0-24.0)
Bulky disease: LD ≥ 5cm, n (%)	63 (52.5)
Bulky disease: LD ≥ 10cm, n (%)	17 (14.2)
Extranodal disease, no (%)	72 (60.0)
Bone marrow involvement, no (%)	50 (41.7)
ECOG performance status, no (%)	
0	42 (35.0)
1	67 (55.8)
2	11 (9.2)
Prior lines of therapy, median (range)	2.0 (1.0-8.0)
1, no (%)	20 (16.7)
2, no (%)	43 (35.8)
3-5, no (%)	56 (46.7)
Prior systemic therapy, no (%)	120 (100)
Prior stem cell transplantation, no (%)	40 (33.3)
ECOG: Eastern Cooperative Oncology Group, CVAD: Cyclophosphamide. Vincristine. Doxorubicin, Dexamethasone, MIPI: Mantle Cell Lymphoma International Prognostic Index. Source: Wang, 2014[39]	

4.11.2.5 SPARK (MCL2001): quality assessment

A quality assessment of SPARK (MCL2001) has been performed based on the Downs and Black checklist for the methodological quality of randomised and non-randomised studies of health care interventions[78]. This quality assessment is presented in Appendix 6.

4.11.2.6 SPARK (MCL2001): primary end-point

The ORR was 62.7% in the RE population, which included a CR of 20.9% (see Table 36) and [redacted] in the treated population (n=120).

Table 36: SPARK (MCL2001) best responses to therapy by IRC

Variable	RE population (n=110)
Response, no (%)	
ORR	69 (62.7%, 95%CI: 53.7; 71.8)
CR	23 (20.9%, 95% CI: 13.3; 28.5)
PR	46 (41.8%, 95% CI: 32.6; 51.0)
SD	16 (14.5%, 95%CI: 8.0; 21.1)
PD	25 (22.7%, 95% CI: 14.9; 30.6)
ORR: overall response rate, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease. Source: Wang, 2014[39]	

4.11.2.7 SPARK (MCL2001): secondary analyses of the primary outcome

Efficacy rates were assessed by the investigators and rates were very similar to those observed by the IRC, ORR of 66.4% for the RE patients and [redacted] for all treated patients.

A pre-specified analysis revealed that response did not vary according to baseline characteristics or the presence of risk factors associated with chemotherapy failure, see Figure 22. Although three subgroups with very few patients (non-Caucasian race, ECOG score of 2 and blastoid histology) did show a lower ORR, given the small patient numbers these findings should be interpreted with caution.

[redacted]

4.11.2.8 SPARK (MCL2001): secondary end-points

Table 37, Figure 23 and Figure 24 show results of the secondary end-points of SPARK (MCL2001).

The median time to initial response by IRC was 2.1 months (1.3-6.3 months) and the median time to a best response (CR or PR) was 2.1 months (1.3-10.6 months). The median DOR by IRC was 14.9 months.

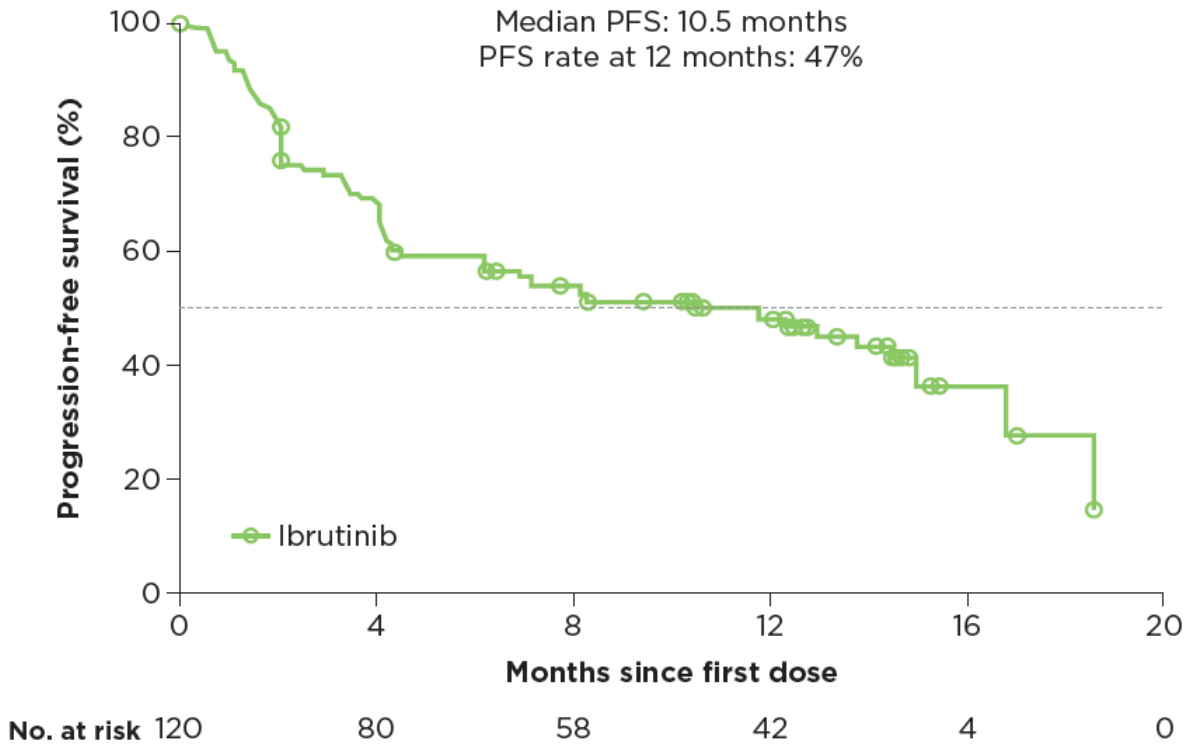
The median PFS was 10.5 months and median OS was not reached at median follow-up of 14.9 months. [redacted] This is again impressive, given the poor life expectancy of this patient population.

Table 37: SPARK (MCL2001) secondary end-points

	Patients (n=120)
Time to initial response, months	
Median (95% CI)	2.1 (1.3-6.3)
DOR, months	
Median (95% CI)	14.9 [redacted]
PFS, months	
Median (95% CI)	10.5 (4.4-15)

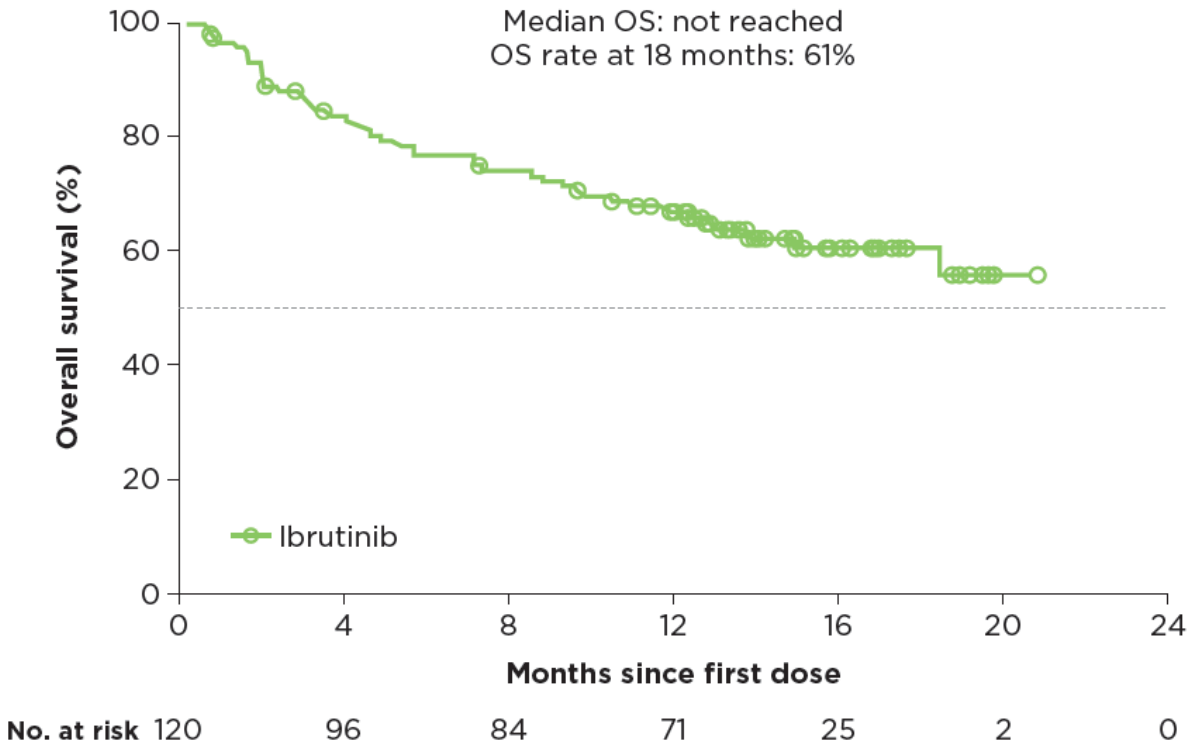
OS, months	
Median (95% CI)	NE [redacted]
CI: confidence interval, NE: non evaluable, DOR: duration of response, PFS: progression-free survival, OS: overall survival Source: Wang, 2014[39]	

Figure 23: KM curve of PFS by IRC (all treated population) in SPARK (MCL2001)



Source: Wang, 2014[39]

Figure 24: KM plot of OS (all treated population) in SPARK (MCL2001)



Source: Wang, 2014[39]

FACT-Lym

[redacted]

EQ-5D-5L

[redacted]

[redacted]

4.11.3 *Compassionate Use Programme (CUP)*

A global, open-label, multicentre CUP was run allowing patients with R/R MCL access to ibrutinib prior to approval[40, 41].

Eligible patients received 560 mg oral ibrutinib once daily until progression, occurrence of unacceptable toxicity, no longer achieving clinical benefit, or the end of the programme. Disease evaluations were conducted according to local standard of care as clinically indicated.

The primary endpoint of the study was patient TOT. The inclusion and exclusion criteria for the CUP were similar to those in RAY (MCL3001), see Section 4.5.2. A total of 715 R/R MCL patients from 26 countries enrolled in the CUP were analysed (median age 69 years; 77.1% male). Of these, 154 patients were from the UK and the programme ran from August 2014 to March 2015 in the UK.

Throughout the CUP, ibrutinib was resupplied every 1-3 months depending upon the stage of the programme. Analysis of the ordering and reordering of ibrutinib supply was then used to estimate patient TOT and provide a conservative approximation of PFS using KM analysis and Cox proportional hazard regression. Reordering data were censored at the date of last ibrutinib supply and patients transferring to commercial ibrutinib after approval were censored at the time of CUP closure in their country.

The baseline characteristics of the patients analysed from the CUP are presented in Table 38.

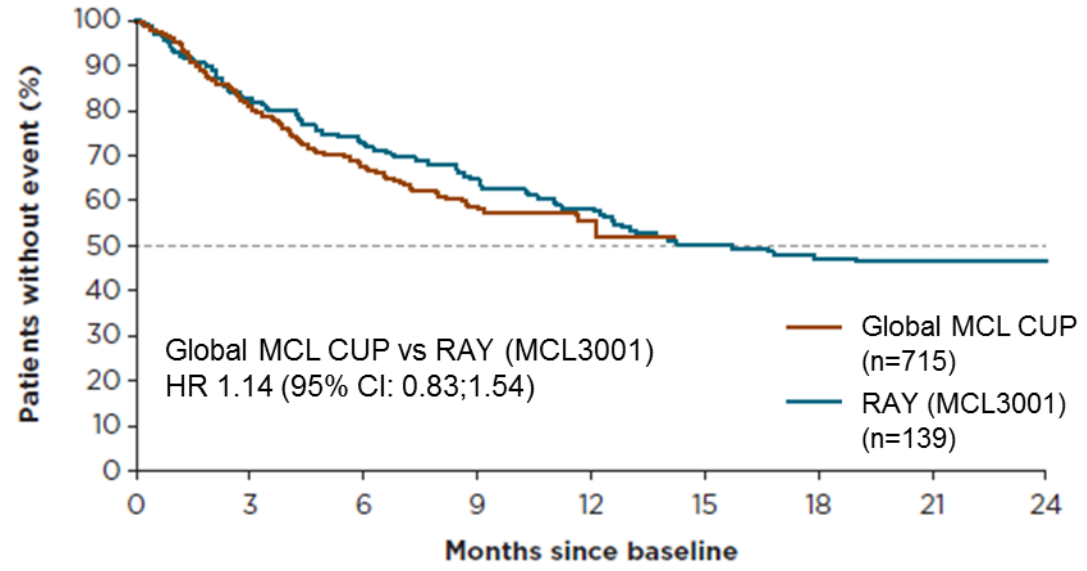
Table 38: Baseline characteristics of the 715 patients in the CUP

[redacted]	**Patients (n=715)**
[redacted]	[redacted]
Sex (male)	77.1%
≥ prior lines of therapy	61.5%
Diagnosed in the last 2 years	43.1%
Progressing on prior therapy in the last 3 months	66.0%
Last response a PR or CR	63.5%
Relapsed disease	75.1%
Refractory disease (lack of PR or better to last therapy)	79.9%
Advanced disease (involvement of bone marrow, extranodal sites, or both)	50.9%
CR: complete response, PR: partial response, SD: standard deviation Source: Rule *et al.* 2016[40, 41]	

Results

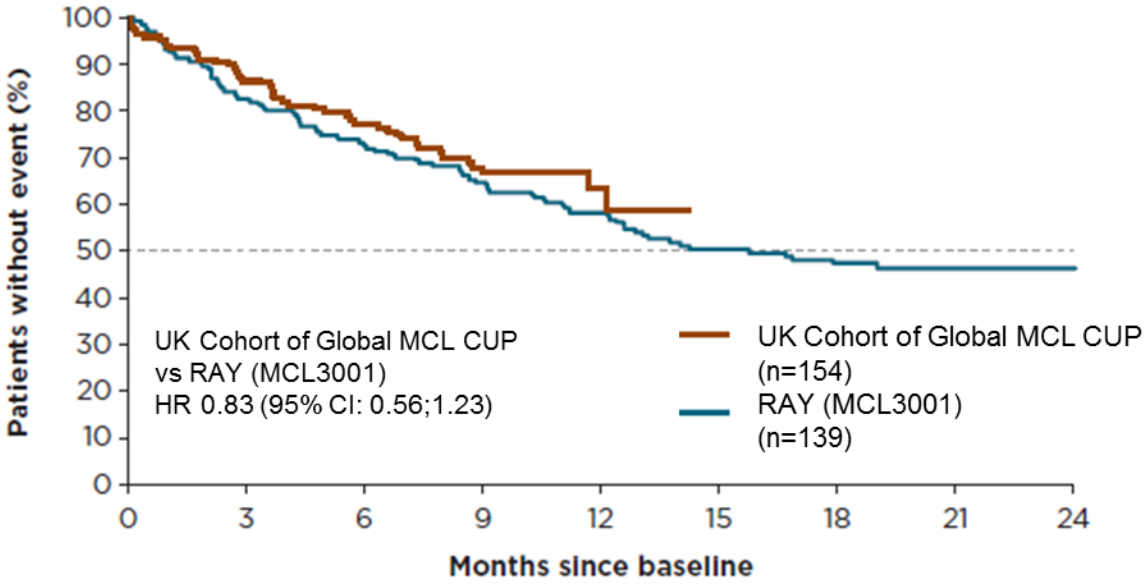
At 12 months, 52.3% (95% CI: 43.5%-60.4%) of the global CUP population were still on treatment. In the UK, the highest enrolling country (n=154), 58.7% (95% CI: 44.5%-70.4%) of patients remained on treatment. These estimates were highly consistent with the 12-month TOT and PFS rates observed with ibrutinib in RAY (MCL3001) which were 57.6% (95% CI: 48.9%-65.3%) and 58.0% (95% CI: 49.3%-65.7%) respectively. In addition, KM curves for TOT (which can be considered a proxy for PFS given the 'treat-to-progression' administration of ibrutinib) for the global or UK CUP population and the RAY (MCL3001) trial population were not statistically different, with HRs of 1.14 (95% CI: 0.83-1.54), and 0.83 (95% CI: 0.56–1.23), see Figure 25 and Figure 26, respectively.

Figure 25: Time-on-treatment for global CUP population versus RAY (MCL3001)



MCL: mantle cell lymphoma, CUP: Compassionate Use Programme, HR: hazard ratio.
Source: Rule *et al.* 2016[41]

Figure 26: Time-on-treatment for UK CUP population versus RAY (MCL3001)

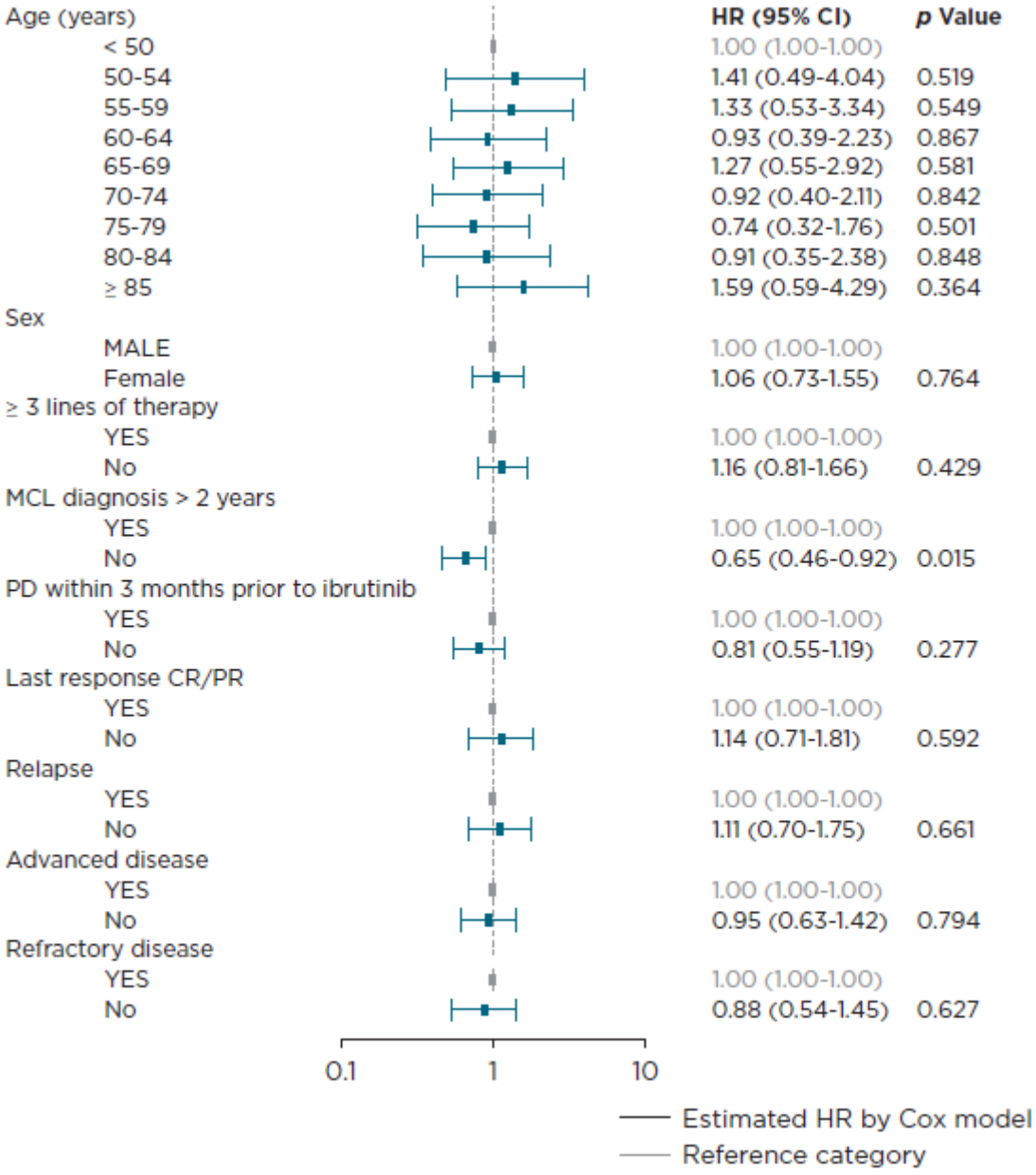


MCL: mantle cell lymphoma, CUP: Compassionate Use Programme, HR: hazard ratio.
Source: Rule *et al.* 2016[41]

Time-on-treatment was further explored via multivariate analysis from the limited baseline information collected at CUP enrolment. Results from this analysis found that timing of MCL diagnosis was the only independently significant variable, with time-on-treatment longer in patients diagnosed with MCL in the previous two years (see Figure 27). Neither age, refractory disease, defined as no response (stable disease or progression) to prior therapy, advanced disease (involvement of the bone marrow, extranodal sites, or both), relapsed

disease, nor prior response with previous therapy were found to be prognostic for a significant difference in time-on-treatment.

Figure 27: Multivariate analysis of time-on-treatment



MCL: mantle cell lymphoma, PD: progressive disease, CR: complete response, PR: partial response, HR: hazard ratio, CI: confidence interval
Source: Rule *et al.* 2016[41]

In the CUP, a total of 168 patients (23.5%) discontinued treatment during the observation period, with the most common reasons for treatment discontinuation being death (10.8%), disease progression (7.3%), or AEs (1.3%).

Although the CUP data were based on physician declarations and were unmonitored, this analysis provides a “real-world” estimate of time-on-treatment, which can be considered a conservative proxy for PFS. As such, since estimates from this analysis were similar to RAY

(MCL3001), this suggests that the results observed in clinical trials with ibrutinib in R/R MCL are reproducible in clinical practice.

4.12 ***Pooled analysis of RAY (MCL3001), PCYC1104 and SPARK (MCL2001)***

A pooled analysis was performed using patient level data from the three clinical trials for ibrutinib in R/R MCL: RAY (MCL3001) and the two phase II clinical trials, PCYC1104 and SPARK (MCL2001)[5]. A total of 370 patients were included in the analysis with the aim to assess the impact of baseline factors on OS.

4.12.1 ***Methodology***

Patient-level data from all three studies were combined into one database and exploratory analyses were conducted using KM estimates for PFS and OS. Univariate and multivariate analyses were also conducted with HRs to allow for comparisons of variables[5].

The pooling of data from all three clinical trials was considered clinically appropriate when presented at the Advisory Board[12]. This was on the basis that these three trials all evaluate patients with R/R MCL, inclusion and exclusion criteria were similar across all three trials, and that exposure or not to bortezomib prior to ibrutinib therapy (the key difference between the SPARK (MCL2001) study and the other two studies) was found not to be prognostic (see Appendix 10). Pooling of data means that the longer-term data from the PCYC1104 study can be used to inform estimates of long-term survival, which is of benefit due to the fact that median OS was not yet reached in the RAY (MCL3001) study at clinical cut-off.

4.12.2 ***Results***

A total of 370 patients were included in this analysis (RAY (MCL3001), n=139; PCYC1104, n=111; SPARK (MCL2001), n=120). Key patient demographics and baseline characteristics can be found in Table 39 below[5]. Full details of the baseline characteristics of the pooled dataset can be found in Appendix 10.

Table 39: Key baseline demographics and patient characteristics from the pooled dataset

	SPARK (MCL2001)	RAY (MCL3001)	PCYC1104	Total
Demographics				
Analysis set: intention-to-treat	120	139	111	370
Age				
Mean (SD)	66.69 (9.98)	66.73 (8.68)	67.14 (8.56)	66.84(9.07)
Sex				
Male	104 (86.67%)	100 (71.94%)	85 (76.58%)	289 (78.11%)
Female	16 (13.33%)	39 (28.06%)	26 (23.42%)	81 (21.89%)
ECOG performance status				
0	42 (35.00%)	67 (48.20%)	51 (45.95%)	160 (43.24%)
1	67 (55.83%)	71 (51.08%)	48 (43.24%)	186 (50.27%)
2	11 (9.17%)	1 (0.72%)	11 (9.91%)	23 (6.22%)
3	0	0	1 (0.90%)	1 (0.27%)
Baseline characteristics				
Simplified MCL international prognostic index				
Low risk (1-3)	28 (23.73%)	44 (31.65%)	15 (13.51%)	87 (23.64%)
Intermediate risk (4-5)	57 (48.31%)	65 (46.76%)	42 (37.84%)	164 (44.57%)
High risk (6-11)	33 (27.97%)	30 (21.58%)	54 (48.65%)	117 (31.79%)
Prior lines of therapy				
1	20 (16.67%)	57 (41.01%)	22 (19.82%)	99 (26.76%)
2	43 (35.83%)	38 (27.34%)	28 (25.23%)	109 (29.46%)
3	29 (24.17%)	28 (20.14%)	24 (21.62%)	81 (21.89%)
4	17 (14.17%)	8 (5.76%)	15 (13.51%)	40 (10.81%)
5	10 (8.33%)	5 (3.6%)	22 (19.82%)	37 (10%)
7	0	2 (1.44%)	0	2 (0.54%)
8	1 (0.83%)	0	0	1 (0.27%)
9	0	1 (0.72%)	0	1 (0.27%)
>=3	57 (47.5%)	44 (31.65%)	61 (54.95%)	162 (43.78%)
Median	2	2	3	2
Blastoid history				
Non-blastoid	109 (90.83%)	123 (88.49%)	94 (84.68%)	326 (88.11%)
Blastoid	11 (9.17%)	16 (11.51%)	17 (15.32%)	44 (11.89%)

ECOG: Eastern Cooperative Oncology Group, MCL: mantle cell lymphoma, SD: standard deviation
Source: Ibrutinib pooled analysis of three trials (data on file), March 2016[6]

The results of the pooled analysis with regards to PFS and OS are shown in Table 40. These results are presented both for the overall population, the subgroups of patients with 1 prior LOT vs >1 prior LOT, and a further breakdown for patients who received >1 prior LOT.

Results of the pooled dataset demonstrate similar estimates of median PFS and OS to the individual trials informing the analysis. The median OS estimate of 25.00 (95% CI 21.59, NE) months is similar to the median OS of 22.5 months reported in PCYC1104 (see Section 4.11.1.8). Median PFS results across the RAY (MCL3001), PCYC1104 and SPARK

(MCL2001) studies were 14.6 months (95% CI: 10.4, NE), 13.0 months (95% CI: 7.0, 17.5) (at longest available follow-up) and 10.5 months (95% CI: 4.4, 15.0), respectively. The pooled median PFS of 12.81 (8.48, 16.56) (by IRC) is therefore consistent with these results.

In addition, results from the pooled analysis in terms of number of prior LOTs reinforce the findings of the *post-hoc* analysis of RAY (MCL3001) presented in Section 4.8.2, clearly demonstrating that an increased benefit is observed when ibrutinib is used early in the treatment pathway for R/R MCL. For all three outcomes, PFS, OS and ORR, the results are improved the fewer prior LOTs the patient has received.

IRC-assessed PFS was used in the CEA (median PFS in overall population = 12.81 months). As no IRC-assessed PFS was available for PCYC1104, the investigator-assessed PFS from PCYC1104 was used in this analysis, where PFS estimates from SPARK (MCL2001) and RAY (MCL3001) were based on IRC. The choice of IRC-assessed PFS for the base case analysis of the CEA was based on the fact that only IRC-assessed PFS was available for the primary comparator source (Hess, 2009) and IRC-assessed PFS was the primary endpoint in the RAY (MCL3001) study, which was used as source of TEM (used as an alternative source of comparative efficacy).

Pooled ORRs are reported in Table 41 for IRC and investigator assessments. Pooled results for CR and PR are presented in Table 42, again by both IRC and investigator assessment. These tables show that the IRC response rates used in the CEA are conservative.

Table 40: Pooled analysis PFS and OS

	PFS IRC * Median (95% CI)	PFS INV Median (95% CI)	OS Median (95% CI)
Overall population (n=370)	12.81 (8.48, 16.56)	[redacted]	25.00 (21.59, NA)
1 LOT (n=99)	[redacted]	[redacted]	[redacted]
>1 LOT (n=271)	[redacted]	[redacted]	[redacted]

LOTs: lines of treatment, PFS: progression-free survival, CI: confidence interval, OS: overall survival, ORR: overall response rate, NE: not evaluable, IRC Independent Review Committee, INV: Investigator.
* No IRC-assessed PFS available for PCYC-1104, therefore for INV-assessed PFS I used for PCYC-1104

Table 41: Pooled analysis ORRs (based on updated datacut of PCYC1104 and SPARK (MCL2001))

	IRC ORR	INV ORR
Overall population (n=370)	245 (66.22%)	[redacted]
1 LOT (n=99)	[redacted]	[redacted]
>1 LOT (n=271)	[redacted]	[redacted]

LOTs: lines of treatment, ORR: overall response rate, IRC Independent Review Committee, INV: Investigator.
Based on updated datacut of PCYC1104 and SPARK (MCL2001)

Table 42: Pooled analysis CR and PR (based on updated datacut of PCYC1104 and SPARK (MCL2001))

	IRC CR	IRC PR	INV CR	INV PR
Overall population (n=370)	[redacted]	[redacted]	[redacted]	[redacted]
1 LOT (n=99)	[redacted]	[redacted]	[redacted]	[redacted]
>1 LOT (n=271)	[redacted]	[redacted]	[redacted]	[redacted]

LOTs: lines of treatment, IRC Independent Review Committee, INV: Investigator, CR: complete response, PR: partial response.
Based on updated datacut of PCYC1104 and SPARK (MCL2001)

4.13 *Adverse reactions*

4.13.1 *Summary of the safety profile of ibrutinib in the three clinical trials*

Table 43: Summary of the safety profile of ibrutinib in the three clinical trials

RAY (MCL3001)[36]	• Although median duration of treatment exposure was nearly 5-fold higher for ibrutinib compared to TEM, ibrutinib was better tolerated than TEM, with grade 3 or higher treatment-emergent AEs reported for 94 (68%) patients on ibrutinib versus 121 (87%) patients on TEM • In the ibrutinib arm, 6.5% of patients discontinued due to AEs versus 25.5% in the TEM arm • The most frequently reported AEs (≥20%) of any grade in the ibrutinib arm were diarrhoea (29%), cough (22%), and fatigue (22%). The most commonly occurring AEs (≥20%) in the TEM arm were thrombocytopenia (56%), anaemia (43%), diarrhoea (31%), fatigue (29%), neutropenia (26%), epistaxis (24%), cough (22%), peripheral oedema (22%), nausea (22%), pyrexia (21%), and stomatitis (21%) • The most common grade ≥3 haematological AEs (≥10%) were neutropenia (13%) in the ibrutinib arm and, thrombocytopenia (42%), anaemia (20%), neutropenia (17%), [redacted] • The most common grade ≥3 non-haematological AEs (≥5%) were [redacted] in the ibrutinib arm and [redacted] in the TEM arm [redacted]
PCYC1104[37, 38]	• At the time of cut off for the primary end-point (26th of December 2012), the most common grade 3 or 4 non-haematological AEs (≥5%) were pneumonia (7%), abdominal pain (5%), atrial fibrillation (AF) (5%), diarrhoea (5%), fatigue (5%) and skin infections (5%) • In long-term follow-up of 26.7 months, the most commonly occurring AEs (≥30%) were diarrhoea (54%), fatigue (50%), nausea (33%) and dyspnoea (32%) • The most common grade ≥3 haematological AEs were neutropenia (17%), thrombocytopenia (14%) and anaemia (11%) • Only 7% of patients discontinued ibrutinib treatment due to AEs at the time of cut off for the primary end-point, and only 11% total discontinued due to AEs in the long-term extension • Infection grade ≥3 occurred in 28% of patients with MCL
SPARK (MCL2001)[39]	• The most commonly occurring AEs (≥20%) were fatigue (43%), diarrhoea (43%), [redacted] • Only 6.7% of patients discontinued due to AEs
AE: adverse event, MCL: mantle cell lymphoma, AF: atrial fibrillation, TEM: temsirolimus	

4.13.2 *Adverse reactions in RAY (MCL3001)*

Median treatment duration was nearly 5-fold in the ibrutinib arm (14.4 months [IQR 15.1]) vs TEM (3.0 months [7.6]). Despite the time difference in exposure between the treatment groups, overall frequencies of most cumulative treatment emergent AEs were lower in the ibrutinib group relative to the TEM group[36].

Ibrutinib has a manageable safety profile. Although nearly all patients experienced an AE (99.3% in both arms), patients in the TEM arm were nearly four times more likely to discontinue treatment due to AEs (25.5% versus 6.5% with ibrutinib). Patients in the TEM arm were also more likely to experience AEs of greater severity (87.1% grade ≥3 versus 67.6% with ibrutinib, [redacted] and have dose reduction due to AEs (43.2% versus 3.6%) as presented in Table 44.

Table 44: Summary of AEs in RAY (MCL3001)

	Ibrutinib (n=139)	**TEM (n=139)**
Any AE	138 (99.3%)	138 (99.3%)
Grade ≥3	94 (67.6%)	121 (87.1%)
Drug related	[redacted]	[redacted]
Any serious AE	[redacted]	[redacted]
Grade ≥3	[redacted]	[redacted]
Drug related	[redacted]	[redacted]
AEs leading to treatment discontinuation	9 (6.5%)	36 (25.5%)
Dose reduction due to AEs	5 (3.6%)	60 (43.2%)
AEs with outcome death	[redacted]	[redacted]

AE: adverse event, TEM: temsirolimus.
Source: Dreyling *et al.*, 2015[36], RAY (MCL3001) CSR[61]

Overall, the most common AEs in the ibrutinib arm (≥ 20% of patients) were diarrhoea (29%), cough (22%) and fatigue (22%). The most common AEs in the TEM arm (≥ 20% of patients) were thrombocytopenia (56%), anaemia (43%), diarrhoea (31%), fatigue (29%), neutropenia (26%), epistaxis (24%), cough (22%), peripheral oedema (22%), nausea (22%), pyrexia (21%) and stomatitis (21%), as shown in Table 45[36]

Table 45: Incidence of AEs occurring in >10% of patients in either arm, RAY (MCL3001), safety analysis set

System organ class Preferred term	Ibrutinib (n=139)	TEM (n=139)	Relative risk (95% CI)
Infections and infestations	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Respiratory tract infection	[redacted]	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Diarrhoea	40 (28.8%)	43 (30.9%)	[redacted]
Nausea	20 (14.4%)	30 (21.6%)	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Stomatitis	4 (2.9%)	29 (20.9%)	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Fatigue	31 (22.3%)	40 (28.8%)	[redacted]
Pyrexia	23 (16.5%)	29 (20.9%)	[redacted]
Oedema peripheral	18 (12.9%)	31 (22.3%)	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]
Mucosal inflammation	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]
Cough	31 (22.3%)	31 (22.3%)	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Epistaxis	12 (8.6%)	33 (23.7%)	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]
Anaemia	25 (18.0%)	60 (43.2%)	[redacted]
Thrombocytopenia	25 (18.0%)	78 (56.1%)	[redacted]
Neutropenia	22 (15.8%)	36 (25.9%)	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]	[redacted]

System organ class Preferred term	Ibrutinib (n=139)	TEM (n=139)	Relative risk (95% CI)
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	[redacted]
Hypercholesterolaemia	[redacted]	[redacted]	[redacted]
Hypertriglyceridaemia	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]
Source: RAY (MCL3001) CSR[61]			

Grade 3 or higher AEs were reported in 67.6% of ibrutinib patients and 87.1% of TEM patients[36]. The most frequently occurring grade 3 or higher AEs (≥ 10% of patients in any treatment arm) were neutropenia (ibrutinib: 12.9%, TEM: 16.5%), thrombocytopenia (ibrutinib: 9.4%, TEM: 42.4%), anaemia (ibrutinib: 7.9%, TEM: 20.1%), [redacted][61].

[redacted][61].

AEs with ibrutinib are manageable and infrequently result in discontinuation. Discontinuation rates due to AEs with ibrutinib were nearly a quarter of those observed with TEM (6.5% versus 25.5%)[36].

Grade 3 or higher AF reported for 5 (3.6%) patients in the ibrutinib arm and 2 (1.4%) patients in the TEM arm. Major bleeding was reported in 14 (10%) patients in the ibrutinib arm and in 9 (6%) in the TEM arm. When adjusted for exposure, the event rate for any major bleeding treatment-emergent AE was 0.8 events per 100 patient-months in the ibrutinib arm and 1.1 events per 100 patient-months in the TEM arm[36].

With regards to malignancy, new diagnoses of other malignancies were observed in 5 (4%) patients in the ibrutinib group and 4 (3%) in the TEM group. Most malignancies were non-melanomatous skin cancers. When adjusted for exposure, frequencies were found to be similar in both treatment groups[36].

4.13.3 *Adverse reactions in the non-randomised studies (PCYC1104 and SPARK[MCL2001])*

Additional information on safety are derived from the two phase II studies, PCYC1104 and SPARK (MCL2001).

The long-term follow-up of PCYC1104 provides data for a median of 26.7 months[37]. Data are provided from the published paper[37]and two posters presented at EHA and ASH, 2014[39, 44]. No new safety signals were observed and frequency and severity of AEs were similar to those in the ibrutinib arm of RAY (MCL3001). Infection, diarrhoea and bleeding were reported more commonly in the first 6 months of therapy than later in treatment (Table 46).

Table 46: PCYC1104 prevalence of select AEs at 6 monthly intervals

Select AEs, n (%)	1-6 months (n=111)	7-12 months (n=72)	13-18 months (n=51)	19-24 months (n=41)	>24 months (n=22)
Any diarrhoea	49 (44)	21 (29)	15 (29)	8 (20)	6 (27)
Grade 3*	5 (5)	0	0	1 (2)	0
SAE	1 (1)	0	0	0	0
Any infection	76 (69)	43 (60)	30 (59)	22 (54)	9 (41)
Grade ≥3	20 (18)	11 (15)	6 (12)	5 (12)	1 (5)
SAE	16 (14)	9 (13)	4 (8)	5 (12)	1 (5)
Any bleeding	46 (41)	17 (24)	17 (33)	14 (34)	5 (23)
Major bleeding	6 (5)	1 (1)	3 (6)	2 (5)	2 (9)

AE: adverse event, SAE: serious adverse event.
Source: Wang, 2014[39]

Rates of diarrhoea decreased after the first 6 months of treatment and the majority were grade 1 in severity. The median time to onset was 8 days and resolution of diarrhoea was 5 days. A similar picture was observed with infection, with a decrease in prevalence over time. The prevalence of grade 3 or higher infections was 27% (n=30), with only one grade 4 infection and three grade 5 infections. The most common grade 3 or above infection was pneumonia (n=8)[44]. AEs occurring in at least 20% of patients are reported in Table 47 for both the interim and final analysis of the PCYC1104 study.

Table 47: Most common AEs (≥20%) for ibrutinib in PCYC1104 for the interim and final analysis

AE, %	Final analysis (26.7 months)	Interim analysis (15.3 months)
Diarrhoea	54.1	50.5
Fatigue	49.5	41.4
Nausea	33.3	30.6
Dyspnoea	32.4	27.0
Constipation	[redacted]	25.2
URTI	[redacted]	23.4
Peripheral oedema	[redacted]	27.9
Vomiting	[redacted]	22.5
Decreased appetite	[redacted]	20.7
Cough	[redacted]	18.0
Thrombocytopenia	21.6	18.0

AE: adverse event, URTI: upper respiratory tract infection
Source: Wang, 2013[38]; Wang 2015[37]

Safety data from SPARK (MCL2001) are provided from the published poster presented at ASH, 2014[39]. In SPARK (MCL2001), the majority of AEs were grade 1 or 2 and self-limiting. Very few (6.7%) of patients discontinued treatment due to AEs. The most common AEs were fatigue and diarrhoea, with the vast majority of these being grade 1. Diarrhoea, when observed, generally occurred early after initial treatment but resolved quickly and was not treatment limiting. The most common grade 3 or above AEs were neutropenia (20.8%), thrombocytopenia (13.3%) and pneumonia (12.5%). AEs occurring in at least 20% of patients in SPARK (MCL2001) are reported in Table 48.

AF was reported in 13 patients (10.8%). Six patients (5%) experienced grade 3 or 4 AF which resolved in 1 to 4 days and 5 of these 6 patients had a history of AF/atrial flutter. No patients discontinued treatment due to AF.

Treatment-related lymphocytosis (absolute lymphocyte count increased ≥ 50% from baseline and ≥ 5 × 109/L) was observed in 27.5% of patients. The median time to onset was 3.14 weeks and resolution occurred for most patients (26 of 33) after a median duration of 6.14 (95% CI: 3.14-10.29) weeks. The percentage of patients with ≥ grade 3 infections in the first six months was 19.2%, and after six months was 15.5%.

Table 48: Most common AEs (≥20%) for ibrutinib in SPARK (MCL2001)

AE, %	Percentage of patients
Fatigue	43.3%
Diarrhoea	42.5%
Cough	25.0%
Thrombocytopenia	24.2%
Neutropenia	23.3%
Peripheral oedema	23.3%
Nausea	21.7%
Muscle spasms	20.8%
Pyrexia	20.8%
AE: adverse event. Source: Wang, 2014[39]	

4.13.4 *Adverse reactions in the pooled dataset of RAY (MCL3001), PCYC1104 and SPARK (MCL2001)*

Pooled rates of Grade 3 or higher AEs across the three clinical studies of ibrutinib presented in this submission are shown below in Table 49.

Table 49: Grade 3+ AEs pooled data rate

Term	RAY (MCL3001) (N=139)	SPARK (MCL2001) (N=120)	PCYC-1104 (N=111)	Pooled (N=370)
Neutropenia	18 (12.9%)	25 (20.8%)	19 (17.1%)	62 (16.8%)
Thrombocytopenia	13 (9.4%)	17 (14.2%)	14 (12.6%)	44 (11.9%)
Anaemia	11 (7.9%)	10 (8.3%)	12 (10.8%)	33 (8.9%)
Pneumonia	11 (7.9%)	11 (9.2%)	8 (7.2%)	30 (8.1%)
Hypokalaemia	8 (5.8%)	5 (4.2%)	2 (1.8%)	15 (4.1%)
Hyperglycaemia	1 (0.7%)	1 (0.8%)	1 (0.9%)	3 (0.8%)
Sepsis	2 (1.4%)	3 (2.5%)	1 (0.9%)	6 (1.6%)
Neutrophil count decreased	7 (5.0%)	2 (1.7%)	0 (0.0%)	9 (2.4%)
Platelet count decreased	2 (1.4%)	0 (0.0%)	0 (0.0%)	2 (0.5%)
Fatigue	6 (4.3%)	4 (3.3%)	5 (4.5%)	15 (4.1%)
Abdominal pain	5 (3.6%)	3 (2.5%)	6 (5.4%)	14 (3.8%)
Atrial fibrillation	5 (3.6%)	7 (5.8%)	7 (6.3%)	19 (5.1%)
Diarrhoea	4 (2.9%)	3 (2.5%)	6 (5.4%)	13 (3.5%)
Hypertension	4 (2.9%)	5 (4.2%)	5 (4.5%)	14 (3.8%)
Major Bleeding	10 (7.2%)	1 (0.8%)	5 (4.5%)	16 (4.3%)

Tumour lysis syndrome	1 (0.7%)	0 (0.0%)	1 (0.9%)	2 (0.5%)
Leukostasis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lymphocytosis	2 (1.4%)	0 (0.0%)	1 (0.9%)	3 (0.8%)
Renal failure	2 (1.4%)	0 (0.0%)	2 (1.8%)	4 (1.1%)
Cytomegalovirus (CMV) reactivation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Abnormal liver function test	0 (0.0%)	1 (0.8%)	1 (0.9%)	2 (0.5%)
Based on updated datacut of PCYC1104 and SPARK (MCL2001)				

4.13.5 ***Adverse reactions in the real-world studies (EAP and CUP)***

Low rates of treatment discontinuation due to AEs were reported in the CUP (1.3%) and no new safety signals were identified[40, 41]. The AEs observed in the clinical studies were confirmed in an EAP in the USA which provided access to ibrutinib prior to market authorisation to patients ineligible for recruitment into clinical trials. A total of 38 US sites enrolled 149 patients into the EAP between May 2013 and April 2014. The results of the US cohort were presented as a poster at ASH in 2014[80]. The safety profile observed in the US cohort was consistent with that observed during the clinical trials for ibrutinib, and no new safety signals were noted. The majority of patients (99/149 [66.4%]) discontinued treatment when ibrutinib received FDA approval and therefore left the programme. Only 4 patients (2.7%) discontinued treatment due to AEs and no new safety signals for ibrutinib were observed throughout the programme. Grade 3 and above AEs were reported in 59 patients (39.6%) and any SAEs were reported in 46 patients (30.9%). Serious non-fatal AE of AF was reported in 3 (2.0%) patients and a serious non-fatal AE of atrial flutter was reported in 1 (0.7%) patient. Two cases of major haemorrhage were reported occurring without precedent trauma or anticoagulation exposure. One patient had an intracranial haemorrhage and one patient had anaemia (grade 3) that resulted from major haemorrhage, which subsequently required two units of packed red blood cells.

4.13.6 ***Safety overview in relation to the decision problem***

The CHMP assessed the safety profile of ibrutinib[1] based on the data presented as part of the regulatory submission and concluded in the EPAR:

"The most frequent adverse reactions related to the use of ibrutinib are infections, neutropenia, and diarrhoea. However, discontinuation due to toxicity was infrequent and overall the toxicity was considered manageable".

"The safety profile was similar across clinical trials and indications with diarrhoea and infections as predominant events and most common grade 3/4 adverse reactions (≥ 5%) were anaemia, neutropenia, pneumonia and thrombocytopenia".

Ibrutinib is well tolerated, with a low rate of treatment discontinuation. Specifically:

- In the phase III RAY (MCL3001) study, although median duration of treatment exposure was nearly 5-fold higher for ibrutinib compared to TEM, ibrutinib was better tolerated than TEM, with grade 3 or higher treatment-emergent AEs reported for 94 (68%) patients on ibrutinib versus 121 (87%) patients on TEM. At the end of the study, 87.9% of patients in the TEM arm discontinued treatment compared to 53.2% in the ibrutinib arm. Considering reasons for discontinuation, 25.5% of patients in the

TEM arm compared to 6.5% in the ibrutinib arm (4-times more) discontinued because of AEs and 11.3% of patients who received TEM refused further treatment compared to only 2.9% of patients who received ibrutinib[36].

- Discontinuation rates were similarly low in PCYC1104 (11% in the long-term extension)[37].
- The incidence of AEs reported with ibrutinib decreases over time. In PCYC1104, AEs (specifically infection, diarrhoea and bleeding) were reported more commonly in the first 6 months of therapy than later in treatment[44]. Most cases of diarrhoea were grade 1 in severity. The median time to onset was 8 days and resolution of diarrhoea was 5 days[44]
- The safety profile of ibrutinib reported in the two real-world studies (EAP and CUP) was consistent with those found in the pivotal trials, with low rates of treatment discontinuation due to AEs.

In conclusion, single-agent ibrutinib is well tolerated in patients with R/R MCL, avoiding the high rates of AEs commonly observed with conventional chemotherapy. Treatment discontinuation is low and most patients are able continue on treatment.

4.14 *Interpretation of clinical effectiveness and safety evidence*

4.14.1 *Clinical benefits and harms*

Ibrutinib provides clear clinical benefit in a disease area in which patients currently face poor outcomes.

Ibrutinib in R/R MCL is supported by data from three clinical trials, all of which show a consistent efficacy profile in the overall population and across each subgroup analysed.

Patients treated with ibrutinib remain progression-free for around one year. This is consistent across all three studies. Median PFS in the pooled dataset combining the three ibrutinib trials was 12.81 months[5]. This compares to median PFS derived from different sources of 6.2 months for TEM in RAY (MCL3001)[36], 2.8 months from the Skåne University Hospital dataset[9] and 1.9 months for the PC arm in Hess, 2009[8], therefore demonstrating the unprecedented benefit offered by ibrutinib in a disease area with a lack of viable treatment options.

Median OS was 25.00 months in the pooled dataset including the three ibrutinib trials[5], 22.5 months in PCYC1104 and was not reached in RAY (MCL3001) or SPARK (MCL2001). Survival of approximately 2 years is considerably higher than the median OS of 10 months or less observed in current clinical practice: 5.2 months from the Skåne University Hospital dataset[9], 8.4 months in HMRN[7] and 9.7 months for the PC arm in Hess, 2009[8]. Given the significant unmet need in the R/R MCL population and the orphan status granted to ibrutinib, the level of uncertainty around OS at the time of regulatory submission (median OS was not reached in PCYC1104 at 15.3 months follow-up[38]) was accepted by the EMA, which granted marketing authorisation based upon single-arm, phase II clinical trial data. Median OS data is now available from PCYC1104 and the pooled analysis, but has not yet been reached in RAY (MCL3001) or SPARK (MCL2001). A new data cut for OS from the RAY (MCL3001) study is scheduled for November 2016 and it is expected to provide a significant OS benefit of ibrutinib compared to TEM. It should be remembered that RAY (MCL3001) was not powered to show a statistical OS benefit at the main data cut and OS estimates have been contaminated by a high proportion (23%) of TEM patients who crossed over to ibrutinib.

Interestingly, the authors of the RAY (MCL3001) publication[36] suggest that the overall treatment effect might be better captured by PFS2 (defined as the time to disease progression or death after the first subsequent therapy), which was longer for ibrutinib than for TEM (median of 19.1 months versus 11.3 months respectively, HR 0.49 (95% CI 0.36-0.69); p<0.0001; see Section 4.7.2.1)[36, 61]. The extended PFS2 with ibrutinib demonstrates that the outcomes of subsequent treatment were not adversely affected by prior ibrutinib therapy.

Response rates achieved with ibrutinib are favourable to those observed with a number of other therapies that may constitute current clinical practice. A recent review by Tucker and Rule, published in 2016, highlighted response rates for a number of chemotherapy regimens that range from 22% to 33%, compared to a pooled ORR of 66% across the three ibrutinib studies[5].

Ibrutinib has a positive impact on patients' QoL

QoL is poor in patients with R/R MCL; fatigue and loss of mobility are commonly observed. Decrements are observed in all areas of QoL, including physical health (mobility and fatigue) and psychological health (anxiety and depression). Older patients and those with active disease have the poorest QoL of all. Patients' ability to enjoy life – their pastimes/hobbies, relationships, professional and social life – is also impaired, which has a considerable impact on QoL and on their relationships with others[11].

QoL improvements on ibrutinib treatment are extraordinary; patients feel well on ibrutinib, with a reduction in disease-related symptoms. In RAY (MCL3001), nearly twice as many patients in the ibrutinib arm of RAY (MCL3001) achieved a clinically meaningful symptoms improvement compared with TEM (61.9% versus 35.5%), with symptoms improvement achieved significantly quicker with ibrutinib (median 6.3 weeks compared to 57.3 weeks with TEM)[3].

Improvements in disease-related symptoms with ibrutinib are accompanied by substantial improvement in HRQoL. In RAY (MCL3001), the FACT-Lym total score showed clinically meaningful improvement from baseline in patients treated with ibrutinib compared to TEM. Across the broader HRQoL domains that contribute to the FACT-Lym total score, patients treated with ibrutinib showed improvement in physical, functional and emotional well-being that was significantly better than change in HRQoL from baseline in patients treated with TEMs. An improvement in QoL with ibrutinib compared to TEM was also observed using the EQ-5D-5L instrument; a significant difference in EQ-5D-5L utility values favouring ibrutinib was observed within 4 weeks and maintained through to week 49 in RAY (MCL3001)[36]. In addition, overall improvement in perceived health captured by the EQ-VAS in patients receiving ibrutinib vs TEM was clinically and statistically significant.

The results from the clinical evidence base demonstrating significant improvements in symptoms and QoL scores with ibrutinib versus TEM would be expected to have a meaningful and valuable positive impact on patients. The FACT-Lym measure of lymphoma symptoms captures a wide range of physical, social emotional and functional aspects of the condition, including lack of energy, pain, confinement to bed, depression, anxiety and ability to enjoy life and work. The meaningful improvements in FACT-Lym and EQ-VAS observed with ibrutinib are likely to reflect important changes to how patients' feel overall and their ability to enjoy components of their lives such as carrying out hobbies, engaging in relationships, returning to work and enjoying social activities. Feedback from clinicians at the advisory board at which these data were presented was strong in supporting the value of the QoL benefit of ibrutinib, and it was suggested that clinicians can visibly "see" which patients are receiving ibrutinib because they are more likely to look healthy as opposed to appearing visibly sick and suffering from hair loss as with rituximab-chemotherapy combination

alternatives[12]. Furthermore, anecdotal evidence from the advisory board reported a rapid response observed with ibrutinib, enabling patients to "*go back to work or play golf within 3 weeks*". Although this latter evidence is anecdotal in nature, it provides helpful context for the interpretation of the quantitative benefits to QoL of ibrutinib versus TEM demonstrated in the RAY (MCL3001) trial. By contrast values captured by the EQ-5D-5L appear to under-estimate the utility gain associated with this meaningful and valuable positive impact on MCL patients' HRQoL.

Ibrutinib has a manageable tolerability profile and most patients are able to remain on treatment

AEs were consistent and predictable across all studies, with most being manageable with standard supportive treatments. Ibrutinib does not require any routine pre-medication or additional monitoring. The majority of patients are able to continue on treatment with ibrutinib, with reported discontinuation rates due to AEs on ibrutinib at latest available data cut-offs of 6.5%, 6.7% and 11% for the RAY (MCL3001), SPARK (MCL2001) and PCYC1104 studies, respectively. In contrast, the discontinuation rate for TEM in RAY (MCL3001) was 25.5%.

When assessing ibrutinib's safety profile against its comparator in the pivotal phase III trial RAY (MCL3001), it must be borne in mind that median treatment duration was nearly 5-fold higher in the ibrutinib arm (14.4 months versus 3.0 months with TEM). Despite the time difference in exposure between the treatment groups, overall frequencies of most cumulative treatment emergent AEs were lower in the ibrutinib group relative to the TEM group[36].

The most common AEs in each study were infections, neutropenia, and diarrhoea; importantly, the incidence of AEs reported with ibrutinib decreases over time. In PCYC1104, AEs (specifically infection, diarrhoea and bleeding) were reported more commonly in the first 6 months of therapy than later in treatment[44]. Most cases of diarrhoea were grade 1 in severity, the median time to onset was eight days and median time to resolution of diarrhoea was five days[44].

Grade 3 or higher AEs in RAY (MCL3001)[36] were observed in 68% patients receiving ibrutinib versus 87% patients receiving TEM. Serious AEs were reported in around one-half of patients (57.6% for ibrutinib versus 48.2% for TEM); most were infection-related, and the majority of serious AEs were not related to ibrutinib. As an AE of special clinical interest, most cases of AF were in patients with risk factors or pre-existing disease and grade 3 or higher AF was reported in 5 (4%) patients in the ibrutinib arm and 2 (1%) patients in the TEM arm[36].

Finally, the safety profile of ibrutinib in MCL is consistent with what was observed in real life (EAP) and the known safety profile of ibrutinib in the CLL indication[1, 36].

4.14.2 *Strengths and weaknesses of the clinical evidence base*

Consistent evidence of treatment effect on progression or death

The evidence to support the benefit of ibrutinib in terms of PFS, response and OS is consistent across all three clinical trials (one randomised study versus TEM and two uncontrolled studies)[36-39]. PFS results were similar between trials and the subgroup analyses on PFS provide further evidence of a consistent benefit of ibrutinib on risk of progression or death. ORR was also consistent across all three studies, ranging from 62.7% in SPARK (MCL2001), 69% in PCYC1104 to 71.9% in RAY (MCL3001).

Robust evidence base for ibrutinib efficacy

The clinical evidence base for ibrutinib consists of an extensive clinical trial program comprising a phase III RCT and two phase II single-arm studies. A pooled analysis across the experimental trials considered a total of 370 patients who received ibrutinib. Pooling of data meant that the longer-term data from the PCYC1104 study could be used to inform estimates of long-term survival, which was of benefit due to the fact that median OS was not yet reached in the RAY (MCL3001) study at clinical cut-off. The evidence base is further enhanced by real-world evidence from a CUP (715 R/R MCL patients of which 154 in UK) and an additional real-world study, the EAP, which provides further safety evidence for ibrutinib. This is a substantial and robust dataset for a rare disease where few clinical trials have previously been conducted.

All three clinical studies have robust internal validity as demonstrated by strong critical appraisal scores. The comparative phase III study, RAY (MCL3001), is a high-quality study. It is open label in design due to the different modes of drug administration; however, outcomes were assessed by an IRC blinded to randomisation in order to avoid bias. Investigator-assessed outcomes were robust and demonstrated a significant efficacy benefit with ibrutinib over TEM[36].

Considerations for potential limitations of the evidence base

Overall survival estimates

Although ibrutinib OS in RAY (MCL3001) showed a trend towards improvement, median OS has not yet been reached at the time of clinical cut-off. A non-statistical difference was observed, potentially due to two confounders: 1) the crossover of 23% of patients from the TEM arm to the ibrutinib arm during the study. Specifically, crossing over to an effective salvage treatment might have affected PPS in the TEM group; 2) subsequent systemic therapies were received more frequently in the TEM group than in the ibrutinib group (see Table 20). Consequently, the benefit of ibrutinib compared to TEM in RAY (MCL3001) could be better captured by PFS2[36]. Furthermore, the study was not powered to show a statistical OS benefit at the time of clinical data cut-off. A more mature data cut for OS from RAY (MCL3001) is anticipated in November 2016 where a significant OS benefit for ibrutinib compared to TEM is expected.

Comparative evidence versus current clinical practice

The pivotal comparative phase III study, RAY (MCL3001), compares ibrutinib to TEM. TEM is not recommended by NICE for R/R MCL[55] and expert opinion from clinicians experienced in the treatment of MCL in the UK within an Advisory Board suggested that is not used in clinical practice[12]. As detailed in Section 1.1, TEM was chosen as comparator in RAY (MCL3001) because it was the only agent licensed for R/R MCL by the EMA at the time of study conception, it is approved for this indication in several countries outside the EU and it is recommended by international treatment guidelines for R/R MCL (McKay 2012; Dreyling 2013). There is no SOC for the treatment of R/R MCL in the UK as described in Section 3.4. Expert haematologists have suggested that the most relevant comparator for ibrutinib in UK clinical practice is R-CHOP (R-CVP or R-Chl can be used in frail patients)[12]. No direct evidence is available comparing ibrutinib to R-CHOP and no published trials are available for R-CHOP or other R-chemo regimens in R/R MCL, which places limitations on estimation of comparative effectiveness of ibrutinib and current clinical practice. Due to the lack of available data for the comparators, estimates of comparative effectiveness to current clinical practice were restricted to a Bucher ITC between the RAY (MCL3001) study and the PC arm of Hess, 2009. As previously noted, the PC arm of Hess, 2009 did not reflect the use of rituximab in current clinical practice, representing a limitation of this analysis. A 'rituximab effect' derived from the HMRN audit was therefore applied to the HR resulting from the ITC in order to address this concern in the economic analysis. Whilst we acknowledge the

limitations of this approach, this was used as a direct result of the paucity of data available for R-chemo, an unlicensed treatment, in a disease area with high unmet need such as R/R MCL. This is uncertainty that we as Janssen can do little about as we could not design an international clinical trial using an unlicensed comparator arm.

Trial populations

As expected in clinical trials, the study populations exclude patients with significant CV disease, those taking warfarin, patients with prior malignancy, patients with significant infection and those with a poor performance score. Given that patients with MCL are generally older, a proportion of patients will fall into these categories and there is a lack of clinical trial evidence in terms of efficacy and safety for these patients. The SmPC notes that warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib. 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[25].

Additionally, the studies were carried out around the world and only 48 patients in the study programme were from the UK (nine UK sites enrolled 27 patients into RAY [MCL3001]; four UK sites enrolled 15 patients into PCYC1104 and two UK sites enrolled 6 patients in SPARK [MCL2001]).For the most part, however, patients were recruited from countries with similar demographics to the UK (Europe, North America). In addition, feedback from the advisory board [12] was that the clinical trial data for ibrutinib is generalisable to clinical practice, with the only major difference being that in clinical practice clinicians would likely use ibrutinib at first relapse (i.e. after fewer prior LOTs than as observed in RAY [MCL3001)]). Further support for the generalisability of the RAY (MCL3001) study results is provided by a comparison of TOT in this study and in the CUP study presented in Section 4.11.3. The CUP, which recruited 715 patients in total, included 154 patients from the UK and found a similar TOT to that observed in the RAY (MCL3001) RCT[40, 41]. Furthermore, the US cohort of the EAP[80] provides 'real world' experience of ibrutinib treatment, as it included a wider range of patients than in the clinical study programme. Specifically, 10% of patients (n=15) received medications of special interest, which included antithrombotic agents, aspirin, filgrastim and blood transfusions. The safety profile of ibrutinib observed in the US cohort of the EAP and the CUP in the UK were consistent with that observed during the clinical trials for ibrutinib and no new safety signals were noted.

4.14.3 *End-of-life criteria*

Table 50: End-of-life criteria

<table>
<tr><th>Criterion</th><th>Data available</th></tr>
<tr><td>The treatment is indicated for patients with a short life expectancy, normally less than 24 months</td><td>UK data from HMRN reveals that median OS was 8.4 months in patients with R/R disease who achieved a response to first-line treatment (n=57)[7].
This is supported by data from two additional sources:
Median OS of 9.7 months in patients receiving PC in a phase III trial by Hess, published in 2009, comparing TEM with PC[8]
Median OS of 5.2 months in a real-world registry of patients treated at the Skåne University Hospital in Sweden between 2000 and 2012[9]
These data provide survival estimates of approximately 5-10 months in current UK clinical practice, well below the life expectancy criterion of 24 months, see Table 51.</td></tr>
<tr><td>There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment</td><td>The pooled analysis of the RAY (MCL3001), SPARK (MCL2001) and PCYC1004 studies found a median OS estimate of 25 months for patients receiving ibrutinib[5]. This is considerably greater than the 5-10 month estimate of survival in clinical practice (see above).

Available literature within MCL indicates that PFS provides a good surrogate for OS and this approach has previously been accepted within front-line MCL[13, 14]. It is therefore helpful to also consider estimates of PFS on ibrutinib with those from sources reflective of clinical practice.

Table 51 provides a summary of the OS and PFS estimates for ibrutinib from the RAY (MCL3001) study and the pooled analysis compared to estimates reflective of routine clinical practice. By measures of both PFS and OS, ibrutinib demonstrates a greater than three month extension to life based on these data.

Table 51: PFS and OS to support end-of-life criteria 1 and 2
<table>
<tr><th></th><th>Median PFS (months)</th><th>Median OS (months)</th></tr>
<tr><td>Ibrutinib, RAY (MCL3001)</td><td>14.6</td><td>NR</td></tr>
<tr><td>Ibrutinib, pooled analysis[5]</td><td>12.81</td><td>25.00</td></tr>
<tr><td>HMRN</td><td>NA</td><td>8.4</td></tr>
<tr><td>PC, Hess, 2009</td><td>1.9</td><td>9.7</td></tr>
<tr><td>Skåne registry</td><td>2.8</td><td>5.2</td></tr>
</table></td></tr>
<tr><td>The treatment is licensed or otherwise indicated for small patient populations</td><td>The number of patients with R/R MCL eligible to receive ibrutinib in England, Wales and Northern Ireland in 2017 is estimated to be 356 (see Section 6). This equates to a patient population smaller than 1 in 50,000. The incidence of CLL is estimated at 7 per 100,000 in England and only 7% of people diagnosed with CLL have the 17p deletion or TP53 mutation described in ibrutinib's licence[81, 82]. Waldenstrom's macroglobulinaemia, the other condition for which ibrutinib holds a marketing authorisation, has an estimated incidence of 0.55 per 100,000. Therefore, the size of the combined population for which ibrutinib is licensed is small[83].</td></tr>
<tr><td colspan="2">HMRN: Haematological Malignancy Research Network, OS: overall survival, NHS: National Health Service, PC: Physician's Choice, NR: not reached, NA: not available</td></tr>
</table>

4.15 ***Ongoing studies***

- RAY (MCL3001) is ongoing with the last study visit planned for the 24th November 2016
- Long-term follow-up data for SPARK (MCL2001) are expected to be published in 2016.

5 Cost effectiveness

Summary

A *de novo* economic model was constructed to assess the cost effectiveness of ibrutinib for the treatment of patients with R/R MCL versus R-CHOP, FCR, R-CVP and RC. Whilst there is no SOC for R/R MCL, R-CHOP was considered the key comparator based upon clinical expert advice. A standard three health-state model was used (pre-progression, progression and death). In order to avoid potentially over-optimistic assumptions regarding benefit for PPS, progression status was used as a surrogate marker for OS and PPS was assumed to be the same for ibrutinib and R-chemo.

The model was informed by OS, PFS and TOT data from the pooled dataset using the RAY (MCL3001), SPARK (MCL2001) and PCYC1104 clinical trials for ibrutinib (described in Section 4.12). Whilst there is a substantial evidence base of data to demonstrate the effectiveness of ibrutinib in R/R MCL, data availability for treatments currently in use in clinical practice (all unlicensed) is limited. Substantial efforts were made to source comparator data suitable to undertake analysis, which resulted in comparison being made to two available datasets and applied as one generic effectiveness estimate of R-chemo. This estimate was then used to inform each single comparator in the NICE scope, i.e. R-CHOP, FCR, R-CVP and RC. Within the model base case, comparison was undertaken versus reported outcomes from an ITC conducted using Hess et al, 2009 and data from the TEM arm of the RAY (MCL3001) study which was used as a proxy for R-chemo. Whilst both data sources available for comparison have limitations, the small variability in CEA results should provide reassurance regarding the cost-effectiveness of ibrutinib in this indication.

Patient HRQoL was modelled using EQ-5D utilities reported by patients in the RAY (MCL3001) and SPARK (MCL2001) trials, with the impact of R-chemo toxicity on HRQoL taken from expert clinical advice and compared to available published literature. Costs were obtained from common UK sources; eMit and MIMs were used to inform drug costs and NHS reference costs to inform resource use costs. As patients progressed through the health states within the model, they incurred costs associated with drug acquisition, drug administration, healthcare visits and managements of AEs. Routine follow-up care costs in PFS were assigned according to the distribution of patients' best overall response to treatment.

Based upon the *de novo* economic model constructed, ibrutinib was estimated to generate an additional 1.23 life years and 0.94 QALYs. This represents a substantial improvement to both length and QoL for patients with an extremely poor prognosis. The mean life years estimated for patients treated with ibrutinib are double those of therapies currently used in clinical practice (see Table 51). Comparing model projections to the only data source available for the OS of patients at second-line in the UK demonstrated the highly conservative nature of the estimates presented.

Key uncertainties in the CEA surrounded the parametric curve fits to the ibrutinib PFS and TOT data; however the use of different curve fits had a limited impact on the overall outcomes of the analysis. Overall, the majority of uncertainty within the CEA related to the estimated QALYs gained (as opposed to the costs encountered from treatment); however, in all cases a substantial QALY improvement is expected for ibrutinib patients compared to those treated with R-chemo (between 0.6 and 1.4 QALYs).

5.1 *Published cost-effectiveness studies*

5.1.1 *Systematic literature review*

A combined economic SLR was performed to identify cost-effectiveness or cost and resource use studies relevant to the decision problem. A separate SLR was performed to identify HRQoL evidence. The aim of the SLRs was to obtain any economic evidence (cost-

effectiveness analyses, cost studies and HRQoL data in the form of utilities) available in the published literature. Similar to the clinical SLR, these searches were conducted before the final scope of this appraisal was determined[49]. A number of interventions that are not relevant to this submission were therefore considered eligible for inclusion in the SLRs; however, all interventions listed in the NICE final scope were captured in the list of eligible interventions (R-CHOP, FCR, R-CVP and RC).

5.1.2 ***Search strategy***

A similar search strategy to that used for the clinical SLR (see Section 4.1.2) was used for the economic SLR. The economic SLR searched the same databases as that searched in the clinical SLR, but additionally searched EconLit and the NHS Economic Evaluation Database (NHS EED). Similarly to the clinical SLR, any identified high quality SLRs published since 2011 served as supplemental data sources through reviews of their bibliographies for potentially relevant references. Congress searching was also performed, with the same five congresses searched as described for the clinical SLR in Section 4.1. As for the clinical SLR, the ASH 2015 congress and ECC 2015 congress were searched as part of an update to the congress searches in February 2016.

The full search strategy is provided in Appendix 12.

5.1.3 ***Study selection***

An identical methodology for study selection as used for the clinical SLR (see Section 4.1.2) was used for the economic and HRQoL SLRs in terms of the review process and the use of PICOS eligibility criteria for screening of identified articles. Inclusion and exclusion criteria specific to the economic and HRQoL SLRs are reported in Table 52. Non-English language studies were considered in the same manner as described for the clinical SLR and the comparator eligibility criteria were similarly only employed for the full text screening stage (not the screening of titles and abstracts).

Table 52: Inclusion criteria for economic and HRQoL studies

Criterion	Inclusion criteria	Exclusion criteria
Population	R/R MCL patients	Patients without at least 85% R/R MCL, i.e. studies involving treatment-naïve MCL patients, other lymphoma subtypes, or patients receiving first/front-line therapies
Interventions / Comparators (applied at full text screening)	• Ibrutinib monotherapy • Ibrutinib combination therapy • Bendamustine and rituximab (BR) • Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) • FC ± M (fludarabine, cyclophosphamide and mitoxantrone) • Fludarabine + (bendamustine or cisplatin or chlorambucil or rituximab or cyclophosphamide) • Chlorambucil + rituximab • Bortezomib monotherapy ± rituximab • Bleomycin monotherapy • Vinblastine monotherapy • Dacarbazine monotherapy • Temsirolimus monotherapy • Doxorubicin monotherapy • Rituximab monotherapy • R-DHAP ± low-dose aracytine (rituximab, dexamethasone, cyatarabine and cisplatin) • Lenalidomide monotherapy • Rituximab and cytarabine (RC) • Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CVP)	

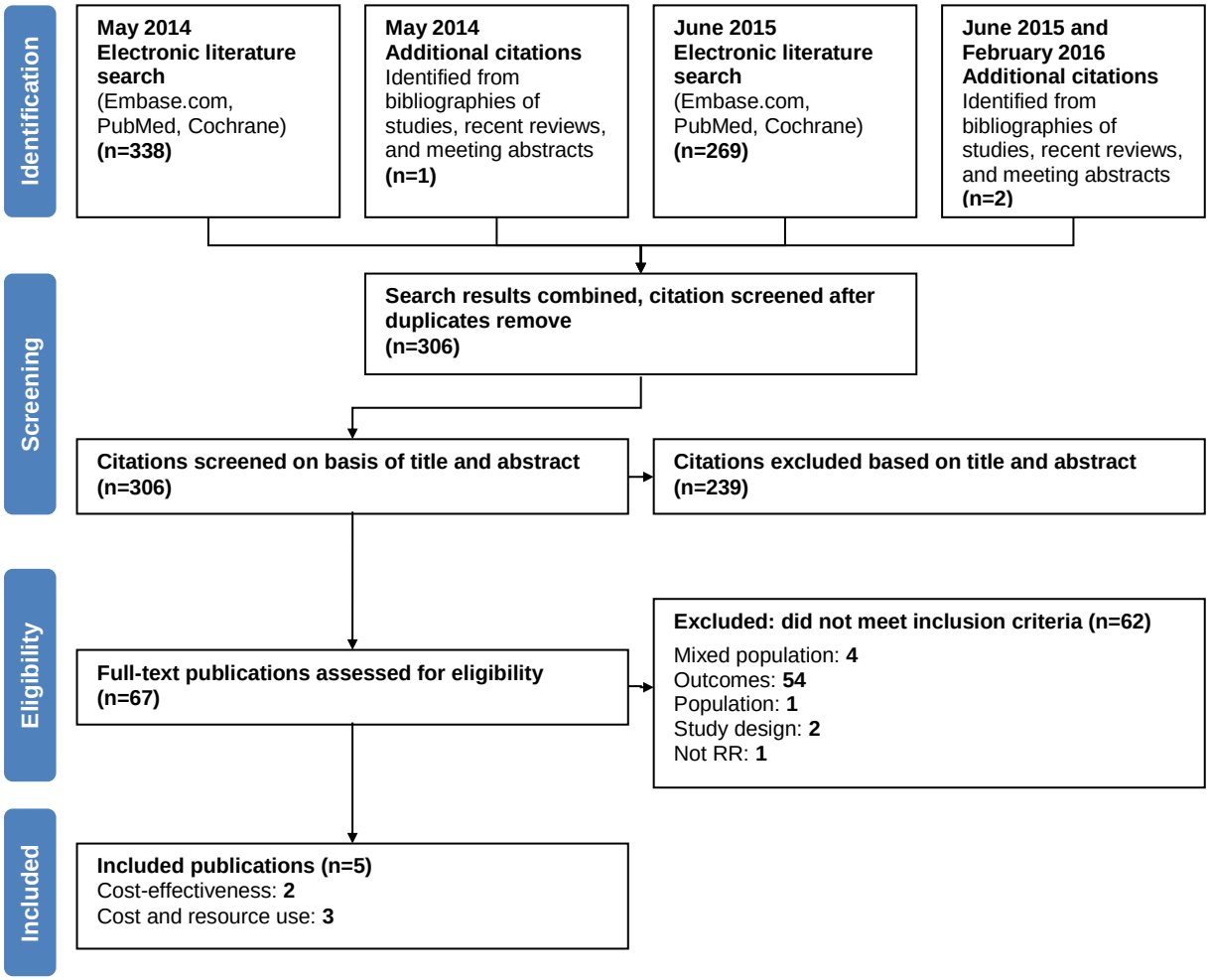
Outcomes	• Value or change in value of PRO/HRQoL scores
	• Economic-related outcomes
	  ○ Quality-adjusted life-years (QALYs)
	  ○ Incremental cost-effectiveness ratio (ICER)
	  ○ Medical resource use and related costs
	  ▪ Emergency room visits
	  ▪ Specialist visit
	  ▪ Rehabilitation visit
	  ▪ Nursing care at home
	  ▪ Hospitalisation
	  ▪ Tests and scans
	  ▪ Procedures
	  ▪ Premedication
	  ▪ Prophylactic medications
	  ○ Intervention-related costs
	  ▪ Drug and drug administration (intervention and prophylactic medications)
	  ▪ Routine care and follow-up
		Publications that do not report economic outcomes, PROs, or HRQoL outcomes for R/R MCL specifically

Criterion	Inclusion criteria	Exclusion criteria
	▪ AEs ▪ Indirect costs ▪ Cost of subsequent treatment ○ Disease progression/end-of-life-related costs ▪ Medication ▪ Inpatient care ▪ Outpatient care ▪ Emergency room visit ▪ Specialist visit ▪ Staff nurse ▪ Procedures ○ Baseline utility ○ Utility increment due to response ○ Post-progression utility decrement ○ Utility increment due to PFS in subsequent line of treatment ○ Disutility of AEs ○ Conclusions • PROs or HRQoL outcomes • PRO or QoL elicitation • Mapping: Yes/No/not applicable (NA) • Valuation • Description of health states and/or AEs • QoL score or change in score with confidence intervals (CIs) or variance estimates • Patient preference score or change in score with CIs or variance estimates • Uncertainty around values • Consistency with reference case • Appropriateness of health states given condition and treatment pathway • Appropriateness of the study for cost-effectiveness analysis • Trend-related to PROs over time • Impact of pharmacological treatments on PROs from real-world studies • Factors associated with impaired PROs	
Study design	• Prospective interventional trials • Observational studies • Retrospective analyses, health technology assessments (HTAs), economic or modelling studies	• Narrative publications, non-systematic reviews, case studies, case reports, and editorials • Non-English, full-text articles or articles without an abstract published in English
Other	English language	Non-English language
AE: adverse event, HRQoL: health-related quality of life, MCL: mantle cell lymphoma, PRO: patient reported outcomes, QoL: quality of life.		

5.1.4 *PRISMA flow diagram for the economic SLR*

After the initial removal of duplicate citations, 306 abstracts were screened according to the pre-specified inclusion and exclusion criteria. Of these, 239 studies were excluded at the abstract level. Among the 67 studies remaining, 62 citations were rejected following further application of the inclusion/exclusion criteria to full-text citations. Five citations met all SLR inclusion and exclusion criteria. A PRISMA (flow diagram) presenting the results of the SLR is provided in Figure 28.

Figure 28: PRISMA flow diagram economic analyses studies



Two studies that reported cost-effectiveness outcomes for a health technology in MCL were identified, but neither of these was relevant to decision-making in the UK. Yoong *et al.* 2009 assessed the cost effectiveness of bortezomib vs FCM and Lachaine *et al.* 2013 assessed the cost effectiveness of BR compared to fludarabine + rituximab[84, 85]. Neither of these studies assess interventions relevant to the NICE scope and both were conducted in the Canadian setting. A summary of these two studies, including individual quality assessments, is provided in Appendix 13.

Cost and resource use papers identified as part of the economic SLR and HRQoL papers identified as part of the HRQoL SLR are discussed in Section 5.5.1 and Section 5.4.3, respectively.

As none of the studies identified within the literature review were directly relevant to the decision problem specified by NICE a *de novo* economic model was constructed.

5.2 *De novo analysis*

5.2.1 *Patient population*

The Phase III RAY (MCL3001) study alongside two Phase II single-arm studies (PCYC1104 and MCL2001) are the key clinical data used to inform the effectiveness of the ibrutinib arm within the economic model. These studies are presented in detail in Section 4. All three clinical trials were conducted within a similar patient population, rendering it appropriate to combine data from all three trials (hereafter referred to as the pooled dataset). The specification that patients in SPARK (MCL2001) had to be previously treated with bortezomib was not considered likely to be prognostic of a different treatment effect; in fact results in subgroups of patients with prior bortezomib treatment vs no prior bortezomib treatment were very similar in PCYC1104 (see Section 4.11.1.7). Clinicians' advice was therefore that the pooled dataset is the most robust and generalisable evidence base for ibrutinib to be used in the economic analysis in terms of patient numbers, length of follow-up and inclusion of patients at all levels of fitness[12]. Data from the pooled ibrutinib trials are therefore used within the model.

Feedback from the advisory board held by Janssen was that patients in the Phase III and Phase II ibrutinib trials can be considered similar to those expected to be observed in UK clinical practice[12]. The similarity of results in these trials to those observed in real-world clinical practice is also reflected in the CUP (see Section 4.11.3).

The only key difference noted between the patient population included within the ibrutinib clinical trials and expected clinical practice in the UK was that clinical experts expect ibrutinib to be given at first relapse for most UK patients. This expectation was based upon the subgroup analysis presented in Section 4.8.2, which demonstrates the benefits of ibrutinib when used earlier in the treatment pathway[12]. In comparison, patients within the Phase III and Phase II trials received a median of two prior LOTs in RAY (MCL3001) and SPARK (MCL2001) and three prior LOTs in PCYC1104. Subgroup analysis is therefore presented for patients according to the number of prior LOTs received (1 prior LOT, >1 prior LOT). All information relating to the subgroup analysis model inputs is presented in Appendix 14.

The baseline characteristics obtained from the pooled dataset were used to inform the economic model, thereby providing a median age of 68 and male/female ratio of 78%/22% (see Table 39).

5.2.2 *Model structure*

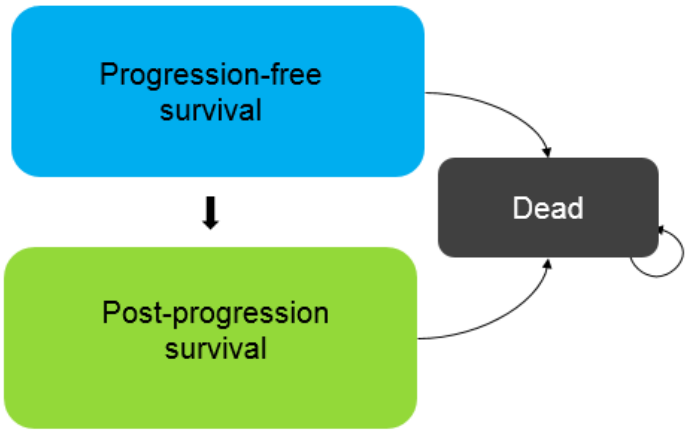
A *de novo* CEM was developed to assess the cost-effectiveness of ibrutinib in the UK for the treatment of R/R MCL. The CEM was developed using a Markov health-state structure, comprising three health states: pre-progression, post-progression and death (Figure 29). This modelling approach is a routinely accepted structure within oncology, and has been used and accepted in many previous oncology models in lymphoma for HTA[15, 86-88]. A standard Markov model structure lends itself to health conditions such as R/R MCL that can be defined by distinct stages of disease (e.g. progression-free, post progression), as these stages can be characterised by mutually exclusive Markov health states between which patients can transition upon defined clinical events, such as disease progression.

Costs and health effects (i.e. utility values) were assigned to each health state. HRQoL data were obtained from EQ-5D data captured in two of the three trials included in the pooled dataset (RAY [MCL3001 and SPARK (MCL2001)]). Costs were obtained from common UK sources; eMit and MIMs were used for drug costs and NHS reference costs for resource use costs. All costs reflect 2014/2015 prices, as these were the most recently available. As

patients progressed through the health states within the model, they incurred costs associated with drug acquisition, drug administration, healthcare visits and management of AEs. Routine follow-up care costs in PFS were assigned according to the distribution of patients' best overall response to treatment.

A 4-week model cycle was used, based on the 4-week dosing schedule for most of the relevant comparators. The CEM applied a 15-year time horizon, which was considered long enough to capture the long-term clinical and economic consequences of R/R MCL, an incurable disease requiring treatment until the end of life, while still minimising the uncertainty that can be introduced by modelling clinical and economic outcomes beyond trial periods.

Figure 29: Model diagram



While an extensive clinical trial program is available to support modelling of the effectiveness of ibrutinib, data to support the effectiveness of the comparators detailed in the final NICE scope are limited. The pivotal comparative Phase III study, RAY (MCL3001), compares ibrutinib to TEM. As explained in previous sections, although TEM is the only treatment other than ibrutinib licensed for R/R MCL in Europe, it is not recommended by NICE, and expert opinion from clinicians experienced in the treatment of MCL in the UK gathered at an Advisory Board suggested that TEM is not used in clinical practice[12, 55].

No RCT (or high quality observational data) is available for any of the comparators listed in the NICE scope. Two approaches were therefore tested to estimate effectiveness for comparator therapies based upon the available evidence, as detailed in Section 5.3.

Data from the HMRN are available on OS for English patients receiving their first treatment for R/R MCL. Data are not, however, available for PFS; therefore alternative primary sources of information were required in order to conduct comparison to R-chemo.

In all cases, the effectiveness of R-chemo is modelled as a group as data are not available for individual treatment regimens at this LOT. Clinical experts consulted expected that the three comparator therapies used in UK practice would rank as follows in terms of effectiveness (most effective first): R-CHOP, R-CVP, FCR (clinical experts advised that RC is not used for R/R MCL but only in newly diagnosed patients who are fit enough to receive it).

- Within the CEM base case, the effectiveness of R-chemo was based on information on the effectiveness of the PC arm in Hess, 2009 via the ITC described in Section 4.10[8]. Given that the PC arm in Hess, 2009 was composed of single chemotherapy

agents, the treatment effect from the ITC was adjusted to account for the addition of rituximab based on information on the benefit of R-chemo vs single agent chemotherapy derived from the HMRN audit[7].

- A scenario analysis was performed assuming that R-chemo has the same efficacy as TEM within RAY (MCL3001), as described in Section 4.
- Testing the PPS of R-chemo by keeping PFS fixed and altering the risk of death during PPS per cycle in R-chemo, minimising the difference between the modelled median OS and observed median OS in HMRN. This produced the PPS required in order for median OS of R-chemo to equate to the one observed in the HMRN audit.

Table 53 summarises the strengths and weaknesses of the two approaches. Due to the uncertainty surrounding these two approaches considerable sensitivity analysis testing is conducted including:

- Threshold analysis to determine how effective R-chemo would need to be in order for ibrutinib to no longer be cost-effective
- Testing the PPS of R-chemo by keeping PFS fixed and altering the risk of death during PPS per cycle in R-chemo, minimising the difference between the modelled median OS and observed median OS in HMRN. This produces the PPS required in order for median OS of R-chemo to equate the one observed in the HMRN audit

Table 53: Approaches taken to estimate comparative efficacy

	Scenario 1 **Hess and RAY (MCL3001) ITC[8]**	**Scenario 2** **Efficacy of TEM (MCL3001)**
Approach	• Using results of an ITC between a published RCT including a PC arm and RAY (MCL3001). Results of the ITC are adjusted for the expected impact of rituximab from HMRN data	• Assuming R-chemo is equivalent to TEM within RAY (MCL3001)
Strengths	• Provides a comparison to R-chemo • Use of a formal ITC maintains randomisation and provides a statistically robust comparison	• Uses information directly from the ibrutinib RCT undertaken in a R/R MCL population • Use of treatment effect from RAY (MCL3001) provides a statistically robust comparison
Weaknesses	• Single chemotherapy agents as used in Hess, 2009 do not reflect standard UK clinical practice • The HR for the rituximab treatment effect is based on a different population sample in newly diagnosed MCL (HMRN data) – these data can be viewed as an upper bound for the effectiveness of the addition of rituximab to chemotherapies in R/R MCL	• TEM is not a relevant comparator in UK clinical practice • No evidence is available to determine whether TEM is more or less effective than R-chemo
ITC: indirect treatment comparison, RCT: randomised controlled trial, PC: physician's choice, R-chemo: rituximab plus chemotherapy, HMRN: haematological malignancy research network, R/R MCL: relapsed or refractory mantle cell lymphoma, TEM: temsirolimus		

While UK experts in the treatment of MCL were confident that ibrutinib would provide a PFS benefit compared to current clinical practice, there was less consensus on what degree of

PPS benefit could be expected. In order to test the impact of the uncertainty around the PPS benefit with ibrutinib compared to clinical practice, two approaches were tested to estimate the long-term OS projection of ibrutinib and R-chemo in the CEM:

1. **Method 1 (base case, '*fixed PPS*'):** PFS + PPS (applied in the same way in both arms). This method is the most conservative and has previously been accepted by NICE[13]. It involves removing the second PFS period (PFS of R-chemo after PFS of ibrutinib described above) from the ibrutinib arm. It therefore assumed that patients will not experience any benefit from the additional treatment options that are available to them due to the use of ibrutinib rather than R-chemo after relapse.

2. **Method 2 (base case, '*sequential approach*'):** PFS of ibrutinib + PFS of R-chemo after ibrutinib (i.e. patients in PFS on next LOT) + PPS. This method was suggested during the advisory board. It aims to capture the fact that R-CHOP is currently seen as the most effective chemotherapy regimen, but that its use as an initial treatment at second line precludes its use further along the treatment pathway, which means that other less effective chemotherapy regimens need to be administered. Increased use of R-CHOP at second line also reflects the fact that BR is no longer available via the CDF or any funding mechanism. Ibrutinib allows a further LOT, and this is captured in this sequential method.

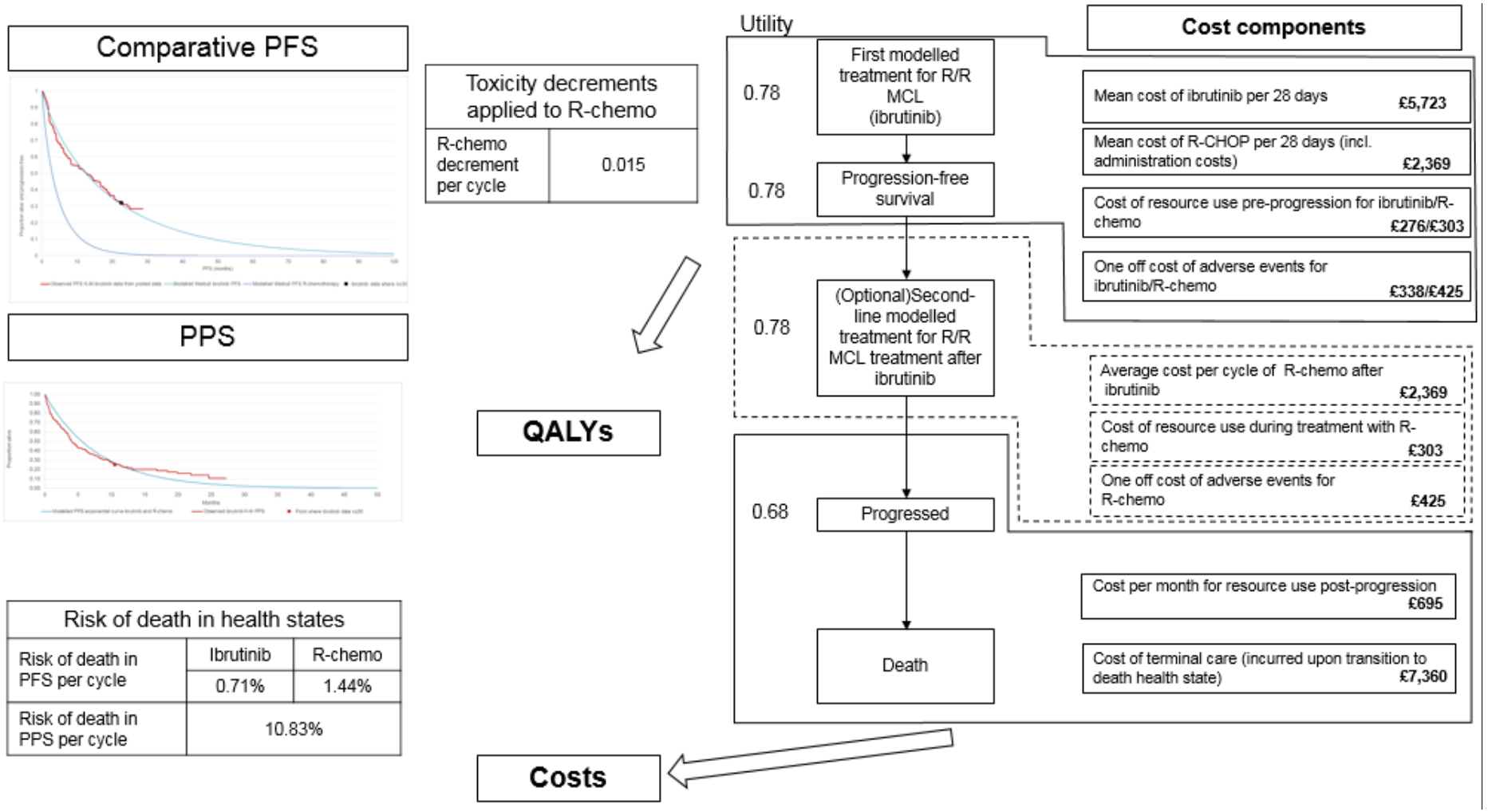
OS trial data were not directly extrapolated due to uncertainty around comparative OS estimates. In particular, ibrutinib data are still relatively immature with median OS only just reached within the pooled dataset and not yet reached within two of the constituent trials. Within the datasets used for comparator effectiveness, OS with TEM is contaminated as 23% of patients cross over to ibrutinib and a significant amount of patients receiving effective salvage therapies after progression. It is unclear what subsequent therapies are used within the Hess 2009 data and the impact of rituximab use on long-term outcomes for R/R MCL is equally unclear. A substantial amount of PFS data is instead available from all ibrutinib trials and these data are mature. It is expected that PPS with ibrutinib is at least as good as what is expected within clinical practice after R-chemo (see Section 4.7.2.2). Scenario analysis is provided using the one dataset which provides clearly relevant data for OS (HMRN data) to test uncertainty surrounding the assumption of equal PPS.

The CEM was designed to represent the decision problem from the perspective of the NHS in the UK. A half-cycle correction was used to adjust for the distribution of costs and benefits accrued throughout the cycle. The main features used in the CEM are reported in Table 54. An overall summary diagram of the model is presented in Figure 30.

Table 54: Features of the *de novo* analysis

Factor	Chosen values	Justification
Time horizon	15 years	Time horizon was considered long enough to capture the long-term clinical and economic impacts of MCL (100% of patients estimated to have died at this time point in both arms of the model)
Were health effects measured in QALYs; if not, what was used?	QALYs	NICE reference case[89]
Discount of 3.5% for utilities and costs	Yes	NICE reference case[89]
Perspective (NHS/PSS)	NHS England and Wales	NICE reference case[89]
PSS, personal social services; QALYs, quality-adjusted life years		

Figure 30: Model summary diagram



5.2.3 *Intervention technology and comparators*

The CEM considered four comparators in line with the requirements of the final NICE scope; R-CHOP, R-CVP, FCR and RC. As detailed in Section 3.4, there is no SOC in the UK for the treatment of R/R MCL; of the four comparators included within the NICE scope, R-CHOP is most frequently used at second-line for fit patients, whereas R-CVP is used in frail patients. FCR is only used by a minority of clinicians, and RC was not considered a relevant comparator during a recent advisory board (feedback was that this would only be used in first line patients fit enough to tolerate it).

The dosing of ibrutinib has been implemented within the model in accordance with its market authorisation[25]. The dosing regimens of comparators were obtained from the available literature; dosing for R-CHOP, R-CVP and FCR was confirmed with UK clinicians at the advisory board. The dosing schedules used for each therapy or combination are summarised in Table 55.

Treatment with ibrutinib should continue until disease progression or no longer tolerated by the patient[25]. In order to model drug costs, parametric survival curves were fitted to the observed TOT for ibrutinib within the clinical trials. This method accurately captures the discontinuation of patients observed within the pooled dataset which was in line with the treatment duration specified within the ibrutinib SmPC. Due to lack of alternative data, patients receiving R-chemo were assumed to discontinue treatment at the same rate as ibrutinib within the fixed treatment duration recommended for each R-chemo regimen (i.e. the same HR observed for PFS between ibrutinib and R-chemo was applied to TOT).

Table 55: Dosing regimen and continuation rules for intervention and comparators

Treatment	Dosing Regimen	Source	Continuation rules implemented in the model
Ibrutinib	560 mg/day (4 capsules) daily	Ibrutinib SmPC[25]	Based on TOT trial data
R-CHOP	• Rituximab: 375mg/m^2 IV on day 1, every 21 days for 6 cycles • Cyclophosphamide: 750mg/m^2 IV on day 1, every 21 days for 6 cycles • Doxorubicin: 50mg/m^2 IV on day 1, every 21 days for 6 cycles • Vincristine: 1.4mg/m^2 IV on day 1, every 21 days for 6 cycles • Prednisolone: 100 mg po on days 1-5, every 21 days for 6 cycles	Rummel, 2013[90]	Patients continue treatment until disease progression or maximum treatment duration
R-CVP	• Rituximab: 375mg/m^2 IV on day 1, every 21 days for 6 cycles • Cyclophosphamide: 750mg/m^2 IV on day 1, every 21 days for 6 cycles • Doxorubicin: 50mg/m^2 IV on day 1, every 21 days for 6 cycles • Prednisolone: 100 mg po on days 1-5, every 21 days for 6 cycles	Flinn 2014[91]	Patients continue treatment until disease progression or maximum treatment duration
FCR	• Fludarabine: 30mg/m^2 IV on days	Badoux 2011, use dosing	Patients continue treatment until disease progression or

Treatment	Dosing Regimen	Source	Continuation rules implemented in the model
	1-3, every 28 days for 6 cycles • Rituximab: 375mg/m^2 IV on day 1, every 28 days for 6 cycles • Cyclophosphamide: 250mg/m^2 IV on days 1-3, every 28 days for 6 cycles	regimen for CLL as a proxy[92]	maximum treatment duration
RC	• Rituximab: 375mg/m^2 IV on day 1, every 28 days for 6 cycles • Cytarabine: 500mg/m^2 IV on days 2-4, every 28 days for 6 cycles	Visco, 2013 (Dosing taken from R-BAC removing bendamustine from the regimen)[93]	Patients continue treatment until disease progression or maximum treatment duration (assumed to be 6 cycles)
R-CHOP: rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone, CLL: chronic lymphocytic leukaemia, IV: intravenous, PO: per os (orally), R-BAC: rituximab, bendamustine and cytarabine, RC: rituximab + cytarabine.			

5.3 *Clinical parameters and variables*

5.3.1 *Clinical evidence from ibrutinib and comparators*

The pooled dataset described in Section 4.12 was used to inform the CEA for ibrutinib per clinicians' advice, as explained in Section 5.2.

Due to the lack of data available in the literature to support the use of any of the treatments currently used in UK clinical practice in R/R MCL and detailed in the NICE scope, modelling the effectiveness of comparator therapies was challenging[49]. Substantial efforts were made to source comparators' data suitable to undertake analysis including:

- Review of all available literature for R/R MCL including non RCT evidence and potential proxy comparators outside of the NICE scope and original SLR criteria (see Section 4.10 and Appendix 9)
- Consultation with clinical experts to identify any unpublished sources clinical data
- Sourcing data from the HMRN audit

After a thorough review of the data derived with the methods highlighted above, three key data sources were used to inform the effectiveness of R-chemo:

- *Hess, 2009:* this study was identified from the SLR conducted to identify clinical evidence in R/R MCL (see Section 4.1). This search identified only one RCT (Hess, 2009[8] - comparing TEM to PC) that could be used to create an ITC with ibrutinib (see Section 4.10).
- *TEM arm of RAY (MCL3001):* due to the lack of relevant existing evidence to inform the R-chemo arm of the model, data for TEM in RAY (MCL3001) were tested as an option for exploring comparative effectiveness. Although not being used in current practice, this analysis can serve as a reasonable proxy for current care in the UK
- *HMRN audit:* this was identified as a relevant source of data to inform the comparative efficacy of R-chemo within the CEA; however, no data are available for PFS in relapsed patients[7]. OS data were available for 57 patients after relapse, but

only a small proportion of these patients received treatments included within the NICE scope (n=17 receiving R-chemo; n=16 receiving either R-CHOP or FCR). The HMRN audit was used in two ways for the modelling:

1. OS has been used to validate projected outcomes for R-chemo in the CEM and within scenario analysis to determine the potential amount of PPS benefit for ibrutinib compared to UK clinical practice
2. To derive a relative treatment effect for patients receiving R-chemo compared to chemotherapy without rituximab.

As outlined in Section 5.2.2 the CEM considered three health states, PFS, PPS and dead. TOT was also modelled from clinical trial data to provide an accurate estimation of drug costs. Long-term TOT and PFS were estimated using parametric curves fit to the clinical trial data using standard methodology according to the NICE Decision Support Unit (DSU) guidance[94]. A fixed rate of death during PPS, derived by fitting an exponential distribution to the pooled dataset, was equally applied to both model arms.

Based upon the data identified, two alternative methodologies were undertaken to estimate the effectiveness of comparator therapies as detailed in Section 5.2.2. Both of these approaches estimated a PFS HR for R-chemo compared to ibrutinib to apply to long-term projections of the ibrutinib pooled dataset. OS was calculated in two different ways, which both assumed a fixed PPS period. Table 56 provides a summary of the application of the clinical trial data within the model. The two model approaches (fixed PPS and sequential approach) are described in Section 5.2.

Table 56: Application of clinical trial data within the model

Outcome	Definition	Application
PFS	Time to progression or death	*All approaches* • Ibrutinib: extrapolated parametric curve from PFS in pooled dataset • R-chemo: effectiveness calculated based upon the estimated HR compared to ibrutinib
TOT	TOT	*All approaches* • Ibrutinib: extrapolated parametric curve from TOT in pooled dataset • R-chemo: based upon the estimated HR for PFS vs ibrutinib
PPS	Time from progression to death for patients who progressed during the trial	*Fixed PPS approach* • Both arms: modelled by applying a fixed risk of death to patients in the PPS state (assumed the same in both arms) *Sequential approach* • Ibrutinib: PPS was split into PFS on R-chemo and PPS after R-chemo • R-chemo: PPS assumed the same as PPS after R-chemo on the ibrutinib arm (equal risk of death per model cycle)
Death	Absorbing state of patients that have died within the model	*All approaches* • Both arms: fixed risk of death in PFS state • Both arms: fixed risk of death in PPS state (assumed the same in both arms)

HR: hazard ratio, OS: overall survival PFS: progression-free survival, PPS: post-progression survival, R-chemo: rituximab plus chemotherapy, TOT: time on treatment.

5.3.2 ***Progression-free survival***

5.3.2.1 Progression-free survival of ibrutinib

PFS was modelled based upon parametric curves fitted to the patient level data from the pooled dataset for ibrutinib. NICE DSU guidance on survival analysis was followed to determine the best approach to extrapolation[94]. Based upon the log-cumulative hazard plot which indicated that the use of a standard parametric model was appropriate (plot shows as a reasonably straight line (see Appendix 15), the following curves were fitted:

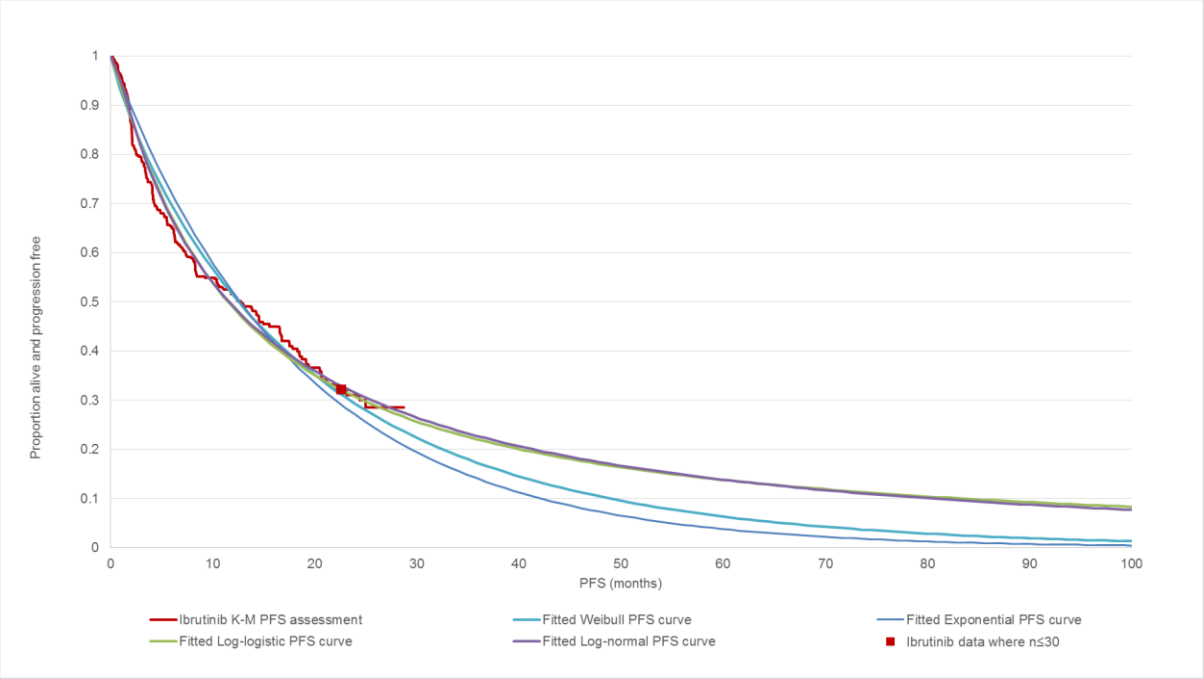
- Exponential
- Weibull
- Log-normal
- Log-logistic

IRC-assessed PFS was used within the model as this represented the primary endpoint within the ibrutinib trials and data from Hess, 2009 was also assessed using IRC. The parametric curve fits to the IRC-assessed PFS KM data are shown in Figure 31. IRC-assessed PFS was not available from PCYC1104 and therefore PFS-INV from PCYC1104 was pooled with IRC-assessed PFS from SPARK (MCL2001) and RAY (MCL3001).

The log-normal and log-logistic curves provide a better fit to the observed KM data both based upon the Akaike's information criterion (AIC), the Bayesian information criterion (BIC) statistics (see Appendix 15) and on visual inspection, however, all four curves provide a reasonably good fit to the data available.

The Weibull curve was selected for use within the base case, based upon clinicians' feedback, who noted that the long tails associated with log-normal and log-logistic curves were not clinically plausible: both these curves project that a 3-4% of patients remain alive and progression-free for up to 20 years[12]. The Weibull curve was selected over the exponential as the log-cumulative hazard plot indicated non-constant hazards (the main feature of the exponential model is a constant hazard) and the Weibull curve represented the next best fitting curve (after the log-normal and log-logistic curves based on the AIC statistic). The impact of alternative curve fit selection was tested within scenario analysis.

Figure 31: Ibrutinib KM data and modelled curve fits for PFS using IRC assessment



Ibr: ibrutinib, IRC: independent review committee, ITT: intention to treat, KM: Kaplan-Meier, PFS: progression-free survival.
Investigator-assessed PFS was used for PCYC1104 as was the only available.

5.3.2.2 Progression-free survival of R-chemo

Comparative efficacy was obtained by applying a HR to the relevant parametric curve selected. Two methods were used to estimate an appropriate HR:

- Hess, 2009 ITC using RAY (MCL3001) + HMRN rituximab effect (base case)
- TEM data from RAY (MCL3001) (scenario)

Comparative PFS of R-chemo: base case

The first method, forming the base case of the analysis, used evidence available from the SLR conducted to identify clinical evidence for comparators in the R/R MCL setting. This search identified only one RCT (Hess, 2009[8] - comparing TEM to PC) that could be used to create an ITC with ibrutinib (see Section 4.10) using the TEM arm in Hess, 2009 and RAY (MCL3001) as common link for comparison. The HR derived via the ITC using the ibrutinib data from RAY (MCL3001) was applied to ibrutinib in the pooled dataset. This assumes that the treatment effect derived from the RAY (MCL3001) trial can be extrapolated to the pooled dataset. This assumption is considered reasonable given the consistency of outcomes observed within the three ibrutinib clinical trials and feedback from the advisory board[12].

The treatments within PC in Hess, 2009 only included single chemotherapy agents. As rituximab is used in routine UK clinical practice, the HR of ibrutinib (from the pooled dataset) versus PC was adjusted to account for the increased effectiveness expected by clinical experts with the addition of rituximab to chemotherapy.

Potential data sources to inform the impact of rituximab on MCL outcomes were identified based upon literature identified from the clinical SLR conducted for this submission and the

MCL SLR conducted by NICE as part of their draft Clinical Guidance of NHL[50], in addition to data available from the HMRN[7].

The evidence available was not conclusive regarding the potential benefit of the addition of rituximab to chemotherapy on PFS (or similar outcomes such as time to 2nd line treatment and event free survival). None of the studies identified reported a significant PFS benefit from the addition of rituximab to chemotherapy. Additionally, all available evidence is from literature on first-line MCL and the impact of adding rituximab to chemotherapy is likely to be lower for patients with R/R MCL as the majority will already have received rituximab at first-line. The HRs retrieved to inform the effect of adding rituximab in PFS are shown in Table 57 (from the most relevant to the least relevant).

The final PFS HR estimated for ibrutinib versus R-chemo using data from ITC plus the effect of adding rituximab was 0.28, based the HR derived from Hess, 2009 equal to 0.19 and the HR for the treatment effect of adding rituximab (0.69): 0.19 * (1/0.69) = 0.28. This was used in the base case of the economic analysis.

In order to provide a conservative estimate of the relative benefit of ibrutinib versus R-chemo the HR obtained from the HMRN audit which reports the impact of using rituximab versus no rituximab as part of chemotherapy on PFS at first-line based upon data adjusted for age at diagnosis and sex was used within the economic model (HR = 0.69)[7].

The final PFS HR estimated for ibrutinib versus R-chemo using data from ITC plus the effect of adding rituximab was 0.28 (0.19. This was used in the base case of the economic analysis.

Table 57: Evidence available for the estimation of the impact of adding rituximab to chemotherapy on PFS outcomes in MCL

Source/type	HR, CI, p	Quality of evidence
HMRN adjusted: rituximab chemotherapy excl. ASCT **Base case**	0.69 (0.42-1.13)	• UK evidence & treatments included relevant to the scope • Statistical adjustment included for differences in patient characteristics • First line MCL • PFS not measured in the same way as in ibrutinib trials • Sample size n=118
HMRN unadjusted: rituximab chemotherapy excl. ASCT	0.75 (0.46-1.22)	• UK evidence & treatments included relevant to the scope • No statistical adjustment included for differences in patient characteristics • First line MCL • PFS not measured in the same way as in ibrutinib trials • Sample size n=118
Griffiths: Time to 2nd line treatment in multivariate analysis	0.89: 95% CI 0.67-1.20: P=0.46	• US evidence • Exact treatment regimens included unclear but most appear relevant • Statistical adjustment included for differences in patient characteristics • First line MCL • Sample size n=638
Kang: event free survival	1.60, 95% CI:	• Korean evidence

Source/type	HR, CI, p	Quality of evidence
(time to failure or death from any cause)	0.93-2.75	• Treatments used mostly in line with UK practice • Unclear whether HRs reported are from multivariate or univariate analysis • Sample size n=131
ASCT: autologous stem cell transplantation, CI: confidence interval, HR: hazard ratio, MCL: mantle-cell lymphoma, PFS: progression-free survival, HMRN: Haematological Malignancy Research Network		

Comparative PFS of R-chemo: scenario analysis

The alternative option to obtain comparative effectiveness for PFS used TEM as a proxy for UK current care. Within this scenario the HR for ibrutinib versus R-chemo was derived directly from the RAY (MCL3001) trial (Section 4.7.2.2). Although TEM is not considered a relevant treatment in UK clinical practice, this scenario was tested as TEM is the only treatment licensed for R/R MCL in Europe (other than ibrutinib) and to make the best use of the only direct comparative RCT data available for ibrutinib. There is no evidence available to inform the relative effectiveness of TEM compared to R-chemo and, therefore, no way to infer if TEM would be more or less effective compared to UK clinical practice.

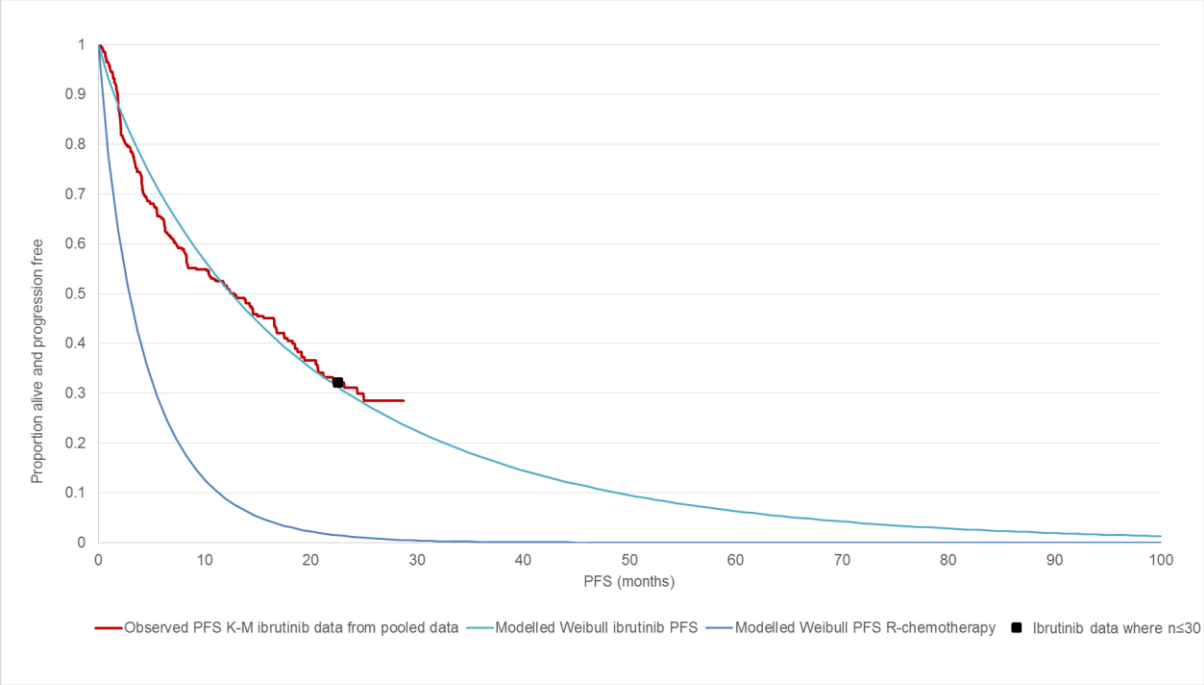
Summary of PFS estimates, PFS HRs and PFS curves used in the CEA

A summary of the HRs used in the CEM to inform the PFS of R-chemo in the base case and scenario analysis are reported in Table 58. The resulting PFS curves are shown in Figure 32.

Table 58: Comparative efficacy: PFS Hazard Ratios

Scenario	Comparative data	PFS HR for ibrutinib vs R-chemo
Base case	ITC with Hess 2009 + R treatment effect	0.28
Scenario	TEM from RAY (MCL3001)	0.43
ITC: indirect treatment comparison, PFS: progression-free survival, R: rituximab, TEM: temsirolimus		

Figure 32: Base case PFS for pooled ibrutinib dataset versus R-chemo



Ibr: ibrutinib, PFS: progression-free survival.

5.3.3 *Mortality during PFS*

A fixed risk of death during PFS was applied to the two arms within the model, which was calculated based on information from the ibrutinib clinical trials. The total number of death events observed as part of the PFS endpoint was obtained from the patient level data for the pooled clinical trial information and an estimated risk of death per 4-week cycle was calculated using the mean follow-up time for PFS within the clinical trials.

Due to the limited data available for comparative evidence, two options were explored in the CEM to estimate the risk of death within PFS for R-chemo:

1. The risk of death during PFS for R-chemo is equal to that of TEM in RAY (MCL3001) (base case). Although TEM is not used in current clinical practice it was assumed that the risk of death for R-chemo would be similar given the similar HRs predicted for PFS

2. The risk of death during PFS for R-chemo is equal to that of ibrutinib (scenario analysis). This is a highly conservative assumption to test the impact of assuming no treatment effect for ibrutinib in terms of risk of death during PFS

Table 59 shows the estimated risk of death during PFS for both ibrutinib and TEM.

Table 59: Risk of death during PFS for ibrutinib and TEM

	Number of events	N	Mean months of follow up for PFS	Risk of death during PFS per 4 weeks	Source
Ibrutinib	38	370	13.39	0.71%	Analyses on pooled dataset[6]
TEM	19	141	8.62	1.4%	Analyses on RAY (MCL3001)[61]
PFS: progression-free survival, TEM: temsirolimus					

5.3.4 *Post progression survival*

5.3.4.1 Post progression survival for ibrutinib

As outlined in Section 5.2.2, two methods were tested to estimate long-term survival in the ibrutinib arm:

- Fixed PPS = PFS + PPS
- Sequential

Fixed PPS approach

This approach is conservative as the method assumes that patients will not experience any benefit from the additional treatment options that are available to them due to the use of ibrutinib as opposed to R-chemo.

This method was previously accepted as appropriate for predicting survival within MCL as part of the TA370 NICE appraisal[13]. Within this submission a review was performed to investigate the relationship between OS in MCL and other outcomes. Based on the two studies identified through the literature search and feedback from UK clinicians, the manufacturer concluded that there was a strong case for the use of PFS as a surrogate for OS in MCL[14, 95].

When using the fixed PPS approach, a fixed PPS period is applied to both model arms, i.e. the same risk of death after progression is assumed for ibrutinib and R-chemo, based upon observed evidence from the ibrutinib pooled dataset:

$$\mathrm{OS}_{\mathrm{ibrutinib}} = \mathrm{PFS}_{\mathrm{ibrutinib}} + \mathrm{PPS}_{\mathrm{ibrutinib}}$$

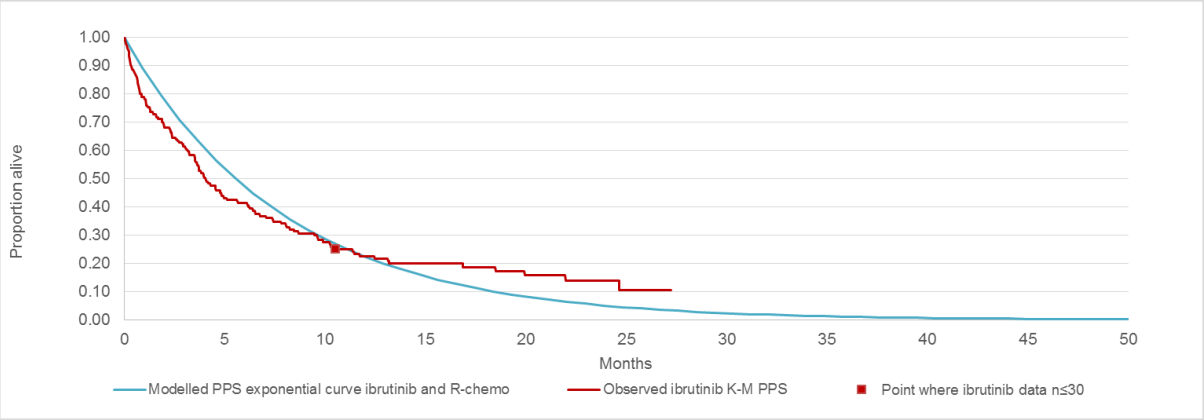
$$\mathrm{OS}_{\mathrm{R-Chemo}} = \mathrm{PFS}_{\mathrm{R-Chemo}} + \mathrm{PPS}_{\mathrm{ibrutinib}}$$

The ibrutinib pooled dataset was selected as the best source of PPS data, given that the TEM arm in RAY (MCL3001) was contaminated by post-progression crossover to ibrutinib and no alternative data sources were identified.

The number of patients entering the PPS health state was calculated by tracking the incidence of progression in the model. PPS was calculated by fitting an exponential curve to the pooled dataset, which assumes a constant rate of mortality throughout the time horizon. A constant rate of mortality of 10.83% per cycle was assumed to avoid the requirement to use tunnel states to track patient movements into PPS.

Figure 33 shows the KM data for ibrutinib PPS from the pooled dataset and the fitted exponential curve. These curves essentially show the OS of ibrutinib from the time of progression to the time of death. The median PPS observed within the pooled dataset was considered to be representative of what would be expected for R-chemo in UK clinical practice during the advisory board[12]. Figure 33 shows the final projected OS for both ibrutinib and the comparator arm based upon the fixed PPS approach.

Figure 33: KM and modelled PPS ibrutinib curves



KM: Kaplan-Meier, OS: overall survival, PFS: progression-free survival, PPS: post-progression survival.

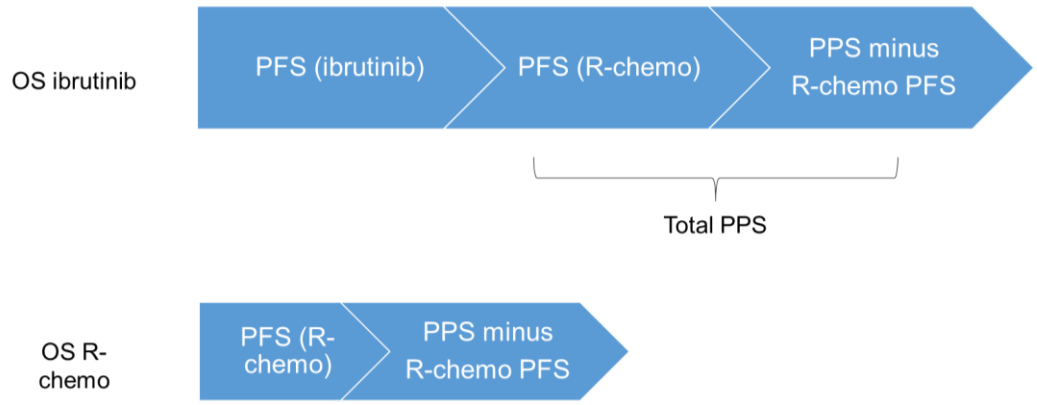
Sequential approach

The *sequential* approach aims to capture the fact that R-CHOP is currently perceived as the most effective chemotherapy regimen, but that its use as an initial treatment at second line precludes its use further along the treatment pathway, which means that other chemotherapy regimens which are perceived to be less effective need to be administered. Ibrutinib allows a further LOT, and this is captured with this method. This methodology was proposed during the advisory board[12]. Clinicians acknowledged that this would be an appropriate method of determining the benefit of ibrutinib, as ibrutinib would provide clinicians with a new effective treatment option for R/R MCL patients.

To estimate the OS for ibrutinib, PFS was calculated using the same approach outlined in Section 5.3.2. PFS for R-chemo was fitted using the exponential curve fitted to PFS data for the ibrutinib pooled dataset and the HR used for R-chemo versus ibrutinib depending on the method used for comparative efficacy (see Section 5.3.2). The result was then used to inform the PFS for subsequent R-chemo on the ibrutinib arm assuming that once patients progress on ibrutinib, they then go on to receive R-chemo (equal to the comparator selected).

To calculate such benefit, PPS in the ibrutinib arm was split into two portions: PFS for subsequent R-chemo treatment for R/R MCL and PPS post subsequent R-chemo treatment for R/R MCL. Figure 34 depicts how patients progress throughout the model with the *sequential* approach in both arms (although death can occur in any state).

Figure 34: OS using the *sequential* approach (ibrutinib and R-chemo)



OS: overall survival, PFS: progression-free survival, R-chemo: rituximab-based chemotherapy

This method assumed a constant rate of progression per cycle during subsequent R/R MCL treatment, estimated based on the formula below:

$$\text{Mean PFS for } \sout{\text{Second}}\text{subsequent R/R MCL treatment} = (\text{Lambda}_{Exponential\ PFS\ curve\ for\ Ibr} \times \text{HR for PFS for R} - \text{chemo vs Ibr} \times \text{PFS HR 2} + \text{ prior } \sout{\text{lines of therapy}}\text{LOTs vs 1 prior } \sout{\text{line}}\text{LOT})^{-1}$$

The mean PFS time for R-chemo following ibrutinib was calculated using a constant rate of progression per model cycle assuming an exponential distribution (15.6% risk of progression per model cycle [4 weeks]).

5.3.5 *Response rates*

IRC-assessed response rates were incorporated within the CEM to inform the estimation of costs and resource use during PFS. Response rates for ibrutinib are presented in Table 60 based upon the pooled clinical trial data (see Section 4.12).

Table 60: Response rates for ibrutinib

Assessment	Proportion responding
Overall response rate	66.22%
Complete response	[redacted]
Partial response	[redacted]

Data to inform the response rates within the comparator arm were sparse, and therefore, four options were tested to estimate comparator response rates within the CEM:

- Apply a relative risk for response calculated using the HMRN audit[7]
- Apply the odds ratio for response based on the ITC between Hess, 2009[8] and RAY with adjustment for the relative risk of response for R-chemo versus chemo in the HMRN audit(MCL3001)
- Use the odds ratio for response for TEM from RAY (MCL3001) as a proxy
- Assume response rate to be equal to ibrutinib

As response rates were not reported within the HMRN audit for R-chemo at second or subsequent LOTs, R-CHOP response rates were calculated based upon the relative risk of response for all therapies comparing first line and second line as shown in Table 61.

Table 61: Response rates for R-chemo derived using the HMRN audit

	n response	%	n no response	%	n	Source
All treatments 1st line	85	41.87%	118	58.13%	203	HMRN audit, Table 5[7]
All treatments 2nd line	30	32.97%	61	67.03%	91	HMRN audit, Table 7[7]
RR 1st line vs 2nd line response		0.79				Calculated: 32.97%/41.87%
R-CHOP 1st line		**75.86%**		24.14%	29	HMRN audit, Table 5[7]
R-CHOP 2nd line		**59.73%**			16	Calculated using RR of response between 1st and 2nd line: 75.86%*0.79
R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone, RR: relative risk						

ORRs estimated using the other approaches described above and odds ratios used to produce these estimates are shown in Table 62.

Table 62: Odds ratios used to inform response of R-chemo and ORRs estimated

Approach to estimate ORR	Odds Ratio	ORR estimated
Hess, 2009 and RAY (MCL3001) ITC + relative risk of response for R	60.26	4%
As per TEM in RAY (MCL3001)	3.98	40%
Assumed equal to ibrutinib	1	70%
ORR: overall response rate, ITC: indirect treatment comparison, R: rituximab, TEM: temsirolimus		

5.4 *Measurement and valuation of health effects*

5.4.1 *Health-related quality-of-life data from clinical trials*

As noted in Section 4.7, EQ-5D estimates were collected as an exploratory endpoint in RAY (MCL3001) and SPARK (MCL2001); no EQ-5D data were collected in PCYC1104. Measurements were taken within RAY (MCL3001) at the beginning of every treatment cycle during the first 6 months, then every 9 weeks up to 15 months, and thereafter every 24 weeks. Pooled data from RAY (MCL3001) and SPARK (MCL2001) were used to inform both PFS and PPS HRQoL within the CEA. Completion rates for the EQ-5D measure are shown in Appendix 16.

A mixed model analysis was carried out to determine the mean QoL pre and post progression for patients in the ibrutinib arm of the two studies. This method was chosen as it accounts for potential autocorrelation of patient QoL scores. Utility estimates based on this analysis are shown below in Table 63.

It should be noted that patient numbers available to inform the PPS health state are low; however, the decrement upon progression predicted using these data (0.1) is considered to be reasonable in light of “upon progression” decrements in other haematological cancers that have been used in previous NICE submissions. A decrement of 0.07 was observed, for

example, between pre and post progression in first-line MCL[13]. It should also be noted that the modelled EQ-5D-5L utility value for progression free patients represents a utility gain of only 0.05 from the 0.73 baseline EQ-5D-5L utility observed in RAY (MCL3001) (section 4.7.2.4). By contrast, clinical experts expected utility values for MCL patients on treatment with ibrutinib to be similar to the general population [12]. This supports concerns that values elicited with the EQ-5D may underestimate the true utility gain associated with the meaningful and valuable positive QoL impact of ibrutinib observed with FACT-Lym and by clinical experts.

Table 63: Health state utilities based upon mixed model analysis performed on RAY (MCL3001) and SPARK (MCL2001) trial data for ibrutinib

Health state	Utility	N	SE	CI Lower	CI Upper
PFS	0.780	234	0.010	0.762	0.799
PPS	0.680	36	0.024	0.634	0.727
CI: confidence interval, PFS: progression-free survival, SE: standard error, Notes: *PCYC1104 did not collect EQ-5D data					

5.4.2 *Mapping*

No mapping was conducted within this analysis.

5.4.3 *Health-related quality-of-life studies*

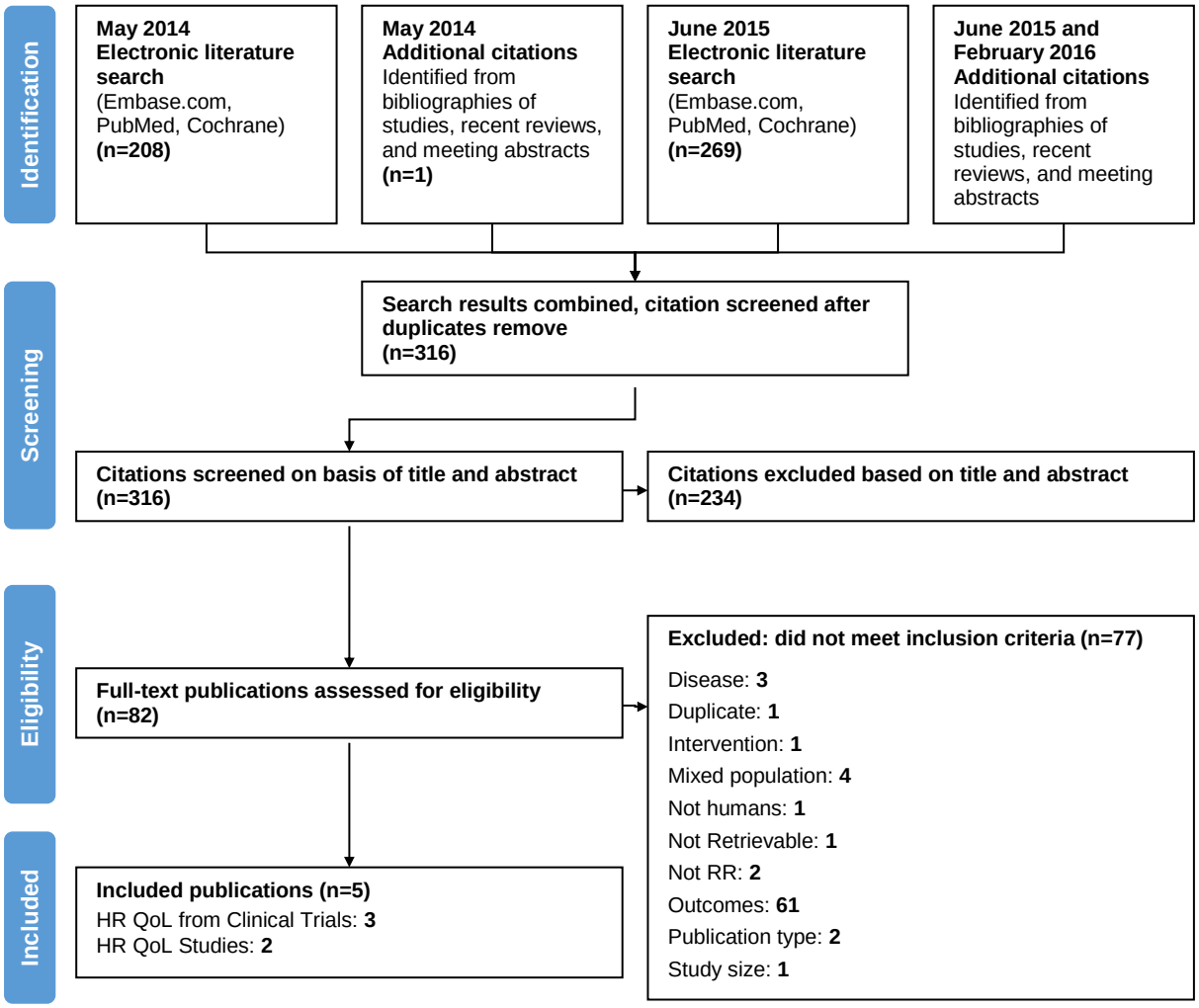
A SLR was performed with the aim of finding utility values to be used as inputs for the economic model. A similar search strategy to that used for the clinical SLR (see Section 4.1.2) was used for the SLR of HRQoL studies. The HRQoL SLR searched the same databases as the economic SLR reported in Section 5.1.1. HRQoL searches had no date limits and were not limited in terms of study design; search algorithms were tailored to identify both prospective and retrospective studies on R/R MCL patients that reported economic and HRQoL data related to treatment with any chemotherapeutic, biologic, or investigational pharmaceutical agents. The inclusion criteria applied to the identified studies are reported in detail in Section 5.1.3. The full search strategy is provided in Appendix 18.

An identical methodology for study selection as used for the clinical SLR (see Section 4.1.2) was used for the HRQoL SLR in terms of the review process and the use of PICOS eligibility criteria for screening of identified articles.

After the removal of duplicate citations, 316 studies were reviewed to identify any that reported HRQoL data. Of the 82 citations accepted during abstract screening, only 5 met the overall inclusion criteria: three from clinical trials and two from HRQoL studies. A PRISMA flow diagram presenting the results of the HRQoL SLR is provided in Figure 35 and the key characteristics of these studies are shown in Appendix 19.

Of the studies identified, only two contained HRQoL information in the form of utilities. Cuyun *et al.* included the EQ-5D index for 58 patients with R/R MCL receiving enzastaurin and reported that ECOG performance status (PS) had a significant impact on QoL both at baseline and treatment discontinuation (utilities of 0.81, 0.68, 0.58 for ECOG PS 0, 1 and 2 respectively at baseline; 0.77, 0.61, 0.28 at treatment discontinuation)[96]. The study also reported no significant association between utility and MIPI. 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[97]. Neither of these studies contained data suitable for use within this CEA.

Figure 35: PRISMA for HRQoL studies



5.4.4 *Adverse reactions*

5.4.4.1 Frequency of adverse events

Section 4.13 reports the incidence of grade 3 or higher AEs within the ibrutinib clinical trials. Inclusion of AEs in the economic model was determined according to clinical importance as assessed by leading experts in the treatment of MCL in the UK. Clinicians were asked to consider AEs which are likely to have a meaningful impact on either NHS costs or patient QoL. All grade 3 or higher AEs that occurred in at least 5% of the patients treated with ibrutinib within the pooled clinical trial data were included in the CEM, unless regarded clinically irrelevant by the clinicians consulted.

In addition to these AEs, clinicians identified several clinically meaningful AEs which occur at lower rates with either treatment with ibrutinib or R-chemo. These events were:

- Bleeding
- Atrial fibrillation
- Tumour lysis syndrome
- Leukostasis

- Lymphocytosis
- Renal failure
- Cytomegalovirus (CMV) reactivation
- Abnormal liver function test

Due to lack of data in R/R MCL, in order to obtain AE rates for the comparators included in the final NICE scope, AE rates were derived from first-line MCL trials identified within the clinical SLR and the NICE MCL SLR included in the draft Clinical Guidance on NHL[50]. The largest trial with the longest follow-up was selected from the available literature in each case. For RC no data were available in MCL at all, therefore the same rate of AEs was assumed as for R-CHOP. Published literature, including product SmPCs, was used where possible to inform AEs not available within trials. All AE rates used in the CEM are reported in Table 64.Use of AE rates from these sources will lead to an underestimation of the impact of R-chemo on patients for two reasons:

- Relapsed / refractory patients are on average substantially less fit, and are therefore more likely to experience treatment-related toxicity than patients at first-line
- There are several AEs for which information was available for ibrutinib but not for R-chemo. The frequency of these AEs for comparators was assumed to be 0%

There is a strong possibility that these rates are biased towards the R-chemo arm of the CEM and do not fully represent the improved tolerability for patients that receive ibrutinib over R-chemo regimens. Clinicians during a recent advisory board strongly argued in favour of the benefit of the ibrutinib tolerability profile[12].

Table 64: AEs included within the economic model (grade 3+)

Adverse event	Ibrutinib pooled data rate	R-CHOP rate (Kluin-Nelemans *et al.* 2012)[98] used to inform R-CHOP and RC N=239	FCR rate (Kluin-Nelemans *et al.* 2012)[98] used to inform FCR n = 246	Flinn *et al.* 2014 for R-CVP (n=116)[91]	Notes
Neutropenia	16.8%	60.0%	69.0%	56.0%	Flinn *et al.* value was based on an absolute neutrophil count
Anaemia	8.9%	12.0%	20.0%	5.0%	Flinn *et al.* value was based on 'Hemoglobin'
Pneumonia	8.1%			1.0%	Flinn *et al.* value based on white blood cell count
Leukopenia		59.0%	18.0%	38.0%	-
Febrile neutropenia		17.0%	11.0%		-
Infection		14.0%	17.0%	7.0%	-
Major bleeding	4.3%	0.6%*	0.6%*	0.6%*	-
Atrial fibrillation	5.1%	5.5%+	5.5%+	5.5%+	-
Tumour lysis	0.5%	0.1%+	0.1%+	0.1%+	-

Adverse event	Ibrutinib pooled data rate	R-CHOP rate (Kluin-Nelemans *et al.* 2012)[98] used to inform R-CHOP and RC N=239	FCR rate (Kluin-Nelemans *et al.* 2012)[98] used to inform FCR n = 246	Flinn *et al.* 2014 for R-CVP (n=116)[91]	Notes
syndrome					
Leukostasis	0.0%				
Lymphocytosis	0.8%				-
Renal failure	1.1%	0.0%+	0.0%+	0.0%+	-
Cytomegalovirus (CMV) reactivation	0.0%	2.0%†	2.0%†	2.0%†	-
Abnormal liver function test	0.5%	1.0%	1.0%	1%	Kluin-Nelemans sources based on total / elevated bilirubin values (which can be a measure of liver function)

R-CHOP: rituximab, cyclophosphamide, vincristine and prednisone, R-CVP: rituximab, cyclophosphamide, vincristine and prednisone, FCR: fludarabine, cyclophosphamide and rituximab, RC: rituximab + cytarabine
* sourced from doxorubicin summary of product characteristics[99]
+ sourced from Mabthera summary of product characteristics[100]
† sourced from Kelesidis *et al.* 2011[101]

5.4.4.2 Utility decrement due to toxicity

The frequency of AEs for ibrutinib was derived from the pooled trial data. Since HRQoL was captured using the EQ-5D instrument within the ibrutinib clinical trials (for RAY (MCL3001) and SPARK (MCL2001)), the utility values obtained for both the pre-progression and post-progression health states for ibrutinib already account for decrements due to the occurrence of AEs. No additional decrements were therefore applied for the ibrutinib arm in the model, in order to avoid double counting.

Utility decrements were applied to the R-chemo arm on AE occurrence to reflect the toxic effect of receiving chemotherapy and the impact on patients' QoL and functioning.

Clinical experts were consulted regarding the impact of treatment with ibrutinib and R-chemo on patients. They commented that ibrutinib has a euphoric effect meaning that it is possible for patients to feel similar to or even better than the general population. Since ibrutinib is an effective oral therapy, patients receiving it may be able to go back to work or go on holiday. Anecdotal reports suggest that some patients have reported *feeling "unbelievably well given their sudden reprieve from death"* and feeling more stable on ibrutinib as they do not see large variation in their blood counts as is observed with R-chemo. One patient was quoted as *"going from a wheelchair to a golf course in 3 weeks"*. NICE have recently reviewed ibrutinib for the treatment of CLL and the committee reported the following conclusions in the draft ACD: "*clinical experts commented… stating that symptoms improve immediately with ibrutinib and patients have a very good quality of life unless they have an adverse event. Having heard the positive experience of patients with ibrutinib, particularly with regard to energy levels and lack of side effects…*"[15].

Patients receiving R-chemo, on the other hand, tend to feel good initially and then decline. Clinical experts described that the greatest impact on patients comes from fatigue and diarrhoea. Patients cannot return to work while receiving chemotherapy and frequently require concomitant medications which may also impact their QoL; in particular patients needing granulocyte-colony stimulating factor (G-CSF) cannot lead a normal life because their schedule must allow for district nurse visits. Impact of R-chemo is greatest within the first 10 days of receipt of each chemotherapy dose, and whilst QoL usually returns to normal 6 months after treatment some patients never regain their QoL. The clinicians consulted noted that receipt of R-chemo is particularly difficult for relapsed or refractory patients (rather than first line patients). Two methods were used to capture the difference in the impact on QoL of ibrutinib and R-chemo:

1. The first method, which is used within the model base case, was based upon the estimated utility decrement provided by clinicians at the advisory board, which suggested that patients receiving R-chemo regimens as opposed to ibrutinib would be likely to incur a decrement of 0.2[12]. This value was then converted into a cyclical decrement (for a 4-week cycle), and applied within the model to patients whilst on treatment with R-chemo. This method was chosen for the model base case as clinicians noted the impact of R-chemo on fatigue as key to patient experience and QoL. Fatigue is well known to be poorly captured within the EQ-5D measure and therefore estimates drawn from the EQ-5D are likely to underestimate the impact of fatigue on patients[102]. In the ACD for CLL "*the committee was concerned that the quality-of-life benefits may not have been appropriately captured, noting that the EQ-5D-5L does not directly measure fatigue*"[15]

2. The second approach was based on the utility of progressed patients from a published study identified within the HRQoL systematic SLR[97]. The utility for progressed patients was 0.61, and was subtracted from the mean PFS utility for ibrutinib (0.78) to estimate a total anticipated decrement for patients receiving R-chemo (0.013). As above, this value was then converted into a cyclical decrement (for a 4-week cycle) and applied within the model to patients whilst on treatment with R-chemo.

Both approaches represent a conservative estimate of the impact of R-chemo on HRQoL given that clinical advice suggested that the impact of treatment with R-chemo often persists even after treatment is stopped.

5.4.5 ***Health-related quality-of-life data used in cost-effectiveness analysis***

In line with the NICE methods guide, EQ-5D data from the RAY (MCL3001) and SPARK (MCL2001) clinical trials were used to inform HRQoL estimates for patients pre- and post-progression in the CEM[89]. Utility decrements were applied when patients were receiving any R-chemo regimen (as explained in Section 5.4.4.2), that is within the comparator arm during treatment (TOT curves are reported in Section 5.5) or within the ibrutinib arm when the *sequential* approach is used for modelling survival. Table 65 provides a summary of the utility values used within the base case analysis of the CEA.

Utility values used within this CEA are broadly in line with the published literature available, which indicate a utility 0.61 for R/R MCL patients receiving anti-neoplastics[97].

Utilities were adjusted to account for the natural decline in QoL associated with age. By estimating the utility values of the general population at different ages, a utility multiplier was created to represent the natural decline in QoL that the population would expect to incur each year. This utility multiplier was then applied to utility in each health state of the model throughout the entire time horizon. The multiplier was calculated based upon published

information from Ara and Brazier which was derived from EQ-5D values for the general population[103]. The formula is shown below:

$$General\ population, EQ-5D = 0.9508 + 0.0212126 * male - 0.0002587 * age - 0.0000332 * age^2$$

A scenario was tested where no age-adjustment was applied.

Table 65: Summary of utility values used in the base case of the CEA

State	Utility value: mean (SE)	HRQoL per 28 days	95% CI	Reference in submission (section and page number)	Justification
Pre-progression	0.78	0.060	0.762 – 0.799	Section 5.4.1	Pooled ibrutinib EQ-5D data from first treatment for R/R MCL
Post-progression	0.68	0.052	0.634 – 0.727	Section 5.4.1	
R-chemo decrement	0.2	0.015	0.1 - 0.3	Section 5.4.1	Clinician feedback[12]
SE: standard error, HRQoL: health related quality of life, CI: confidence interval, R/R MCL: relapsed or refractory mantle cell lymphoma, R-chemo: rituximab plus chemotherapy					

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

5.5.1 *Resource identification, measurement and valuation studies*

As noted in Section 5.1.1 a combined SLR was produced for cost effectiveness and cost and resource use evidence within R/R MCL. Three studies were identified as part of the cost and resource use SLR. None of these provided evidence which could be used within the economic model.

Senbetta *et al.* analysed the budget impact of adding ibrutinib to a US health plan[104]. Both Wade *et al.* and Feinberg *et al.* 2015 analysed US claims data to understand predictors of healthcare resource use for patients with newly diagnosed and relapsed MCL[105, 106]. A summary of these three studies is provided in Appendix 13. Wade *et al.* concluded that the treatment costs for MCL were the highest during the first 3 months of treatment in each LOT then declined and stabilised to about 25%-30% of the initial costs. They concluded that this pattern suggests that prolongation of time to progression may yield economic as well as humanistic benefits. Feinberg *et al.* concluded that AEs, supportive care, and increased duration of chemotherapy treatment were all associated with increases in hospitalisations and emergency room (ER) visits. They concluded that these data warrant consideration of age and comorbidity-adjusted treatment in MCL patients eligible for treatment with antineoplastics.

Both articles indicate that reductions in the cost associated with the management of R/R MCL are likely to be expected with ibrutinib due to a prolongation of time to progression and a reduction in the requirement for use of chemotherapy with associated decreases in hospitalisations and ER visits related to toxicity and requirements for use of supportive care. It is unlikely that all of these benefits have been adequately captured within the current

economic model due to a lack of evidence and understanding of the full impact of toxicity related to current treatments on either patients or the NHS in the UK.

5.5.2 *Intervention and comparators' costs and resource use*

5.5.2.1 Unit costs for drug acquisition and administration

Drug acquisition and administration costs are presented in Table 66 and Table 67, respectively. The cost presented for ibrutinib represents the list price. As stated in Section 2.3, a simple PAS is currently in place for ibrutinib [redacted] Cost-effectiveness results including the current discount can be found in Appendix 20.

Clinical experts were surveyed to assess what types of prophylactic medications are used in combination with each active treatment in the model and whether any additional resources (e.g. monitoring, testing) specific to treatment type are relevant to UK clinical practice. Feedback indicated that the costs of prophylactic medication and treatment-specific resource use were minimal and likely to be slightly greater for R-chemo[12]. Due to the minimal impact that the inclusion of prophylactic medication and treatment-specific resource would be expected to have on model results and in an effort to reduce complexity, the cost of prophylaxis was not included within the economic model.

Table 66: Drug acquisition costs

Treatment	Unit size	Tablet / Vial Size	Administration method	Unit cost (£)	Source
Ibrutinib	140mg	1	Oral	51.10	MIMS Online accessed: January 2016[107]
Cyclophosphamide	500mg	1	IV	9.00	eMIT version released November 2015[108]
Doxorubicin	2.0mg/ml	25ml	IV	4.16	eMIT version released November 2015[108]
Fludarabine	50.0mg/ml	1ml	IV	149.92	MIMS Online accessed: January 2016[107]
Prednisolone*	5.0mg	1ml	Oral	0.0157	eMIT version released November 2015[108]
Rituximab	10.0mg/ml	50ml	IV	873.15	MIMS Online accessed: January 2016[107]
Vincristine	1.0mg/ml	1.0ml	IV	13.47	MIMS Online accessed: January 2016[107]
Cytarabine	20.0mg/ml	5.0ml	IV	4.33	eMIT version released November 2015[108]
*As no price was available for prednisone on eMIT the price of prednisone was assumed to be the same as the price of prednisolone					

Table 67: Administration Costs

Administration	Unit Cost	Source
IV	£329.32	NHS reference costs 2014/2015 – Day-case visit; SB13Z Deliver more complex Parenteral Chemotherapy at first attendance
IV: Intravenous administration, NHS: National Health Service.		

5.5.2.2 Number of vials required per administration for IV drugs

Within the base case it was assumed that patients received only whole vials and that there was no vial sharing. Using RAY (MCL3001), SPARK (MCL2001) and PCYC1104 body surface area (BSA) data, the average number of vials that would be required to satisfy one administration of each of the IV administered drugs was calculated using the *method of moments*[109]. A log-normal distribution was fitted to the observed patient BSAs and this distribution was used to calculate the proportion of patients requiring each number of vials to produce an accurate estimate of the mean number of vials required per patient per dose when wastage is taken into account.

Table 68 shows the combination of vials on average required per patient per dose based upon the BSA of patients included within the clinical trials (mean BSA of 2.01 for males and 1.73 for females). Male and female BSA was separated to accurately estimate the total cost based on the ratio of males to females within the model (78% male and 22% female).

Table 68: Average number of vials required per administration of IV drugs dosed

Drug	Dose needed	Vial size(mg)	Mean number of vials per patient per dose
Cyclophosphamide (dose used within FCR)	250mg/m^2	500	1.40
Cyclophosphamide (dose used within R-CHOP and R-CVP)	750mg/m^2	500	3.40
Doxorubicin	50mg/m^2	50	2.40
Fludarabine	30mg/m^2	50	1.87
Rituximab	375mg/m^2	100	7.80
Vincristine	1.4mg/m^2	1	3.19
Cytarabine	500mg/m^2	100	10.23
IV: intravenous, R-CHOP: rituximab, cyclophosphamide, vincristine and prednisone, R-CVP: rituximab, cyclophosphamide, vincristine and prednisone, FCR: fludarabine, cyclophosphamide and rituximab.			

5.5.2.3 Dosing assumptions

The dosing regimens applied within the model are outlined in Table 55. The mean dose intensity for ibrutinib was 94.21% based on the pooled dataset. As no information was available to inform the dose intensity of R-chemo, this was assumed to be the same as ibrutinib. All drug and administration costs within the model were multiplied by their dosing intensity.

5.5.2.4 Summary of acquisition and administration costs

Table 69 summarises the drug acquisition and administration costs associated with ibrutinib and the comparators considered within the model. The table presents the number of administrations assumed per visit and the total cost per cycle.

Table 69: Drug acquisition and administration costs

Regimen (cycle length)	Drug	Drug Cost		Administration cost	
		Each component	Total cost per cycle (based on regimen)	Number of administrations per cycle	Administration cost
Ibrutinib	Ibrutinib	£5,723	£5,723	0	£0
R-CHOP (21 days)	Rituximab	£1362	£1,447	1	£329
	Cyclophosphamide	£31			
	Doxorubicin	£10			
	Vincristine	£43			
	Prednisone	£2			
R-CVP (21 days)	Rituximab	£1362	£1,437	1	£329
	Cyclophosphamide	£31			
	Vincristine	£43			
	Prednisone	£2			
FCR(28 days)	Fludarabine	£843	£2,243	3	£988
	Cyclophosphamide	£38			
	Rituximab	£1362			
RC (28 days)	Rituximab	£1362	£1,495	4	£1,317
	Cyatarabine	£133			
R-CHOP: rituximab, cyclophosphamide, vincristine and prednisone, R-CVP: rituximab, cyclophosphamide, vincristine and prednisone, FCR: fludarabine, cyclophosphamide and rituximab, RC: rituximab + cytarabine.					

5.5.2.5 Time on treatment

In order to accurately estimate the proportion of patients receiving ibrutinib treatment during each model cycle, information for the observed TOT was derived from the pooled dataset. All drug costs and administration costs for both ibrutinib and the R-chemo were multiplied by the proportion of patients on treatment within each model cycle. TOT information for R-chemo was used up until a maximum TOT corresponding to the fixed number of cycles specified for the R-chemo regimen (see Table 55). In other words, R-chemo patients are modelled to stay on treatment for the maximum number of cycles permitted for the specific chemotherapy that they receive, unless they discontinue earlier.

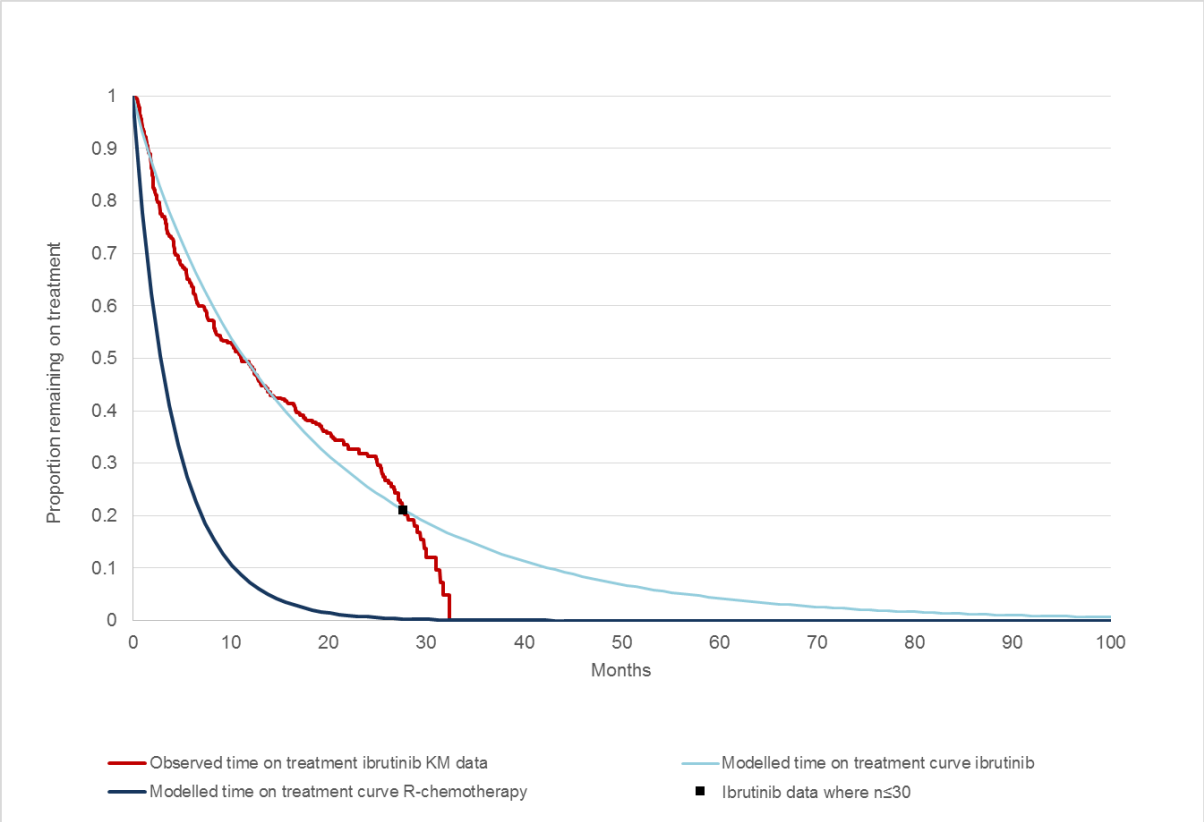
TOT for ibrutinib was modelled based upon parametric curves fitted to the patient level data from the pooled dataset. NICE DSU guidance on survival analysis was followed to determine the best approach to extrapolation[94]. Based upon the log-cumulative hazard plot which indicated that the use of a standard parametric model was appropriate (plot shows as a reasonably straight line, see Appendix 15), the following curves were fitted:

- Weibull
- Log normal
- Log-logistic
- Exponential

Similarly to PFS, the choice of parametric model was based upon the AIC, the BIC statistics (see Appendix 15) and on visual inspection; however, all four curves provide a good fit to the data available. Ibrutinib is administered until either progression or unacceptable toxicity, therefore TOT is heavily dependent upon the progression status of the patient. Within the model, for consistency, the same curve fit was selected for TOT as for PFS (Weibull).

The TOT curve for both arms of the model is shown in Figure 36.

Figure 36: ibrutinib KM data and modelled curve fits for TOT



5.5.2.6 Composition of the blended comparator presented for UK current care

As there is no SOC for the treatment of R/R MCL in the UK, in addition to comparing to the comparators from the NICE scope, a scenario analysis is presented comparing to a blended comparator based upon clinicians' feedback from the advisory board as to the proportion of patients receiving each of the treatments listed within the scope (Table 70)[12].

Table 70: Estimated proportion of patients receiving each of the treatments listed within the NICE scope in UK clinical practice

Treatment	Proportion receiving each treatment
R-CHOP	85%
R-CVP	10%
FCR	5%
RC	0%
R-CHOP: rituximab, cyclophosphamide, vincristine and prednisone, R-CVP: rituximab, cyclophosphamide, vincristine and prednisone, FCR: fludarabine, cyclophosphamide and rituximab, RC: rituximab + cytarabine.	

5.5.2.7 Subsequent treatment

Of the 370 patients in the pooled dataset only 118 received subsequent treatment for MCL. As this represents only a proportion of patients and no information is available on the use of subsequent treatment for R-chemo, the cost of subsequent therapy was not included within either arm of the model except when modelling OS using the sequential approach for ibrutinib where both the costs and benefits of including an additional line of R-chemo are included within the ibrutinib arm. This is a conservative assumption as it would be expected that patients would require subsequent treatment more rapidly on the comparator arm (as

ibrutinib delays progression). It is unlikely that much difference would be observed between model arms, however, as the majority of patients on both arms would be expected to progress and require subsequent treatment within their lifetime.

A scenario analysis was provided where patients are assumed to incur subsequent therapy with FCR after progression. FCR was chosen as the subsequent therapy based on clinicians' feedback from the advisory board[12]. In addition to this, FCR was the second most common treatment provided as subsequent therapy in the HMRN audit (the first-was R-CHOP, and therefore not a relevant subsequent treatment as it forms the base case comparison)[7]. The cost of subsequent treatment was applied as a *one-off* cost to all patients progressing within the model. Both drug and administration costs of FCR were applied in line with the costs outlined in Table 69.

5.5.3 ***Health-state unit costs and resource use***

A survey was designed to obtain the types and frequency of MRU (including visits, procedures, and tests) for an average patient. Data were generated via a custom, on-line survey launched in November and December 2014 and 100 actively practicing, NHS haematologists and oncologists were invited to participate. A total of 52 participants (15 oncologists, 19 haematologists and 18 haematologist oncologists) provided CRs or PRs[110]. Expert opinion from leading UK haematologists experienced in MCL was sought to validate the outcomes of the resource use survey[12].

Routine follow-up care required by patients was differentiated based upon a patient's response to treatment (non-responder/stable disease, PR and CR) and health state (progression-free or progressed). Applying different costs of care according to response status is a common approach in HTAs in similar indications, for example,[111] the recent ibrutinib and idelalisib + rituximab submissions to NICE for CLL[15, 86].

Costs associated with resource use based upon clinicians' feedback are presented in Table 71. All costs used within the CEM to inform resource use were obtained from the latest NHS reference costs (2014/2015) and the PSSRU 2015[112, 113].

Table 71: Total annual resource use by health state and response status (calculated as unit cost x frequency)

Resource use component	Frequency in SD	Frequency in CR	Frequency in PR	Frequency in PPS	Unit Cost of Resource	NHS Reference Cost Used
Full blood count	6	4	4	9	£3.01	DAPS05: Haematology[112]
X-ray	1	1	1	1	£30.23	DAPF: Direct Access Plain Film[112]
Blood glucose	0	0	0	0	£1.19	DAPS05: Clinical Biochemistry[112]
LDH	4	3	3	5	£1.19	DAPS05: Clinical Biochemistry[112]
Lymphocyte Counts	6	4	4	9	£3.01	DAPS05: Haematology[112]
Bone marrow exam	1	1	0	0	£288.45	Outpatient - Clinical Haematology - SA33Z[112]
Haematologist	6	4	4	9	£150.38	WF01A Consultant Led, Non-admitted face to face follow-up Service code: 303[112]
Inpatient non-surgical/Medical	1	0	0	2	£2,922.50	Weighted average of Chronic Lymphocytic Leukaemia, including Related Disorders, with CC Score 0-7+ Elective and Non-elective inpatient stays. SA32A[112]
Biopsy	1	1	0	0	£4,212.69	Weighted average Major General Abdominal Procedures, 19 years and over, with CC Score 0 - 10+,(FZ12L-FZ12U).Complex General Abdominal Procedures with CC Score 0- 6+ (FZ79C-FZ79E) and Procedures on the Lymphatic System with CC Score 0- 1+ (WH54A-B)[112]
Blood transfusion	1	1	0	4	£288.23	Outpatient Procedures, Clinical haematology, SA13A, Single Plasma Exchange, Leucophoresis or Red Cell Exchange, 19 years and over[112]
Platelet infusion	0	0	0	2	£288.23	Outpatient Procedures, Clinical haematology, SA13A, Single Plasma Exchange, Leucophoresis or Red Cell Exchange, 19 years and over[112]
CR; complete response, LDH; lactate dehydrogenase, PPS; post-progression survival, PR; partial response, SD; stable disease						

A summary of the health state unit costs applied within the model is reported in Table 72.

Table 72: Health state costs applied within the model

Health State	Health state cost per cycle: ibrutinib	Health state cost per cycle: R-chemo
PFS	£258	£301
PPS	£695	
PFS: progression-free survival, PPS: post-progression survival		

5.5.4 *Adverse reaction unit costs and resource use*

The cost of treating grade 3 and 4 AEs in the model was calculated based on the frequency with which each event occurred, multiplied by the unit cost of each AE. The frequency of AEs was derived from the pooled dataset for ibrutinib and available literature for R-chemo (see Table 64 in Section 5.4). Table 73 shows the unit costs used for each AE. The NHS Reference Costs codes used to derive AE costs were consistent with the TA370 submission in first-line MCL for all AEs which had been reported within that submission[13, 112].

Table 73: Adverse event costs

AE	Cost per AE	NHS Reference Cost Used[112]
Neutropenia	£ 162	Outpatient visit. Costed as weighted average of non-admitted clinical haematology visit codes: WF01A, WF01B, WF01C, WF01D, WF02A, WF02B, WF02C, WF02D
Anaemia	£ 162	
Leukopenia	£ 162	
Atrial fibrillation	£ 162	
Tumour lysis syndrome	£ 162	
Leukostasis	£ 162	
Lymphocytosis	£ 162	
Abnormal liver function test	£ 162	
Pneumonia	£ 2,720	Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 0-7 (DZ11Q). Costed as weighted average of: • Elective Inpatient • Non-elective inpatient (long and short stay) • Day case
Febrile neutropenia	£ 633	Other Haematological or Splenic Disorders, with CC Score 0-2 (SA08J). Costed as weighted average of: • Elective Inpatient • Non-elective inpatient (long and short stay) • Day case
Infection	£ 563	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 short stay) • Day case
Cytomegalovirus (CMV) reactivation	£ 563	
Major bleeding	£ 738	Gastrointestinal Bleed without Interventions, with CC Score 0-4 (FZ38P). Costed as weighted average of: • Elective Inpatient

AE	Cost per AE	NHS Reference Cost Used[112]
		• Non-elective inpatient (long and short stay) • Day case
Renal failure	£ 3,055	General Renal Disorders with Interventions, with CC Score 0-2 (LA09L) Costed as weighted average of: • Elective Inpatient • Non-elective inpatient (long and short stay) • Day case
AE: adverse event, CC: Complexity and Comorbidity, NHS: National Health Service.		

5.5.5 *Miscellaneous unit costs and resource use*

A *one-off* terminal care cost was applied within the model based on Nuffield 2014; which was inflated to reflect current prices (using the hospital and community health service (HCHS) inflation indices reported within the PSSRU)[113]. 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*

5.6.1 *Summary of base-case de novo analysis inputs*

Appendix 21 summarises the base case economic variables in terms of their point estimate value and their assumed distribution. This table guides the reader towards the sections of the submission where each of the respective variables is outlined. The scale of uncertainty around estimated was informed by data or assumptions for key parameters.

5.6.2 *Assumptions*

The base case analysis, which used data from the pooled dataset for ibrutinib and data from the Hess, 2009 ITC, was subject to several key assumptions. These key assumptions are summarised in Table 74 and described throughout Section 5. Table 75 provides a summary of the scenario analyses performed within the CEA. The key parameters explored in scenario analysis test the underlying structural uncertainty within the model based on comparative efficacy and other areas where there are key evidence data gaps.

Table 74: Key assumptions within the base case

Type	Assumption	Rationale
Safety and effectiveness		
Comparative effectiveness of R-chemo	All R-chemos assumed to have equal impacts on toxicity and effectiveness	Data are not available for individual treatment regimens at this LOT.
Ibrutinib PFS	PFS was best characterised by a Weibull curve fitted to ibrutinib data	The log-normal and log-logistic curves were perceived as unrealistic due to the long tails, and Weibull was the next best fit to the ibrutinib data
R-chemo PFS	Based on a hazard ratio using the Hess, 2009 ITC reported in Section 4.10	Most relevant dataset available for both OS and PFS
Risk of death during PFS for R-chemo	Assumed equal to TEM risk of death from RAY (MCL3001) trial data	Most reliable data available to inform risk of death for the comparator
Ibrutinib TOT	The ibrutinib TOT curve selected was assumed the same as the PFS curve (Weibull)	Given that TOT and PFS are very strongly linked as ibrutinib is given until progression or until treatment is no longer tolerated by the patient, assuming the same curve shape avoids inconsistencies between TOT and PFS which may arise from selecting different parametric curves
R-chemo TOT	The same relationship between TOT and PFS is the same as for ibrutinib during the fixed duration of treatment with R-chemo	Due to lack of alternative data
Use of fixed PPS	PPS was assumed equal for both arms within the economic model	In the absence of good quality data for R-chemo, this was a highly conservative approach which assumed that ibrutinib offers no benefit after progression. Available literature and clinical opinion indicate that PFS is a good surrogate for OS in MCL. Approach previously accepted in the TA370 submission for first-line MCL[13]
Mean duration of PPS	A constant rate of death from PPS was applied in the PPS state which was applied to both arms	Used to estimate OS where OS = PFS + PPS. Estimate obtained using an exponential curve fit to PPS data (assumed to be 10.83% in the base case). More complex curve fits not used to avoid over-complication and the requirement for tunnel states.
R-chemo response rates	Response rates derived from HMRN audit	Most reliable data available for estimating ORRs for R-CHOP (most relevant comparator listed within the NICE scope)

Type	Assumption	Rationale
Rituximab effect	The rituximab effect on PFS from the HMRN audit provides a suitable upper bound for the impact of adding rituximab to chemotherapy in R/R MCL	Only data available for estimating a rituximab treatment effect is in first-line MCL
AEs		
AEs severity	Grade 3+ AEs that occurred in at least 5% of patients in either arm of the model and that clinicians deemed clinically relevant were included, plus a select list of AEs experienced by less than 5% of patients at Grade 3+ identified by clinicians as clinically important	Include relevant AEs that would be likely to incur a cost in a real life setting
Costs		
R-chemo wastage and dose intensity	Vial wastage was included within cost calculations. Dose intensity for R-chemo was assumed to be the same as ibrutinib	It is unrealistic in a small patient population such as MCL that patients would be able to vial share Assumption for dose intensity due to lack of alternative evidence
Resource use costs	Resource use costs were dependent upon progression status and the level of response experienced in each treatment arm	Clinical advice that resource use involving various tests and clinical visits would vary based on not only health state but the level of response experienced by a patient. Similar assumption used in NICE submissions for other lymphomas
AE costs	Applied as a fixed *one off* cost in the first model cycle	Simplifying assumption. Realistic to assume that the majority of AEs would incur within the first cycle of treatment and last between 7-10 days based on clinician feedback
Subsequent therapy	No subsequent therapy costs were included	Only a proportion of patients received subsequent therapy within the ibrutinib trials and information relating to both the impact of subsequent therapy on survival and the expected subsequent therapies in UK clinical practice was weak. This is a conservative assumption as it would be expected that patients would require subsequent treatment more rapidly on the comparator arm (as ibrutinib delays progression).
QoL		
QoL health states	QoL dependent upon progression status	Informed by a mixed treatment model estimating EQ-5D utilities for ibrutinib for pre and post-progression health states

Type	Assumption	Rationale
Magnitude of QoL decrement for ibrutinib and R-chemo	No additional decrement to QoL assumed for ibrutinib. An overall utility decrement of 0.2 was assumed to apply to the R-chemo arm	Data collected from the ibrutinib trials already capture the utility decrement associated with any AE related to ibrutinib within the trial. The decrement for R-chemo was based on consulted clinical experts, who suggested that patients receiving R-chemo regimens experience considerable impact from treatment to several aspects of life whereas patients receiving ibrutinib feel similar to the general population.
Duration of QoL decrement for R-chemo	QoL decrement applied to the comparator (to account for AEs) was based on TOT	Conservative assumption that the decrement encountered by patients receiving R-chemo regimens only lasts whilst they are receiving treatment
AE: adverse event, LOT: line of treatment, PFS: progression-free survival, OS: overall survival, PPS: post-progression survival, R/R MCL: relapsed or refractory mantle cell lymphoma, TOT: time on treatment, QoL: quality of life, ORR: overall response rate, R-chemo: rituximab in combination with chemotherapy		

Table 75: Summary of scenario analyses

Scenario	Description	Assumption tested
Comparative efficacy used to inform the model	An alternative method was explored for the estimation of comparative effectiveness assuming that R-chemo has the same PFS as TEM	Assessed the sensitivity of the model to the evidence available that could be used to inform the efficacy of the comparator
Length of model time horizon	2 scenarios tested for a different time horizon 10 and 20 years to examine the sensitivity of results to the extrapolation of efficacy and costs over time	Assessed the sensitivity to the level of extrapolation to examine the degree to which the time horizon affects the ICER
Comparators	4 scenarios were tested exploring the use of drug costs for different comparator treatments specified within the NICE scope: • R-CVP • FCR • RC • Treatment mix	Assessed the sensitivity of the ICER to different treatment costs (given that no information was available to inform differential comparative effectiveness)
Wastage	1 scenario was tested that explored the impact of allowing vial sharing within the model	Assessed the sensitivity of the ICER to vial wastage
OS method	A scenario was tested to explore OS based upon a sequential approach to modelling ibrutinib that allows R-chemo to be administered after ibrutinib suggested during the advisory board	Assessed the structural sensitivity of the overall costs and health outcomes to assumptions regarding OS methods and subsequent therapy
Subsequent treatment	Subsequent treatment with FCR applied to patients in both arms. Applied as a *one off* lump sum cost	Testing the sensitivity of subsequent treatment on the model results
Parametric curve fit to PFS KM data	3 alternative curve fits were tested: • Exponential • Log-normal • Log-logistic	Assessed the impact of the parametric function chosen to extrapolate PFS data
Risk of death during PFS for the comparator arm	Assumption was tested that the risk of death during PFS for R-chemo was equal to ibrutinib	Assessed the sensitivity of the model to conservatively assuming to treatment benefit for ibrutinib on PFS
Response rates within the model	3 different assumptions tested in scenario analysis that vary the ORR for R-chemo: • Using response rates based on TEM within RAY (MCL3001)	Assessed the sensitivity of the model to changes in assumptions related to cost of resource use with R-chemo

Scenario	Description	Assumption tested
	• Assuming response rates based on the Hess, 2009 ITC • Assuming response rates are equal to ibrutinib	
QoL assumptions	2 different assumptions tested in scenario analysis: • QoL decrement for R-chemo informed by Schenkel 2014 data for HRQoL post progression[97] • Assuming no age adjustment to utilities	Assessed the sensitivity of the model to assumptions around QoL
Rituximab PFS HR assumptions	4 different assumptions tested in scenario analysis which vary the PFS HR of rituximab applied to the Hess, 2009 ITC • No benefit from rituximab (HR=1) • Rituximab effect applied (HR=0.75) • Rituximab effect applied (HR = 0.89) • Rituximab effect applied (HR=1.6)	Assessed the sensitivity of the model to assumptions around rituximab effect informing comparative efficacy
PPS adjustment	Adjusting the time spent in PPS for the comparator to be as close as possible to HMRN data which suggest OS for patients at 2nd line treatment of 8.4 months[7]. This was conducted by applying a HR to the ibrutinib PPS to calculate an increased risk of death during PPS for R-chemo which reduces survival to be as close as possible to the HMRN data	Assessed the sensitivity of the model to the survival data
KM: Kaplan-Meier, ITC: indirect treatment comparison, OS: overall survival, PFS: progression-free survival, TEM: temsirolimus, ORR: overall response rate, R-chemo: rituximab in combination with chemotherapy, QoL: quality of life, HRQoL: health-related quality of life, HR: hazard ratio		

5.7 *Base-case results*

Results presented within this section are at list price for ibrutinib. Economic analysis incorporating the current simple PAS is presented in Appendix 20.

5.7.1 *Base-case incremental cost effectiveness analysis results*

Base case results of the economic comparison between ibrutinib and R-CHOP discounted at 3.5% for costs and QALYs over the 15-year time horizon are presented in Table 76.

Ibrutinib was estimated to generate an additional 1.23 life years and 0.94 QALYs. This represents a substantial improvement to both length and QoL for patients with an extremely poor prognosis. The mean life years estimated for patients treated with ibrutinib are over double compared to what estimated for R-chemo.

Table 76: Base case discounted results, ibrutinib versus R-CHOP

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Ibrutinib	[redacted]	[redacted]	[redacted]	£94,239	1.23	0.94	£100,647
R-CHOP	[redacted]	[redacted]	[redacted]				
ICER: incremental cost-effectiveness ratio, QALYs:, quality-adjusted life years, R-CHOP: rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone							

5.7.2 *Clinical outcomes from the model*

Table 77 summarises the median results estimated by the CEA in comparison to median results observed in the ibrutinib pooled dataset for the key clinical outcomes[5]. The model predicted the median PFS accurately and predicted the median OS conservatively. The median OS predicted within the model for R-chemo is relatively high compared to the OS information available from published data sources indicating that a highly conservative comparison of the relative effectiveness of ibrutinib to R-chemo has been presented.

Table 77: Summary of model results compared with clinical data (months)

Outcome	Ibrutinib pooled dataset	Ibrutinib model results	R-chemo literature information	R-chemo model results
Median PFS	12.81 (8.48, 16.56)[5]	12.88	1.9 from Hess, 2009[8] 2.8 in Skåne registry[9]	2.76
Median OS	25.00 (21.59, NE)[5]	20.24	8.4 in HMRN[7] 9.7 in Hess, 2009[8] 5.2 in Skåne registry[9]	10.12
NE: not evaluable, OS: overall survival, PFS: progression-free survival, R-chemo: rituximab in combination with chemotherapy, HMRN: Haematological Malignancy Research Network				

5.7.3 *Disaggregated results of the base case incremental cost effectiveness analysis*

Table 78 summarises the total QALYs for both arms of the base case model, disaggregated by the model health states. Table 79 summarises the total life years accrued over the time horizon for both arms of the model. As expected, the majority of the difference between the two model arms is observed in the pre-progression health state. Table 80 shows the

predicted total incremental costs for ibrutinib versus R-CHOP. The majority of the costs are incurred within the pre-progression health state, and represent the drug costs associated with treating patients with R/R MCL. Table 81 shows these data further split by the category of cost incurred within the model.

Table 78: Base case: total discounted QALYs gained by health state

	QALY ibrutinib	QALY R-CHOP	Increment
PFS	[redacted]	[redacted]	0.99
PPS	[redacted]	[redacted]	-0.05
Total	[redacted]	[redacted]	0.94

QALY: quality-adjusted life year, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone, PFS: progression-free survival, PPS: post-progression survival

Table 79: Base case: total undiscounted LYs gained by health state

	LY ibrutinib	LY R-CHOP	Increment
PFS	[redacted]	[redacted]	1.29
PPS	[redacted]	[redacted]	-0.06
Total	[redacted]	[redacted]	1.23

LY: life year, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone, PFS: progression-free survival, PPS: post-progression survival

Table 80: Base case: total discounted costs accrued in each health state

	Costs ibrutinib	Costs R-CHOP	Increment
PFS	[redacted]	[redacted]	£95,218
PPS	[redacted]	[redacted]	-£979
Total	[redacted]	[redacted]	£94,239

LY: life year, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone, PFS: progression-free survival, PPS: post-progression survival

Table 81: Base case: category of discounted costs accrued within the model

Item	Cost ibrutinib	Cost R-CHOP	Increment
PFS drug cost	[redacted]	[redacted]	£92,573
PFS administration cost	[redacted]	[redacted]	-£1,427
PFS routine follow up	[redacted]	[redacted]	£4,158
AE cost	[redacted]	[redacted]	-£86
Subsequent treatment	[redacted]	[redacted]	£0
PPS routine follow up cost	[redacted]	[redacted]	-£693
Terminal care cost	[redacted]	[redacted]	-£286
Total costs	[redacted]	[redacted]	£94,239

AE: adverse event, PFS: progression-free survival, PPS: post-progression survival, R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

5.8 *Sensitivity analyses*

5.8.1 *Probabilistic sensitivity analysis*

Probabilistic sensitivity analysis (PSA) was performed within the CEA for 1,000 iterations of ibrutinib versus R-CHOP, randomly sampling parameters within their chosen distributions. This analysis demonstrates the impact of parameter uncertainty within the economic model. The results of this analysis are presented in Figure 37, which shows the incremental costs and QALYs for each iteration. Incremental QALYs range from approximately 0.6-1.4, while incremental costs range from £80,000 to £120,000. The largest spread of uncertainty was across the x axis reporting the incremental QALYs. Overall the average incremental QALYs gained from ibrutinib was 0.94 with a mean incremental cost of £94,428, resulting in a mean probabilistic ICER of £101,912. The overall average results were very close to the deterministic base case results (0.94 and £94,239 incremental QALYs and costs respectively), indicating that there is no bias in the deterministic ICER caused by skewed uncertainty within the model parameters.

Based on the 1,000 iterations performed within the PSA, a cost-effectiveness acceptability curve (CEAC) was constructed and is presented in Figure 38. This graph shows the likelihood that each treatment is the most cost-effective option at different willingness to pay (WTP) thresholds.

Figure 37: Cost-effectiveness plane from 1,000 PSA iterations

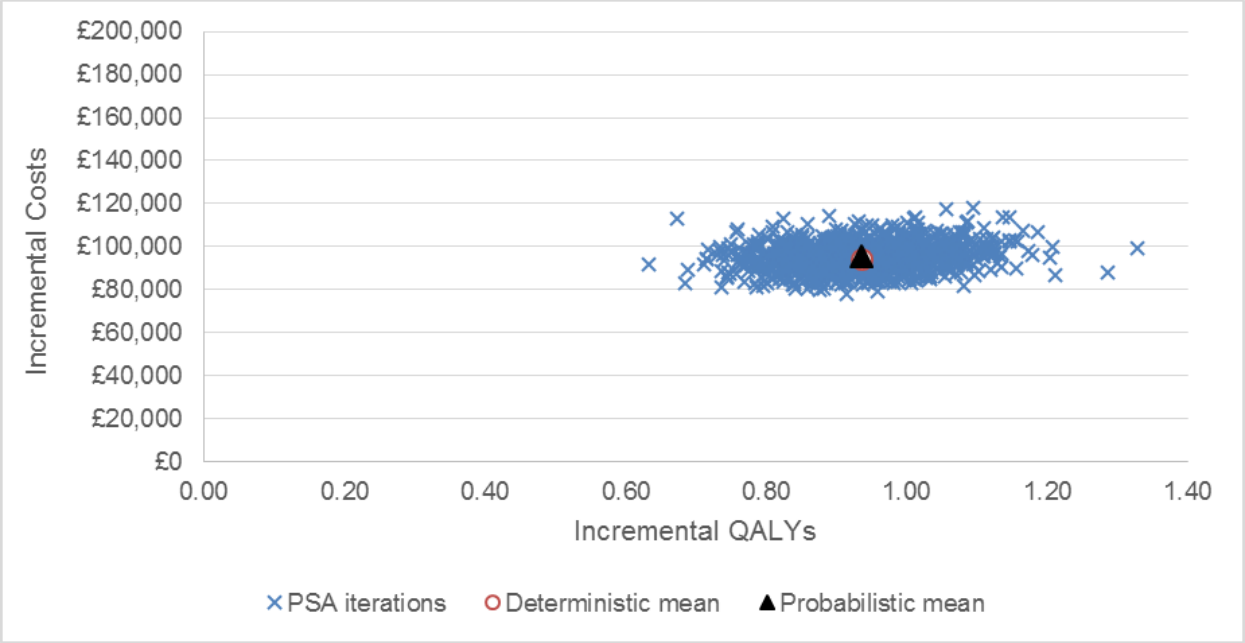
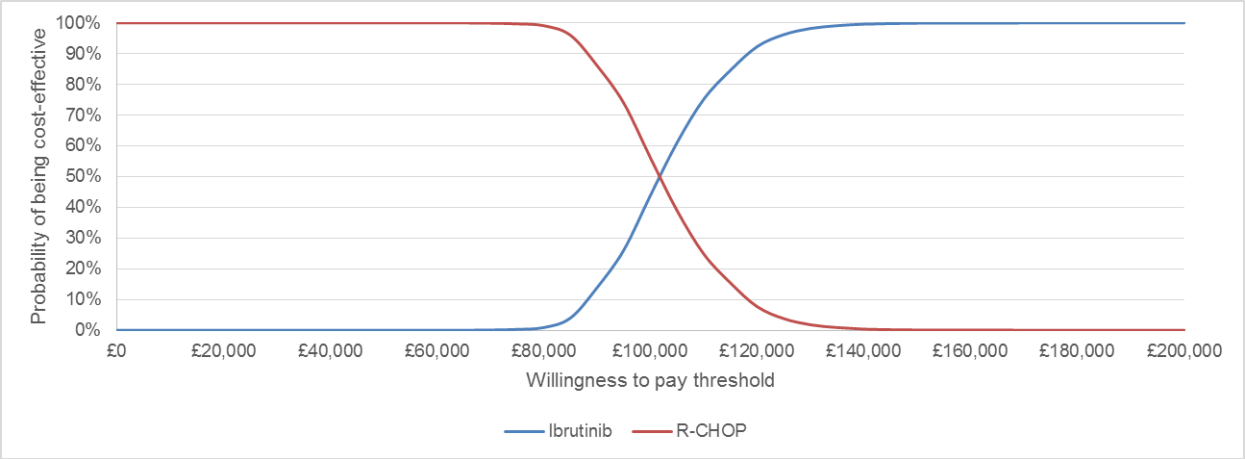


Figure 38: Incremental cost-effectiveness acceptability curve



5.8.2 ***Deterministic sensitivity analysis***

Figure 39 presents a tornado diagram showing the parameters with the greatest impact on the net monetary benefit (NMB) of ibrutinib, with descending sensitivity.

The NMB was calculated as:

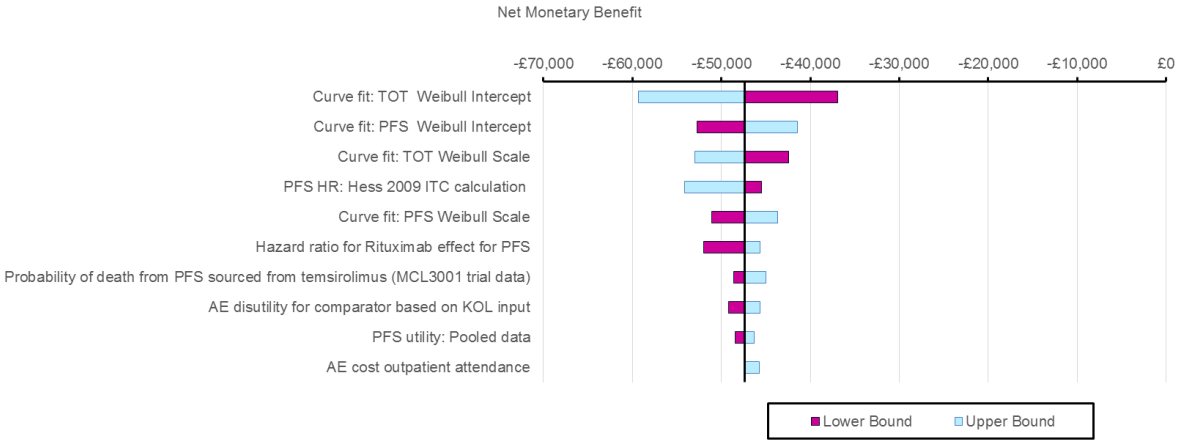
$$NMB = (WTP \times Incremental\ QALYs) - Incremental\ Costs$$

The WTP was set at £50,000/QALY, as ibrutinib meets the *end-of-life* criteria in this indication (see Section 4.14.3).

NMB was used in order to account for any issues which may arise as a result of dominant or dominated results where negative ICERs are created. Where the NMB is positive, ibrutinib represents a cost-effective treatment based on a WTP threshold of £50,000 per QALY. Figure 39 shows the ten most influential parameters. The NMB was most sensitive to the uncertainty within the curve fit parameters for TOT and PFS. Parameters informing the HR for comparative efficacy were also influential within the CEA as would be expected. The

utility data informing the model were also influential, with both the PFS utility and the disutility associated with R-chemo appearing within the top 10 parameters.

Figure 39: Tornado diagram



5.8.3 ***Scenario analysis***

Table 82 shows the results of the extensive scenario analyses performed which tested the structural uncertainty within the model and are described in Section 5.6. Overall the model was most sensitive to the PPS assumed for the R-chemo arm. Within the PPS scenario a HR was applied to the PPS for R-chemo that reduced the time spent in PPS. The HR selected minimised the difference between the median OS within the model and the median survival reported within the HMRN data (which was estimated to be 8.4 months for patients on second line treatment regimens)[7].

The model was also sensitive to the dataset used to inform PFS of R-chemo. Testing the PFS of TEM from RAY (MCL3001) as a proxy for R-chemo increased the ICER as the estimate used to inform R-chemo here was higher than the one in the base case. It should be noted that no evidence is available regarding the comparative effectiveness of TEM and R-chemo.

In general, results from scenario analyses were consistent with the base case results, demonstrating the minimal amount of uncertainty in the key assumptions.

Table 82: Scenario analyses conducted within the economic model

Scenario	Ibrutinib			R-CHOP			Incremental outcomes			
	Total Costs	Total QALYs	Total LYs	Total Costs	Total QALYs	Total LYs	Inc. Costs	Inc. QALYs	Inc. LYs	ICER
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£94,239	0.94	1.23	£100,647
Comparator efficacy HR for PFS using TEM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£92,151	0.82	1.01	£112,983
Time horizon: 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£93,922	0.93	1.22	£101,178
Time horizon: 20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£94,261	0.94	1.24	£100,591
Comparator: R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£95,564	0.94	1.23	£102,062
Comparator FCR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£92,071	0.94	1.23	£98,332
Comparator RC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£93,298	0.94	1.23	£99,642
Treatment mix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£94,263	0.94	1.23	£100,673
No wastage included	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£94,665	0.94	1.23	£101,103
Utility decrement for R-chemo based on Schenkel *et al.* 2014	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£94,239	0.93	1.23	£101,818
No age-adjusted utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£94,239	0.95	1.23	£99,337
Sequential approach (OS ibrutinib = PFS ibrutinib + PFS R-chemo + PPS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£106,331	1.08	1.43	£98,518
Including FCR as subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£92,657	0.94	1.23	£98,958
PFS curve: exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£89,910	0.83	1.06	£107,891

Scenario	Ibrutinib			R-CHOP			Incremental outcomes			
	Total Costs	Total QALYs	Total LYs	Total Costs	Total QALYs	Total LYs	Inc. Costs	Inc. QALYs	Inc. LYs	ICER
PFS curve: log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£123,293	1.30	1.88	£94,898
PFS curve: log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£129,751	1.32	1.93	£98,306
Risk of death during PFS for R-chemo assumed equal to ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£93,992	0.92	1.21	£102,458
Response rates of R-chemo equal to TEM response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£93,980	0.94	1.23	£100,372
Response rates of R-chemo equal to response in Hess, 2009 Y	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£93,063	0.94	1.23	£99,392
Response rates of R-chemo equal to ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£94,374	0.94	1.23	£100,792
No benefit from rituximab in PFS HR (rituximab HR = 1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£95,931	1.00	1.35	£95,934
Rituximab PFS HR applied to Hess, 2009 ITC = 0.75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£94,625	0.95	1.26	£99,289
Rituximab PFS HR applied to Hess, 2009 ITC = 0.89	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£95,409	0.98	1.32	£97,082
Rituximab PFS HR applied to Hess 2009 ITC = 1.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£97,869	1.05	1.44	£93,204
Applying a HR to PPS of R-chemo to adjust survival to be as close as possible to HMRN anticipated survival (8.4 months for patients on 2nd line treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£146,837	1.87	2.64	£78,541

HR: hazard ratio, PFS: progression-free survival, TEM: temsirolimus, R-CVP: rituximab + cyclophosphamide + vincristine + prednisone, FCR: fludarabine + cyclophosphamide + rituximab, RC: rituximab + cytarabine, R-chemo: rituximab-based chemotherapy, OS: overall survival, ITC: indirect treatment comparison, PPS: post-progression survival, HMRN: haematological malignancy research network, QALY: quality-adjusted life year, LY: life year, Inc: incremental

5.8.4 ***Summary of sensitivity analyses results***

PSA indicates that the results obtained within the base case were robust to parameter uncertainty, with average PSA results very similar to the deterministic results. The model results showed that the majority of uncertainty lays within the estimated QALYs, however, in all cases a substantial QALY improvement was expected for ibrutinib compared to R-chemo (QALY gains expected to lie between 0.6 and 1.4).

Key uncertainties within the model parameterisation surrounded the parametric curve fits to TOT and PFS and the HR assumed for comparative efficacy within the model. Within scenario analysis the model was also sensitive to the PPS assumed for R-chemo, with the ICER reducing when HMRN data were used to inform PPS. The model was also sensitive to the dataset used to inform the PFS of R-chemo, with the use of the TEM arm of RAY (MCL3001) as proxy for R-chemo producing an increased estimate of the ICER.

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

5.8.5 ***Subgroup analysis***

Results of the economic comparison between ibrutinib and R-CHOP for subgroups of 1 prior LOT versus 2+ prior LOTs are presented in Table 83 and Table 84. Substantially higher estimates of LYs and QALYs were produced for ibrutinib in the subgroup of patients only receiving one prior LOT. These results are consistent with the findings of the *post-hoc* analysis of RAY (MCL3001) presented in Section 4.8.2, clearly demonstrating that an increased benefit is observed when ibrutinib is used early in the treatment pathway for R/R MCL, which were also confirmed in the pooled dataset (Section 4.12.2). In those patients with 1 prior LOT, ibrutinib produces 3.65 LYs, compared to 1.91 LYs in patients with 2+ prior LOTs. This strongly suggests that whilst all R/R MCL patients can benefit from ibrutinib, the benefit is more pronounced the earlier they receive it.

Table 83: Base case discounted results, ibrutinib versus R-CHOP: 1 prior LOT

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Ibrutinib	[redacted]	[redacted]	[redacted]	£144,286	2.34	1.67	£86,194
R-CHOP	[redacted]	[redacted]	[redacted]				
ICER: incremental cost-effectiveness ratio, QALYs:, quality-adjusted life years, R-CHOP: rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone							

Table 84: Base case discounted results, ibrutinib versus R-CHOP: 2 + prior LOTs

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Ibrutinib	[redacted]	[redacted]	[redacted]	£80,121	0.92	0.72	£111,764
R-CHOP	[redacted]	[redacted]	[redacted]				
ICER: incremental cost-effectiveness ratio, QALYs:, quality-adjusted life years, R-CHOP: rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone							

5.8.6 *Threshold analysis on comparative efficacy*

Due to the paucity of data available to inform the effectiveness of the comparators in the NICE scope, a high level of uncertainty specifically lies within the PFS HR estimate used to inform the comparative effectiveness of R-chemo. As explained in previous sections, this is not an uncertainty that Janssen could have addressed, due to the unlicensed nature of R-chemo. We have therefore presented an extensive analysis below showing how much the estimated benefit of R-chemo (in terms of PFS HR for ibrutinib vs. R-chemo, and the specific HR for the effect of adding rituximab to chemo) would need to increase in order to produce a meaningful increase in the ICER (i.e., how a decrease in the relative benefit of ibrutinib vs. R-chemo impacts the ICER).

Table 85 shows how the ICER changes with an increase in HR of R-chemo (i.e., decreasing the comparative effectiveness of ibrutinib over R-chemo). The analysis shows that the ICER is relatively insensitive to any increase in R-chemo HR. Even when the HR is increased by as much as 90% (HR=0.53) the ICER only increases by 23.39%. This HR of 0.53 could be considered clinically implausible as this would represent a mean PFS for R-chemo of 10.09 months, which is considerably greater than that observed in clinical practice (1.9 months in Hess, 2009 and 2.8 months in Skåne).

A similar conclusion can be drawn from the 'threshold' analysis on the effect of adding rituximab to the HR derived from Hess, 2009 (Table 86). Decreasing the HR of adding rituximab (which increases the overall PFS HR of R-chemo, thus reducing the estimate of comparative efficacy of ibrutinib over R-chemo) does not impact the ICER substantially (for example, a decrease of 45% only raises the ICER by 19.59%). The ICER raises substantially only when unrealistic HRs for the rituximab effect are tested, such as a HR of 0.17, which would mean that rituximab would add an additional benefit of 83% to the one observed in Hess, 2009.

Consequently, these 'threshold' analyses show how, despite there being uncertainty in the estimates of the comparative efficacy of comparators from the NICE scope in this submission, the ICER remains relatively stable.

Table 85: Threshold analysis on the PFS HR of R-chemo

Increase in HR of R-chemo	R-chemo HR	ICER	Increase in ICER
Base case	0.28	£100,647	
15%	0.32	£103,843	3.17%
30%	0.36	£107,098	6.41%
45%	0.41	£110,729	10.02%
50%	0.42	£112,027	11.31%
60%	0.45	£114,762	14.02%
75%	0.49	£119,234	18.47%
90%	0.53	£124,192	23.39%
105%	0.57	£129,696	28.86%
120%	0.62	£135,819	34.95%
135%	0.66	£142,655	41.74%
150%	0.70	£150,317	49.35%

R-chemo: rituximab in combination with chemotherapy, HR: hazard ratio, ICER: incremental cost-effectiveness ratio

Table 86: Threshold analysis on the PFS HR for the effect of adding rituximab

Increase in HR of the effect of rituximab	Effect of rituximab HR	ICER	Increase in ICER
Base case	**0.69**	£100,647	
-15%	0.59	£103,966	3.30%
-30%	0.48	£109,597	8.89%
-45%	0.38	£120,368	19.59%
-60%	0.28	£148,112	47.16%
-75%	0.17	£319,549	217.49%
R-chemo: rituximab in combination with chemotherapy, HR: hazard ratio, ICER: incremental cost-effectiveness ratio			

5.9 *Validation*

5.9.1 *Validation of* de novo *cost-effectiveness analysis*

The model was quality-assured by the internal processes of the economists who produced the economic model. In these processes, an economist not involved in the model adaptation reviewed the model for coding errors, inconsistencies and the plausibility of inputs. The model was also subjected to an internal and external checklist of known modelling errors, and the assumptions were questioned.

Further to this, the conceptual model and key assumptions were validated at an advisory board with practising haematologists in the UK[12]. The shared content was comprised of the clinical trial data package, the model structure, the assumptions regarding the treatment pathway, the preliminary survival analysis undertaken, the preliminary EQ-5D analysis undertaken and the methodology used for costs and resource use. The opinions provided by these clinical experts were used to determine the datasets used within the model and the model base case in terms of survival analysis and utilities.

5.9.2 *Clinical validity*

Long-term trial projections compared reasonably well to the available Kaplan–Meier data (Figure 32 and Figure 33) with conservative assumptions regarding long-term survival chosen based upon clinical advice received. The comparison of modelled medians to observed information for both ibrutinib and R-chemo indicates that a highly conservative comparison of the relative effectiveness of ibrutinib to R-chemo has been presented (Table 77).

Utility values measured in the pooled dataset used in the model base case were 0.78 for PFS of ibrutinib and 0.58 for PFS of R-chemo. This can be compared to a utility value of 0.78 for the UK general population for persons aged 65-74[114]. The assumption that patients on ibrutinib have the same QoL as the UK general population is in line with clinical advice, suggesting that patients receiving ibrutinib feel similar to or even better than the general population. Utilities for patients receiving R-chemo are broadly in line with the published literature available, which indicate a utility 0.61 for R/R MCL[97].

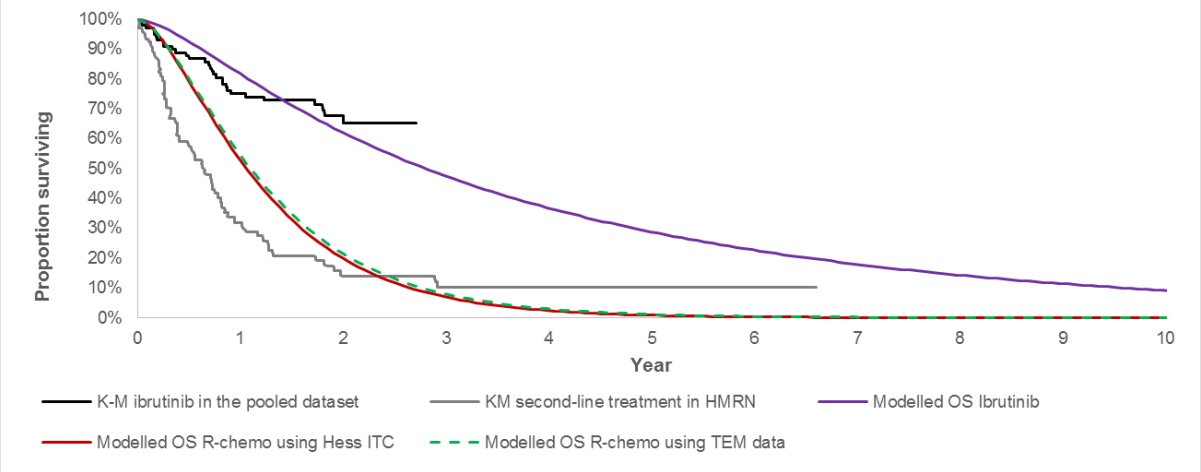
5.9.3 *Generalisability*

Feedback from clinical experts was that the clinical trial data for ibrutinib are generalisable to clinical practice, with the only major difference being that in clinical practice clinicians would

likely use ibrutinib at first relapse (i.e. after fewer prior LOTs than as observed in RAY [MCL3001)])[12]. Further support for the generalisability of the RAY (MCL3001) study results is provided by the similarity of TOT observed in the ibrutinib clinical trials to real-world evidence from the CUP study presented in Section 4.11.3.

Whilst a substantial data package is available to demonstrate the effectiveness of ibrutinib in R/R MCL the same cannot be said for the unlicensed treatments currently used in UK clinical practice. This represents uncertainty that Janssen can do little to address. When model projections were compared to the only data source available for the OS of patients at second-line in the UK the conservative nature of model projections for R-chemo can easily be observed (Figure 40)[7].

Figure 40: Modelled versus observed data for OS in patients with 1 prior LOT



Outcomes using the Hess, 2009 + R ITC and TEM data are similar for patients with 1 prior LOT as the HR calculated for Hess, 2009 + R using the ITC (HR=0.28) is assumed to apply to all LOTs whereas the comparison to TEM observed data indicates an improvement in the HR (favouring ibrutinib) for patients who have only received 1 prior LOT (HR=0.30)

5.10 *Interpretation and conclusions of economic evidence*

The economic analysis presented within this section has demonstrated the cost-effectiveness of ibrutinib for patients with R/R MCL from the perspective of the NHS and PSS. There is a wealth of evidence available to support the clinical efficacy of ibrutinib within the model including a pivotal phase III comparative study RAY (MCL3001). Although there is a large gap in evidence available to inform the effectiveness of R-chemo, two options have been presented based on the evidence that is available. Where possible, methodology and model assumptions have been validated by expert clinicians in the treatment of MCL in the UK. Overall, the CEA demonstrated the benefit of ibrutinib as shown within the clinical trials, and estimated an additional 1.23 life years gained as a result of treatment with ibrutinib (0.94 QALYs), all of which were a result of increased time spent in PFS (where patients experience a greater QoL) with no benefits assumed to PPS (a highly conservative assumption). The mean life years estimated for patients treated with ibrutinib are more than double those estimated for R-chemo and what is observed in the literature.

The introduction of this clinically effective treatment regimen offers an important improvement in prognosis for patients with current expected median survival of 5 – 10 months. In addition, the use of ibrutinib offers substantial improvements to patient QoL and may provide a further LOT for patients, delaying treatment with toxic chemotherapy regimens and potentially further improving prognosis through increased ability of patients to benefit from subsequent treatment.

To fulfil the NICE scope requirements, comparisons were provided for ibrutinib versus R-CHOP (which formed the base case analysis as it was considered the most appropriate comparator within the R/R MCL patient population), R-CVP, FCR, and RC. The model also provided a comparison against a treatment mix which weighted the comparator by the anticipated use in real-life UK practice (based on clinicians' feedback). As no robust evidence was available to make a clinical assessment, only the drug costs were varied under these comparisons. The model predicted similar ICERs across these various comparisons.

Whilst a substantial data package is available to demonstrate the effectiveness of ibrutinib in R/R MCL the same cannot be said for the unlicensed treatments currently in use in clinical practice. When model projections were compared to the only data source available for the OS of patients at second-line in the UK the highly conservative nature of model projections for R-chemo can easily be observed.

Extensive efforts were made to source comparators' data suitable to undertake analysis which resulted in comparison being made to two available datasets. Whilst both data sources available for comparison have limitations, the stability of CEA results to the data source chosen should provide reassurance regarding the cost-effectiveness of ibrutinib in this indication.

Key uncertainties within the model surrounded the parametric curve fits to the ibrutinib PFS and TOT data; however, the use of different curve fits had only a small impact on the overall outcomes of the model. The model was also sensitive to the methods used to estimate comparative efficacy, such as the data used to inform R-chemo, which would be expected given the paucity of evidence that exists to inform the comparator arm of the economic analysis.

Overall the majority of uncertainty within the model surrounded the estimated QALYs gained (as opposed to the costs encountered from treatment), however in all cases a substantial QALY improvement was expected for ibrutinib patients compared to those treated with R-chemo. The PSA and the extensive scenario analysis conducted within the model presented indicate that the total additional benefit of treating patients with ibrutinib is expected to be between 0.6 and 1.4 QALYs; almost doubling the QALYs expected currently for R-chemo.

6 Assessment of factors relevant to the NHS and other parties

Summary

A budget impact analysis (BIA) was performed by comparing the budget impact to the NHS 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 on the R/R MCL population, which was estimated to be 356 patients in 2017 rising to 367 patients in 2021.

Market share data were estimated based on from IMS Harmony data (August 2014 to January 2016) and drug acquisition and administration costs used were the same as those applied in the CEA (Section 5).

The results of the BIA estimated the introduction of ibrutinib to be associated with a budget impact of £10,394,534 in 2017 and a cumulative budget impact of £69,773,686 over the 5 years after NICE recommendation.

6.1 *Overview of the budget impact analysis*

The budget impact of introducing ibrutinib for the treatment of R/R MCL to NHSE was estimated using a Microsoft Excel budget impact model (BIM). The BIM calculates the difference in total costs to NHSE in treating patients with R/R MCL in two Scenarios:

- World without ibrutinib: ibrutinib is not recommended for R/R MCL
- World with ibrutinib: ibrutinib is recommended for R/R MCL

The model calculates drug acquisition and administration costs on a 5-year time horizon for R/R MCL patients from a NHSE perspective.

Displaced therapies included in the BIM reflect treatment options routinely used in the UK to treat R/R MCL patients who have failed one prior line of treatment, consistent with the NICE final scope[49].

A confidential discount has been agreed with the DH, therefore the budget impact of ibrutinib has been estimated separately using the list price and the price after the currently agreed discount associated with ibrutinib. Scenario analyses were performed to test the uncertainty in the prevalence of R/R MCL estimate and in the market shares.

6.2 *Patient numbers*

Patient numbers were estimated using a simple 3-step methodology (see Table 87):

1. Total overall population: the population in England, Wales, and Northern Ireland in 2014 was reported by the Office of National Statistics (ONS) in February 2016[115]. The growth rate of each devolved nation, also from the ONS, was individually applied to each population and the sum was used to derive the total overall population from 2017 to 2021[115]

2. No published data were found on the prevalence of R/R MCL in the UK. Therefore, prevalence of all MCL in England was obtained from the HMRN website[7]. The

database reported prevalence rates for people diagnosed with MCL in the previous 3, 5 and 10 years. However, given that the median OS of newly diagnosed MCL patients is 3-4 years[33], the 3-year rate was deemed most appropriate for use in the budget impact analysis (BIA)

3. The HMRN audit[7] provides an estimate of the number of MCL patients who receive second line treatment (among all MCL patients within the audit). The proportion of patients receiving second line MCL treatment was used as a proxy for R/R MCL.

The prevalence of R/R MCL estimated 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 R/R MCL will change in the short-term.

Ibrutinib is indicated for the treatment of R/R MCL patients, without further restriction to any sup-population. Accordingly, the number of patients eligible for ibrutinib was modelled to be equal to the number of patients with R/R MCL. The population of patients estimated to be eligible to treatment with ibrutinib for R/R MCL is reported in Table 88. Given that NICE recommendation is expected in early 2017, the full year is considered.

Table 87: Inputs used in the estimation of the BIA population

Description of input	Input value	Source
England population in 2014	54,300,000	ONS: Overview of the UK Population, Table 4[115]
Wales population in 2014	3,100,000	ONS: Overview of the UK Population, Table 4[115]
Northern Ireland population in 2014	1,800,000	ONS: Overview of the UK Population, Table 4[115]
England population growth rate	0.71%	ONS: Overview of the UK Population, Table 4[115]
Wales population growth rate	0.45%	ONS: Overview of the UK Population, Table 4[115]
Northern Ireland population growth rate	0.71%	ONS: Overview of the UK Population, Table 4[115]
Prevalence of MCL	0.0016%	Prevalence of MCL in people diagnosed in the previous 3 years from HMRN[7]
Prevalence of R/R MCL (among MCL)	36.69%	HMRN Audit. Patients who received second line MCL treatment / all MCL patients (91/248)[7]
R/R MCL: relapsed or refractory mantle cell lymphoma, ONS: Office of National Statistics		

Table 88: BIA estimated eligible population

	2017	2018	2019	2020	2021
Projected population (total)	60,577,755	61,044,165	61,514,202	61,987,893	62,465,267
Projected population of England	55,597,103	56,036,320	56,479,007	56,925,192	57,374,901
Projected population of Wales	3,142,039	3,156,178	3,170,381	3,184,647	3,198,978
Projected population of Northern Ireland	1,838,613	1,851,667	1,864,814	1,878,054	1,891,388
Estimated number of people with MCL (prevalent cases)	969	977	984	992	999
Patients receiving 2nd line therapy (R/R) MCL	356	358	361	364	367
R/R MCL: relapsed or refractory mantle cell lymphoma					

6.3 *Market shares*

Market shares were estimated for the world without and with ibrutinib based on market research data from IMS Health (data from August 2014 to January 2016)[54], feedback from a recent advisory board with three leading KOLs in the treatment of MCL in the UK[12], and the market penetration of ibrutinib observed from the CDF orders since the listing of ibrutinib in January 2015[34, 35]. IMS Health data from October 2015, November 2015 and January 2016 reveal that, at second-line, ibrutinib has become the most frequently prescribed treatment (54% in October, 64% in November and 37% in January) for MCL due to CDF funding.

As detailed in Section 3.4.2, R-CHOP is the most commonly used treatment as first relapse for less fit patients. R-CVP is the most common treatment for frail patients, FCR is used in some centres for historical reasons and RC is only used in fit newly diagnosed MCL patients[12].

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 (50%) after NICE recommendation in 2017. This share is expected to increase constantly and reach 75% 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 89.

Table 89: Market shares in the world without/with ibrutinib

	2016	2017	2018	2019	2020
World without ibrutinib					
Ibrutinib	0.00%	0.00%	0.00%	0.00%	0.00%
R-CHOP	85.00%	85.00%	85.00%	85.00%	85.00%
R-CVP	10.00%	10.00%	10.00%	10.00%	10.00%
FCR	5.00%	5.00%	5.00%	5.00%	5.00%
RC	0.00%	0.00%	0.00%	0.00%	0.00%
World with ibrutinib					
Ibrutinib	50.00%	60.00%	70.00%	75.00%	75.00%
R-CHOP	42.50%	34.00%	25.50%	21.25%	21.25%
R-CVP	5.00%	4.00%	3.00%	2.50%	2.50%
FCR	2.50%	2.00%	1.50%	1.25%	1.25%
RC	0.00%	0.00%	0.00%	0.00%	0.00%
Patients expected to receive ibrutinib	178	215	253	273	275

R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone, R-CVP: rituximab + cyclophosphamide + vincristine + prednisone, FCR: fludarabine + cyclophosphamide + rituximab, RC: rituximab + cytarabine

6.4 *Cost inputs included in the BIA*

The same drug acquisition and administration costs for ibrutinib and comparators as used in the CEA (see Section 5.5.2) were used in the BIA (Table 90).

Table 90: Annual drug acquisition and administration costs used in the BIA

	Drug acquisition costs per patient per annum	Administration costs per patient per annum
Ibrutinib	£71,671	£0
R-CHOP	£11,577	£1,674
R-CVP	£8,623	£1,674
FCR	£13,456	£5,022
RC	£5,979	£4,464

R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone, R-CVP: rituximab + cyclophosphamide + vincristine + prednisone, FCR: fludarabine + cyclophosphamide + rituximab, RC: rituximab + cytarabine

6.5 *Results of the BIA*

6.5.1 *Base case analysis (with no discount)*

Table 91 presents the base case budget impact of introducing ibrutinib without the discount. The net total budget impact ranged from £10,394,534 in 2017 increasing to £16,077,618 in 2021.

Table 91: Budget impact of introducing ibrutinib to NHSE (with no discount)

	World without ibrutinib	World with ibrutinib	Budget impact
2017	£4,700,662	£15,095,196	£10,394,534
2018	£4,736,855	£17,306,333	£12,569,478
2019	£4,773,328	£19,550,634	£14,777,306

2020	£4,810,085	£20,764,834	£15,954,749
2021	£4,847,128	£20,924,746	£16,077,618
Total	**£23,868,058**	**£93,641,744**	**£69,773,686**

Table 92: Total (drug acquisition + administration) costs in the world with ibrutinib

	2017	2018	2019	2020	2021
Ibrutinib	£12,744,865	£15,411,591	£18,118,636	£19,562,313	£19,712,964
R-CHOP	£2,002,920	£1,614,673	£1,220,330	£1,024,772	£1,032,664
R-CVP	£183,115	£147,620	£111,567	£93,689	£94,410
FCR	£164,296	£132,449	£100,101	£84,060	£84,707
RC	£0	£0	£0	£0	£0
Total	£15,095,196	£17,306,333	£19,550,634	£20,764,834	£20,924,746
R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone, R-CVP: rituximab + cyclophosphamide + vincristine + prednisone, FCR: fludarabine + cyclophosphamide + rituximab, RC: rituximab + cytarabine					

6.5.2 *Results of the Scenario analyses (with no discount)*

The estimate of MCL prevalence together with the proportion of patients receiving 2nd therapy from the HMRN audit, used as proxy for R/R MCL, were varied by ±20% to test the impact on the budget impact results (Scenario 1, Table 93). These variables were chosen due to the paucity of available data on the prevalence of R/R MCL and, therefore, the potential uncertainty related to the figures used.

Table 93: Description and results of Scenario analysis 1 of the BIA (with no discount)

	Base case	High Scenario (+20%)	Low Scenario (-20%)
Inputs varied			
Prevalence of MCL	0.0016%	0.0019%	0.0013%
Prevalence of R/R MCL (among MCL)	36.69%	44.03%	29.35%
Results			
2017	£10,394,534	£14,811,451	£6,755,333
2018	£12,569,478	£17,910,588	£8,168,814
2019	£14,777,306	£21,056,582	£9,603,666
2020	£15,954,749	£22,734,352	£10,368,878
2021	£16,077,618	£22,909,431	£10,448,729
Total	**£69,773,686**	**£99,422,404**	**£45,345,420**
R/R MCL: relapsed or refractory mantle cell lymphoma			

Higher and lower figures (±20%) were also tested for the market penetration of ibrutinib (Scenario 2). Given that ibrutinib was assumed to gain markets shares from comparators equally, the same assumption was used in the Scenario analysis and all market shares were therefore recalibrated accordingly (Table 94). The resulting budget impact of ibrutinib from the Scenario 2 is presented in Table 95.

Table 94: Description of Scenario analysis 2 of the BIA (with no discount)

	2016	2017	2018	2019	2020
World with ibrutinib (base case)					
Ibrutinib	50.00%	60.00%	70.00%	75.00%	75.00%
R-CHOP	42.50%	34.00%	25.50%	21.25%	21.25%
R-CVP	5.00%	4.00%	3.00%	2.50%	2.50%
FCR	2.50%	2.00%	1.50%	1.25%	1.25%
RC	0.00%	0.00%	0.00%	0.00%	0.00%
Patients expected to receive ibrutinib	178	215	253	273	275
World with ibrutinib (high Scenario, +20%)					
Ibrutinib	60.00%	72.00%	84.00%	90.00%	90.00%
R-CHOP	34.00%	23.80%	13.60%	8.50%	8.50%
R-CVP	4.00%	2.80%	1.60%	1.00%	1.00%
FCR	2.00%	1.40%	0.80%	0.50%	0.50%
RC	0.00%	0.00%	0.00%	0.00%	0.00%
Patients expected to receive ibrutinib	213	258	303	328	330
World with ibrutinib (low Scenario, -20%)					
Ibrutinib	40.00%	48.00%	56.00%	60.00%	60.00%
R-CHOP	51.00%	44.20%	37.40%	34.00%	34.00%
R-CVP	6.00%	5.20%	4.40%	4.00%	4.00%
FCR	3.00%	2.60%	2.20%	2.00%	2.00%
RC	0.00%	0.00%	0.00%	0.00%	0.00%
Patients expected to receive ibrutinib	142	172	202	218	220

R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone, R-CVP: rituximab + cyclophosphamide + vincristine + prednisone, FCR: fludarabine + cyclophosphamide + rituximab, RC: rituximab + cytarabine

Table 95: Results of Scenario analysis 2 of the BIA (with no discount)

	Base case	High Scenario (+20%)	Low Scenario (-20%)
2017	£10,394,534	£12,473,441	£8,315,627
2018	£12,569,478	£15,083,374	£10,055,583
2019	£14,777,306	£17,732,768	£11,821,845
2020	£15,954,749	£19,145,699	£12,763,799
2021	£16,077,618	£19,293,142	£12,862,094
Total	**£69,773,686**	**£83,728,423**	**£55,818,949**

The BIA estimates were sensitive to variations in the estimate of R/R MCL prevalence. A variation of +20% increased the budget impact by 42% each year (from £14,811,451in 2017 to £22,909,431 in 2021) and a variation of -20% decreased the budget impact by 35% equally each year (from £6,755,333 to £10,448,729). An increase/decrease of ±20% in the ibrutinib uptake had a direct impact of ±20% increase/decrease in the budget impact each year (from £12,473,441in 2017 to £19,293,142 in 2021 when increased and from £8,315,627 in 2017 to £12,862,094 in 2021 when decreased).

6.6 ***Discussion***

Given the unprecedented benefits in terms of, ORR, DOR, PFS, OS, and QoL demonstrated in the clinical trial programme, and in light of the lack of effective therapeutic options for R/R MCL in the UK, a rapid market penetration for ibrutinib is expected (50% share of the market in 2017; a similar uptake has been observed for ibrutinib in R/R MCL thus far in England via the CDF notifications and IMS Harmony data (see Section 2.5)

The net budget impact of introducing ibrutinib as a treatment option of R/R MCL in the UK is expected to range between £10,394,534 in 2017, to £16,077,618 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.

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8 Appendices

Appendix 1: Summary of Product Characteristics (SmPC)

The Summary of Product Characteristics for ibrutinib is accessible on the European Medicines Agency website at the following link[25]:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003791/WC500177775.pdf

Appendix 2: European Public Assessment Report (EPAR)

The European Public Assessment Report for ibrutinib is accessible on the website of the European Medicines Agency at the following link[1]:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003791/WC500177777.pdf

Appendix 3: Search strategy for relevant clinical studies

Database Search Terms

The search terms used for the original (2014) clinical SLR for efficacy and safety outcomes are presented in Table 96 to Table 100 for the different database searches. The search terms used for the update SLR in 2015 are presented subsequently in Table 101 to Table 105.

Search terms for original clinical SLR

Table 96: Embase search terms (original SLR – 2014)

Search Number	Embase RR-MCL Clinical Search String	Yield
Patients Population		
1	'mantle cell lymphoma'/exp	6,592
2	('mantle cell lymphoma':ab,ti) OR ('mantle-cell lymphoma':ab,ti)	4,277
3	('mantle cell':ab,ti OR 'mantle-cell':ab,ti) AND (lymphoma:ab,ti OR lymphomas:ab,ti)	4,867
4	#1 OR #2 OR #3	6,852
Intervention or comparator		
5	'salvage chemotherapy':ab,ti OR 'salvage treatment':ab,ti OR 'salvage therapy'/exp OR 'resistant chemotherapy':ab,ti OR 'chemotherapy resistant':ab,ti OR 'treatment resistant':ab,ti	30,847
6	'second line' OR '2nd line' OR ('second':ab,ti AND 'line':ab,ti)	43,756
7	'third line' OR 'third-line' OR '3rd line' OR ('third':ab,ti AND 'line':ab,ti)	14,888
8	refractory:ab,ti OR refractor*:ab,ti OR resistant:ab,ti OR relaps*:ab,ti OR recurrent:ab,ti OR 'previously treated' OR 'drug resistance':ab,ti OR 'previously treated':ab,ti	880,324
9	failed:ab,ti OR failure:ab,ti AND (treatment:ab,ti OR therapy:ab,ti OR prior:ab,ti OR previous:ab,ti)	376,529
10	chemotherapy:ab,ti OR treatmen*:ab,ti OR regime*:ab,ti OR medication*:ab,ti OR therap*:ab,ti AND (refractory:ab,ti OR recurrent:ab,ti OR resistant:ab,ti OR rescue:ab,ti OR salvage:ab,ti OR failed:ab,ti OR failure:ab,ti)	713,541
11	#5 OR #6 OR #7 OR #8 OR #9 OR #10	1,307,615
Study design		
12	[Controlled Clinical Trial]/lim OR [Randomized Controlled Trial]/lim OR [Article in Press]/lim	616,444
13	'clinical trial'/exp OR random* OR placebo:ab,ti	1,707,323
14	#12 OR #13	1,803,070

Limitations			
15		[Cochrane Review]/lim OR [Systematic Review]/lim OR [Meta Analysis]/lim OR [Review]/lim	2,089,743
16		[Editorial]/lim OR [Erratum]/lim OR [Letter]/lim OR [Note]/lim OR [Short Survey]/lim	2,497,280
17		[2011 -2014]/py	4,168,257
18		[2013 -2014]/py	1,599,006
PICO Combined			
19	Clinical trials	(#4 AND #11 AND #14) NOT 16	1,009
20	Recent reviews	(#4 AND #11 AND #15 AND #17) NOT #16	143
21	Recent citations	(#4 AND #11 AND #18) NOT #16	393
22	Combined	# 19 OR #20 OR #21	1,235

Table 97: Embase In-Process search terms (original SLR – 2014)

Search Number	Embase RR-MCL Clinical Search String	Yield
Patients Population		
1	'mantle cell lymphoma'	6,600
2	'mantle-cell lymphoma'	6,600
3	('mantle cell' OR 'mantle-cell') AND (lymphoma OR lymphomas)	6,868
4	#1 OR #2 OR #3	6,868
Intervention or comparator		
5	'salvage chemotherapy' OR 'salvage treatment' OR 'salvage therapy' OR 'resistant chemotherapy' OR 'chemotherapy resistant' OR 'treatment resistant'	31,338
6	'second line' OR '2nd line' OR ('second' AND 'line')	59,834
7	'third line' OR 'third-line' OR '3rd line' OR ('third' AND 'line')	21,593
8	refractory OR refractor* OR resistant OR relaps* OR recurrent OR 'previously treated' OR 'drug resistance' OR 'previously treated'	1,111,007
9	failed OR failure AND (treatment OR therapy OR prior OR previous)	801,350
10	chemotherapy OR treatmen* OR regime* OR medication* OR therap* AND (refractory OR recurrent OR resistant OR rescue OR salvage OR failed OR failure)	1,179,413
11	#5 OR #6 OR #7 OR #8 OR #9 OR #10	1,917,356
Study design limits		
12	[Editorial]/lim OR [Erratum]/lim OR [Letter]/lim OR [Note]/lim OR [Short Survey]/lim	2,499,269
13	[2013 -2014]/py	800,617

PICO Combined		
14	(#4 AND #11 AND #13) NOT #12	141

Table 98: PubMed search terms (original SLR – 2014)

Search Number		PubMed RR-MCL Clinical Search String	Yield
Patient population			
1		("mantle cell"[tiab] OR "mantle-cell"[tiab]) AND (lymphoma[tiab])	3,168
2		“mantle cell lymphoma” OR “mantle-cell lymphoma”	3,190
3		"Lymphoma, Mantle-Cell"[Mesh]	1,949
4		(#1 OR #2 OR #3)	3,434
Intervention or comparator			
5		"salvage chemotherapy" OR "salvage treatment" OR "salvage therapy" OR “salvage therapy”[Mesh]	13,476
6		"resistant chemotherapy" OR "chemotherapy resistant" OR "treatment resistant"	5,444
7		“second line" OR second-line OR "2nd line" OR "2'nd line" OR (second[tiab] AND line[tiab])	31,695
8		“third line” OR “third-line” OR “3rd line” OR "3'rd line" OR ("third"[tiab] AND "line"[TIAB])	10,827
9		(refractory[tiab] OR refractor*[tiab] OR resistant[tiab] OR relaps*[tiab] OR recurrent[tiab] OR “drug resistance, neoplasm”[MeSH] OR "previously treated"[tiab])	699,910
10		((failed[tiab] OR failure[tiab]) AND (treatment[tiab] OR therapy[tiab] OR prior[tiab] OR previous[tiab]))	532,413
11		(chemotherapy[tiab] OR treatmen*[tiab] OR regime*[tiab] OR medication*[tiab] OR therap*[tiab]) AND (refractory[tiab] OR recurrent[tiab] OR resistant[tiab] OR rescue[tiab] OR salvage[tiab] OR failed[tiab] OR failure[tiab])	664,630
12		(#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	1,246,457
Study design			
13		“clinical trial”[ptyp] OR random* OR placebo[tiab] OR “Classical Article”[ptyp] OR “Comparative Study”[ptyp] OR “Controlled Clinical Trial”[ptyp] OR “Observational Study”[ptyp] OR “Technical Report”[ptyp]	4,100,616
Relevant SLR			
14		"review"[ptyp] OR “Systematic”[sb] OR “Meta-Analysis”[ptyp]	2,006,078
15		(Editorial[ptyp] OR "Published Erratum"[ptyp] OR Letter[ptyp] OR Comment[ptyp])	1,315,561
16		"2011/01 /01"[PDat] : "2014/12/31"[PDat]	3,823,463
17		"2013/01 /01"[PDat] : "2014/12/31"[PDat]	1,563,858
PICO Combined			
18	Clinical trials	(#4 AND #12 AND #13) NOT #15	325
19	Recent reviews	(#4 AND #12 AND #14 AND #16) NOT #15	82

20	Recent citations	(#4 AND #12 AND #17) NOT #15	31
21	Combined	(#18 OR #19 OR #20)	426

Table 99: PubMed In-Process search terms (original SLR – 2014)

Search Number	PubMed RR-MCL Clinical Search String	Yield
Patient population		
1	("mantle cell" OR "mantle-cell") AND (lymphoma)	3,439
2	“mantle cell lymphoma” OR “mantle-cell lymphoma”	3,152
3	"Lymphoma, Mantle-Cell”	1,860
4	(#1 OR #2 OR #3)	3,439
Intervention or comparator		
5	"salvage chemotherapy" OR "salvage treatment" OR "salvage therapy"	13,490
6	"resistant chemotherapy" OR "chemotherapy resistant" OR "treatment resistant"	5,458
7	“second line" OR second-line OR "2nd line" OR "2'nd line" OR (second AND line)	48,966
8	“third line” OR “third-line” OR “3rd line” OR "3'rd line" OR ("third" AND "line")	17,689
9	(refractory OR refractor* OR resistant OR relaps* OR recurrent OR “drug resistance, neoplasm” OR "previously treated")	700,789
10	((failed OR failure) AND (treatment OR therapy OR prior OR previous))	533,103
11	(chemotherapy OR treatmen* OR regime* OR medication* OR therap*) AND (refractory OR recurrent OR resistant OR rescue OR salvage OR failed OR failure)	665,552
12	(#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	1,268,609
Study design limits		
13	(Editorial[ptyp] OR "Published Erratum"[ptyp] OR Letter[ptyp] OR Comment[ptyp])	1,315,561
14	"2013/01 /01"[PDat] : "2014/12/31"[PDat]	1,563,858
PICO Combined		
15	(#4 AND #12 AND #14) NOT #13	68

Table 100: CENTRAL/Cochrane search terms (original SLR – 2014)

ID	CENTRAL/Cochrane Search	Yield
Patient population		
#1	("mantle cell":ti,ab,kw or "mantle-cell":ti,ab,kw) and lymphoma:ti,ab,kw	0
#2	mantle cell lymphoma or "mantle-cell lymphoma"	133
#3	Lymphoma, Mantle-Cell	0
#4	#1 or #2 or #3	133

ID	CENTRAL/Cochrane Search	Yield
Intervention or comparator		
#5	salvage chemotherapy or "salvage treatment" or "salvage therapy"	917
#6	resistant chemotherapy or "chemotherapy resistant" or "treatment resistant"	1,106
#7	second line or second-line or "2nd line" or "2'nd line" or (second:ti,ab,kw and line:ti,ab,kw)	3,217
#8	third line or "third-line" or "3rd line" or "3'rd line" or ("third":ti,ab,kw and "line":ti,ab,kw)	682
#9	(refractory:ti,ab,kw or refractor*:ti,ab,kw or resistant:ti,ab,kw or relaps*:ti,ab,kw or recurrent:ti,ab,kw or "Drug Resistance, Neoplasm" or "previously treated":ti,ab,kw)	39,259
#10	((failed:ti,ab,kw or failure:ti,ab,kw) and (treatment:ti,ab,kw or therapy:ti,ab,kw or prior:ti,ab,kw or previous:ti,ab,kw))	37,221
#11	(chemotherapy:ti,ab,kw or treatmen*:ti,ab,kw or regime*:ti,ab,kw or medication*:ti,ab,kw or therap*:ti,ab,kw) and (refractory:ti,ab,kw or recurrent:ti,ab,kw or resistant:ti,ab,kw or rescue:ti,ab,kw or salvage:ti,ab,kw or failed:ti,ab,kw or failure:ti,ab,kw)	58,572
#12	#5 or #6 or #7 or #8 or #9 or #10 or #11	79,704
PICO Combined		
#13	#4 and #12	58

Search terms for clinical SLR update

Table 101: Embase search terms (update SLR – 2015)

#	Embase RR-MCL Clinical Search String	Hits
Population		
#1	'mantle cell lymphoma'/exp	7,205
#2	'mantle cell lymphoma':ab,ti OR 'mantle-cell lymphoma':ab,ti	5,160
#3	'mantle cell':ab,ti OR 'mantle-cell':ab,ti AND (lymphoma:ab,ti OR lymphomas:ab,ti)	5,830
#4	#1 OR #2 OR #3	8,045
Intervention/comparators		
#5	'salvage chemotherapy':ab,ti OR 'salvage treatment':ab,ti OR 'salvage therapy'/exp OR 'resistant chemotherapy':ab,ti OR 'chemotherapy resistant':ab,ti OR 'treatment resistant':ab,ti	33,431
#6	'second line' OR '2nd line' OR (second:ab,ti AND line:ab,ti)	50,263
#7	'third line' OR 'third-line' OR '3rd line' OR (third:ab,ti AND line:ab,ti)	17,102
#8	refractory:ab,ti OR refractor*:ab,ti OR resistant:ab,ti OR relaps*:ab,ti OR recurrent:ab,ti OR 'previously treated' OR 'drug resistance':ab,ti	976,423
#9	failed:ab,ti OR failure:ab,ti AND (treatment:ab,ti OR therapy:ab,ti OR prior:ab,ti OR previous:ab,ti)	419,563
#10	chemotherapy:ab,ti OR treatmen*:ab,ti OR regime*:ab,ti OR medication*:ab,ti OR therap*:ab,ti AND (refractory:ab,ti OR recurrent:ab,ti OR resistant:ab,ti OR	800,236

	rescue:ab,ti OR salvage:ab,ti OR failed:ab,ti OR failure:ab,ti)	
#11	#5 OR #6 OR #7 OR #8 OR #9 OR #10	1,452,327
Study design/limits		
#12	[controlled clinical trial]/lim OR [randomized controlled trial]/lim OR [article in press]/lim	706,398
#13	'clinical trial'/exp OR random* OR placebo:ab,ti	1,753,299
#14	#12 OR #13	1,901,326
#15	[cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [review]/lim	2,212,267
#16	[editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim	2,636,955
#17	[2013-2015]/py	3,173,960
PICOS combined		
#18	#4 AND #11 AND #14 NOT 16	272
#19	#4 AND #11 AND #15 AND #17 NOT #16	100
#20	#18 OR #19	365

Table 102: Embase In-Process search terms (update SLR – 2015)

#	Embase RR-MCL Clinical Search String	Hits
Population		
#1	'mantle cell lymphoma'	7,771
#2	'mantle-cell lymphoma'	7,771
#3	'mantle cell' OR 'mantle-cell' AND (lymphoma OR lymphomas)	8,090
#4	#1 OR #2 OR #3	8,090
Intervention/comparators		
#5	'salvage chemotherapy' OR 'salvage treatment' OR 'salvage therapy' OR 'resistant chemotherapy' OR 'chemotherapy resistant' OR 'treatment resistant'	29,112
#6	'second line' OR '2nd line' OR (second AND line)	68,949
#7	'third line' OR 'third-line' OR '3rd line' OR (third AND line)	24,821
#8	refractory OR refractor* OR resistant OR relaps* OR recurrent OR 'drug resistance' OR 'previously treated'	1,153,974
#9	failed OR failure AND (treatment OR therapy OR prior OR previous)	778,954
#10	chemotherapy OR treatmen* OR regime* OR medication* OR therap* AND (refractory OR recurrent OR resistant OR rescue OR salvage OR failed OR failure)	1,299,941
#11	#5 OR #6 OR #7 OR #8 OR #9 OR #10	1,956,173
Study design/limits		
#12	[editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim	2,637,512
PICOS combined		
#13	#4 AND #11 NOT #12	3,020
#14	#13 AND [in process]/lim	7

Table 103: PubMed search terms (update SLR – 2015)

#	PubMed RR-MCL Clinical Search String	Hits
Population		
#1	("mantle cell"[tiab] OR "mantle-cell"[tiab]) AND (lymphoma[tiab])	3,454
#2	“mantle cell lymphoma” OR “mantle-cell lymphoma”	3,480
#3	"Lymphoma, Mantle-Cell"[Mesh]	2,054
#4	#1 OR #2 OR #3	3,736
Intervention/comparators		
#5	"salvage chemotherapy" OR "salvage treatment" OR "salvage therapy" OR “salvage therapy”[Mesh]	14,562
#6	"resistant chemotherapy" OR "chemotherapy resistant" OR "treatment resistant"	6,203
#7	“second line" OR second-line OR "2nd line" OR "2'nd line" OR (second[tiab] AND line[tiab])	34,479
#8	“third line” OR “third-line” OR “3rd line” OR "3'rd line" OR (third[tiab] AND line[TIAB])	11,690
#9	refractory[tiab] OR refractor*[tiab] OR resistant[tiab] OR relaps*[tiab] OR recurrent[tiab] OR “drug resistance, neoplasm”[MeSH] OR "previously treated"[tiab]	742,660
#10	(failed[tiab] OR failure[tiab]) AND (treatment[tiab] OR therapy[tiab] OR prior[tiab] OR previous[tiab])	295,112
#11	(chemotherapy[tiab] OR treatmen*[tiab] OR regime*[tiab] OR medication*[tiab] OR therap*[tiab]) AND (refractory[tiab] OR recurrent[tiab] OR resistant[tiab] OR rescue[tiab] OR salvage[tiab] OR failed[tiab] OR failure[tiab])	568,608
#12	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	1,081,636
Study design/limits		
#13	“clinical trial”[ptyp] OR random* OR placebo[tiab] OR “Classical Article”[ptyp] OR “Comparative Study”[ptyp] OR “Controlled Clinical Trial”[ptyp] OR “Observational Study”[ptyp] OR “Technical Report”[ptyp]	2,818,081
#14	"review"[ptyp] OR “Systematic”[sb] OR “Meta-Analysis”[ptyp]	2,102,627
#15	(Editorial[ptyp] OR "Published Erratum"[ptyp] OR Letter[ptyp] OR Comment[ptyp])	1,406,214
#16	“2013/01/01”[PDat] : “2015/12/31”[PDat]	2,605,774
PICOS combined		
#17	(#4 AND #12 AND #13) NOT #15	343
#18	(#4 AND #12 AND #14 AND #16) NOT #15	57
#19	#17 OR #18	392

Table 104: PubMed In-Process search terms (update SLR – 2015)

#	PubMed RR-MCL Clinical Search String	Hits
Population		
#1	("mantle cell" OR "mantle-cell") AND (lymphoma)	3,785
#2	“mantle cell lymphoma” OR “mantle-cell lymphoma”	3,480
#3	"Lymphoma Mantle-Cell”	2,060
#4	#1 OR #2 OR #3	3,785
Intervention/comparators		
#5	"salvage chemotherapy" OR "salvage treatment" OR "salvage therapy"	14,562

#6	"resistant chemotherapy" OR "chemotherapy resistant" OR "treatment resistant"	6,203
#7	“second line" OR second-line OR "2nd line" OR "2'nd line" OR (second AND line)	53,313
#8	“third line” OR “third-line” OR “3rd line” OR "3'rd line" OR (third AND line)	19,218
#9	refractory OR refractor* OR resistant OR relaps* OR recurrent OR “drug resistance neoplasm” OR "previously treated"	751,001
#10	(failed OR failure) AND (treatment OR therapy OR prior OR previous)	565,532
#11	(chemotherapy OR treatmen* OR regime* OR medication* OR therap*) AND (refractory OR recurrent OR resistant OR rescue OR salvage OR failed OR failure)	714,418
#12	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	1,355,108
Study design/limits		
#13	Editorial[ptyp] OR "Published Erratum"[ptyp] OR Letter[ptyp] OR Comment[ptyp]	1,406,214
#14	"2014/12/01"[PDat] : "2015/12/31"[PDat]	652,549
PICOS combined		
#15	(#4 AND #12 AND #14) NOT #13	70

Table 105: CENTRAL/Cochrane search terms (update SLR – 2015)

#	CENTRAL/Cochrane RR-MCL Clinical Search String	Hits
Population		
#1	("mantle cell":ti,ab,kw or "mantle-cell":ti,ab,kw) and lymphoma:ti,ab,kw	172
#2	“mantle cell lymphoma” or "mantle-cell lymphoma"	163
#3	MeSH descriptor: [Lymphoma, Mantle-Cell] explode all trees	48
#4	#1 or #2 or #3	182
Intervention/comparators		
#5	“salvage chemotherapy” or "salvage treatment" or "salvage therapy"	1,021
#6	“resistant chemotherapy” or "chemotherapy resistant" or "treatment resistant"	1,315
#7	“second line” or “second-line” or "2nd line" or "2'nd line" or (second:ti,ab,kw and line:ti,ab,kw)	3,576
#8	“third line” or "third-line" or "3rd line" or "3'rd line" or (third:ti,ab,kw and line:ti,ab,kw)	860
#9	(refractory:ti,ab,kw or refractor*:ti,ab,kw or resistant:ti,ab,kw or relaps*:ti,ab,kw or recurrent:ti,ab,kw or "previously treated":ti,ab,kw)	44,963
#10	MeSH descriptor: [Drug Resistance, Neoplasm] explode all trees	346
#11	(failed:ti,ab,kw or failure:ti,ab,kw) and (treatment:ti,ab,kw or therapy:ti,ab,kw or prior:ti,ab,kw or previous:ti,ab,kw)	39,023
#12	(chemotherapy:ti,ab,kw or treatmen*:ti,ab,kw or regime*:ti,ab,kw or medication*:ti,ab,kw or therap*:ti,ab,kw) and (refractory:ti,ab,kw or recurrent:ti,ab,kw or resistant:ti,ab,kw or rescue:ti,ab,kw or salvage:ti,ab,kw or failed:ti,ab,kw or failure:ti,ab,kw)	64,218
Combined		
#13	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12	88,104
#14	#4 and #13	88
#15	#4 and #13 - *results for “Trials”*	78
#16	#4 and #13 - *results for “Cochrane Reviews”*	7
#17	#4 and #13 - *results for “Other Reviews”*	1

Appendix 4: List of included and excluded studies from clinical systematic review

As noted in Section 4.1, a total of 28 studies were identified by the original and update SLR, with a total of 75 identified publications. A full list of these 28 studies, their primary publication, and their relevance or not to the submission is provided in Table 106 for RCTs and Table 107 for non-RCTs. Only those studies deemed relevant to the decision problem outlined for this submission have been written-up in detail within this submission.

A full list of citations excluded at the full text review of the SLR is provided in Table 108.

Table 106: RCTs identified by the SLR (total of 4 RCTs)

	Trial identifier	Primary publication identified by SLR	Linked secondary publications identified by the SLR	MCL population or MCL sub-population?	Intervention	Relevance to submission
1	RAY (MCL3001)	Rule S (2015)[62]	Hess G (2015)[3]	MCL as primary population	Ibrutinib monotherapy vs TEM monotherapy	Relevant to the decision problem. Presented in submission main body
2	OPTIMAL	Hess, 2009[8]	Herbrecht R (2008)[116] Verhoef G (2008)[117] Hess G (2008)[118]	MCL as primary population	TEM monotherapy vs TEM monotherapy vs PC	Provides an estimate of PFS and OS on PC therapy. The interventions comprising the PC arm were single-agent chemotherapy options that are not used in current UK clinical practice. However, as the only identified RCT that permitted an ITC with the RAY (MCL3001) study via the common TEM comparator, this study was used for the ITC presented in Section 4.10 and therefore informed the cost-effectiveness modelling.
3	MCL002 (SPRINT)	Trneny, 2014[119]	Trneny M (2015a)[120] Trneny M (2015b)[121]	MCL as primary population	Lenalidomide monotherapy vs Investigators' choice	Not relevant. Although this study contained an investigator's choice arm, similarly to Hess, 2009 these interventions were single-agent chemotherapy options that are not used in current UK clinical practice. However, unlike Hess, 2009, the lenalidomide comparator in this study does not permit an ITC with the RAY (MCL3001) study. Therefore, this study could not be used to inform the submission. See Appendix 9 for further discussion.
4	German Low-Grade Lymphoma Study Group	Forstpointner 2004[60]	Forstpointner R (2006)[122] Dreyling M (2003a)[123] Dreyling M (2006)[124] Dreyling M (2003b)[125]	MCL as sub-population	FCM vs FCMR	Not relevant. Interventions considered are not relevant to the decision problem. See Appendix 9 for further discussion.

	Trial identifier	Primary publication identified by SLR	Linked secondary publications identified by the SLR	MCL population or MCL sub-population?	Intervention	Relevance to submission
			Hidderman W (2003)[126] Dreyling M (2005)[127] Unterhalt M (2006)[128]			

CHOP: cyclophosphamide, doxorubicin, vincristine and prednisolone, FCM: fludarabine + cyclophosphamide + mitoxantrone, FCMR: fludarabine, cyclophosphamide, mitoxantrone, rituximab, MCL: mantle cell lymphoma, NR: not reported, OS: overall survival, PC: physician's choice, PFS: progression-free survival, UK: United Kingdom

Table 107: Non-RCTs identified by the SLR (total of 25 non-RCTs)

	Trial identifier	Primary publication identified by SLR	Linked secondary publications identified by the SLR	MCL population or MCL sub-population?	Intervention	Relevance to submission
1	NR	Agathocleous A (2010)[129]	None	MCL as sub-population	Bortezomib + rituximab	Not relevant. Interventions considered are not relevant to the decision problem.
2	North Central Cancer Treatment Group	Ansell SM (2008)[130]	None	MCL as primary population	Temsirolimus monotherapy	Not relevant. Interventions considered are not relevant to the decision problem.
3	NR	Baiocchi RA (2011)[131]	None	MCL as sub-population	Bortezomib + rituximab	Not relevant. Interventions considered are not relevant to the decision problem.
4	NR	Bauwens D (2005)[132]	None	MCL as primary population	Chlorambucil + rituximab	Not relevant. Interventions considered are not relevant to the decision problem.
5	National Cancer Institute of Canada Clinical Trials Group trial IND.50	Belch A (2007)[133]	None	MCL as primary population	Bortezomib monotherapy	Not relevant. Interventions considered are not relevant to the decision problem.
6	BRIL06 of Intergruppo Italiano Linfomi (IIL)	Chiappella A (2010a)[134]	Chiappella A (2010b)[135] Chiappella A (2009)[136] Chiappella A (2015)[137]	MCL as sub-population	Bortezomib + rituximab	Not relevant. Interventions considered are not relevant to the decision problem.
7	NR	Chong, E. (2015)[138]	None	MCL as sub-population	Lenalidomide + rituximab	Not relevant. Interventions considered are not relevant to the decision problem.
8	NR	Czuczman MS (2012)[139]	Czuczman MS (2014)[140] Rule S (2016)[141]	MCL as primary population	Bendamustine + rituximab	Not relevant. Interventions considered are not relevant to the decision problem.

	Trial identifier	Primary publication identified by SLR	Linked secondary publications identified by the SLR	MCL population or MCL sub-population?	Intervention	Relevance to submission
9	NR	Eve HE (2012)[142]	Eve HE (2010)[143]	MCL as primary population	Lenalidomide monotherapy	Not relevant. Interventions considered are not relevant to the decision problem.
10	NR	Fisher RI (2006)[144]	Goy A (2009)[145] Goy A (2010)[146] Kane RC (2007)[147] Schwab C (2006)[148]	MCL as primary population	Bortezomib monotherapy	Not relevant. Interventions considered are not relevant to the decision problem.
11	NR	Foran JM (2000)[149]	None	MCL as sub-population	Rituximab monotherapy	Not relevant. Interventions considered are not relevant to the decision problem.
12	Group for Clinical Cancer Research (SAKK)	Ghielmini M (2005)[150]	None	MCL as primary population	Rituximab monotherapy	Not relevant. Interventions considered are not relevant to the decision problem.
13	MCL-001 EMERGE	Goy A (2013a)[151]	Goy A (2013b)[152] Goy A (2013c)[153] Goy A (2012)[154] Williams ME (2013)[155] Goy A (2013d)[156] Goy A (2013e)[157] Goy A (2015)[158]	MCL as primary population	Lenalidomide monotherapy	Not relevant. Interventions considered are not relevant to the decision problem.
14	NHL-002	Habermann TM (2009)[159]	Wiernik PH (2008)[160]	MCL as sub-population	Lenalidomide monotherapy	Not relevant. Interventions considered are not relevant to the decision problem.
15	IDEC-C2B8 Study Group	Igarashi T (2002)[161]	None	MCL as sub-population	Rituximab monotherapy	Not relevant. Interventions considered are not relevant to the decision problem.
16	EAP (US cohort)	Martin, P (2014)[80]	None	MCL as primary population	Ibrutinib monotherapy	Relevant to the decision problem. Presented in submission main body

	Trial identifier	Primary publication identified by SLR	Linked secondary publications identified by the SLR	MCL population or MCL sub-population?	Intervention	Relevance to submission
17	NR	O'Connor OA (2009)[162]	O'Connor OA (2005)[163]	MCL as sub-population	Bortezomib monotherapy	Not relevant. Interventions considered are not relevant to the decision problem.
18	NR	Robinson KS (2008)[164]	None	MCL as sub-population	Bendamustine + rituximab	Not relevant. Interventions considered are not relevant to the decision problem.
19	NR	Rummel MJ (2005)[165]	None	MCL as sub-population	Bendamustine + rituximab	Not relevant. Interventions considered are not relevant to the decision problem.
20	NR	Strauss SJ (2006)[166]	None	MCL as sub-population	Bortezomib monotherapy	Not relevant. Interventions considered are not relevant to the decision problem.
21	PCYC1104	Wang ML (2013a)[38]	Wang ML (2012)[167] Wang ML (2011)[168] Wang ML (2013b)[169] Rule S (2014)[44] Wang ML (2014c)[170] Rule S (2015)[171] Wang ML (2013c)[172]	MCL as primary population	Ibrutinib monotherapy	Relevant to the decision problem. Presented in submission main body
22	SPARK (MCL2001)	Wang, M (2014a)[39]	None	MCL as primary population	Ibrutinib monotherapy	Relevant to the decision problem. Presented in submission main body
23	NR	Wang, M (2014b)[173]	None	MCL as primary population	Ibrutinib + Rituximab	Not relevant. Interventions considered are not relevant to the decision problem.
24	North Central Cancer Treatment Group	Witzig TE (2005)[174]	None	MCL as primary population	Temsirolimus monotherapy	Not relevant. Interventions considered are not relevant to the decision problem.
25	NHL-003	Zinzani PL (2013)[175]	Zinzani PL (2012)[176] Witzig TE (2009a)[177] Reeder CB (2009)[178]	MCL as sub-population	Lenalidomide monotherapy	Not relevant. Interventions considered are not relevant to the decision problem.

	Trial identifier	Primary publication identified by SLR	Linked secondary publications identified by the SLR	MCL population or MCL sub-population?	Intervention	Relevance to submission
			Witzig TE (2011)[179] Witzig TE (2009b)[180] Zinzani PL (2009)[181]			
MCL: mantle cell lymphoma, NR: not reported						

Table 108: List of citations excluded at full text review of the clinical SLR

#	Author	Title	Journal	Year	Volume	Issue	Page
1	Aue G, Njuguna N, Tian X, Soto S, Hughes T, *et al.*	Lenalidomide-induced upregulation of CD80 on tumor cells correlates with T-cell activation, the rapid onset of a cytokine release syndrome and leukemic cell clearance in chronic lymphocytic leukemia	Haematologica	2009	94	9	1266-1273
2	Chang BY, Francesco M, Steggerda S, Chang S, Magadala P, *et al.*	Ibrutinib inhibits malignant cell adhesion and migration and reduces tumor burden in lymph node and bone marrow in a murine model of mantle cell dissemination and progression	Cancer Research	2013	73	8	
3	Donelan J, Bannerman B, Bano K, Babcock T, Hales P, *et al.*	Antitumor activity of MLN9708, a second-generation proteasome inhibitor, in preclinical models of lymphoma	Blood	2009	114	22	
4	Osterweil N	Relapsed mantle cell lymphoma: Ibrutinib response in 60%	Oncology Report	2013	FEB	7	
5	Faham MB, J.Kohrt, H. E.Logan, A. C.Advani, R. H.Czerwinski, D. K.Weng, W. K.Negrin, R.Carlton, V.Levy, R.	Deep B and T cell repertoire sequencing to evaluate minimal residual disease and T cell responses in a therapeutic vaccine trial for mantle cell lymphoma	Blood	2012	120	21	
6	Crump M, Shepherd L and Lin B	A randomized phase III study of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin as salvage chemotherapy followed by post-transplantation rituximab maintenance therapy versus observation for treatment of aggressive B-Cell and T-Cell non-Hodgkin's lymphoma	Clin Lymphoma	2005	6	1	56-60
7	Hitz F, Fischer N, Pabst T, Caspar C, Berthod G, *et al.*	Rituximab, bendamustine, and lenalidomide in patients with aggressive B cell lymphoma not eligible for high-dose chemotherapy or anthracycline-based therapy: phase I results of the SAKK 38/08 trial	Ann Hematol	2013			

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8	Kaiser U, Uebelacker I, Abel U, Birkmann J, Trumper L, *et al.*	Randomized study to evaluate the use of high-dose therapy as part of primary treatment for "aggressive" lymphoma	J Clin Oncol	2002	20	22	4413-4419
9	Kasteng F, Erlanson M, Hagberg H, Kimby E, Relander T, *et al.*	Cost-effectiveness of maintenance rituximab treatment after second line therapy in patients with follicular lymphoma in Sweden	Acta Oncol	2008	47	6	1029-1036
10	Mey UJ, Orlopp KS, Flieger D, Strehl JW, Ho AD, *et al.*	Dexamethasone, high-dose cytarabine, and cisplatin in combination with rituximab as salvage treatment for patients with relapsed or refractory aggressive non-Hodgkin's lymphoma	Cancer Invest	2006	24	6	593-600
11	Monfardini S, Aversa SM, Zoli V, Salvagno L, Bianco A, *et al.*	Vinorelbine and prednisone in frail elderly patients with intermediate-high grade non-Hodgkin's lymphomas	Ann Oncol	2005	16	8	1352-1358
12	Pangalis GA, Vassilakopoulos TP, Michalis E, Roussou P, Vrakidou E, *et al.*	A randomized trial comparing intensified CNOP vs. CHOP in patients with aggressive non-Hodgkin's lymphoma	Leuk Lymphoma	2003	44	4	635-644
13	Pettengell R, Coiffier B, Narayanan G, de Mendoza FH, Digumarti R, *et al.*	Pixantrone dimaleate versus other chemotherapeutic agents as a single-agent salvage treatment in patients with relapsed or refractory aggressive non-Hodgkin lymphoma: a phase 3, multicentre, open-label, randomised trial	Lancet Oncol	2012	13	7	696-706
14	Rube C, Nguyen TP, Kloss M, Loeffler M, Trumper L, *et al.*	Consolidation radiotherapy to bulky disease in aggressive NHL. First results of the NHL B-94 trial of the DSHNHL	Ann Hematol	2001	80 Suppl 3		B84-85
15	Sawada M, Tsurumi H, Yamada T, Hara T, Fukuno K, *et al.*	A prospective study of P-IMVP-16/CBDCA: a novel salvage chemotherapy for patients with aggressive non-Hodgkin's lymphoma who had previously received CHOP therapy as first-line chemotherapy	Eur J Haematol	2002	68	6	354-361

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16	Tobinai K, Igarashi T, Itoh K, Kobayashi Y, Taniwaki M, *et al.*	Japanese multicenter phase II and pharmacokinetic study of rituximab in relapsed or refractory patients with aggressive B-cell lymphoma	Ann Oncol	2004	15	5	821-830
17	Vellenga E, van Putten WL, van 't Veer MB, Zijlstra JM, Fibbe WE, *et al.*	Rituximab improves the treatment results of DHAP-VIM-DHAP and ASCT in relapsed/progressive aggressive CD20+ NHL: a prospective randomized HOVON trial	Blood	2008	111	2	537-543
18	Weidmann E, Kim SZ, Rost A, Schuppert H, Seipelt G, *et al.*	Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma	Ann Oncol	2002	13	8	1285-1289
19	Yamazaki T, Sawada U, Kura Y, Ito T, Kaneita Y, *et al.*	Dose-intensified CHOP (double-CHOP) followed by consolidation with high-dose chemotherapy for high and high-intermediate risk aggressive non-Hodgkin's lymphomas	Leuk Lymphoma	2002	43	11	2117-2123
20	Zinzani PL, Tani M, Stefoni V, Albertini P, Bendandi M, *et al.*	Efficacy of vinorelbine, epirubicin and prednisone combination regimen in pretreated elderly patients with aggressive non-Hodgkin's lymphoma	Haematologica	2001	86	3	287-290
21	Zwick C, Birkmann J, Peter N, Bodenstein H, Fuchs R, *et al.*	Equitoxicity of bolus and infusional etoposide: results of a multicenter randomised trial of the German High-Grade Non-Hodgkins Lymphoma Study Group (DSHNHL) in elderly patients with refractory or relapsing aggressive non-Hodgkin lymphoma using the CEMP regimen (cisplatinum, etoposide, mitoxantrone and prednisone)	Ann Hematol	2008	87	9	717-726
22	Leblond V, Johnson S, Chevret S, Copplestone A, Rule S, *et al.*	Results of a randomized trial of chlorambucil versus fludarabine for patients with untreated Waldenstrom macroglobulinemia, marginal zone lymphoma, or lymphoplasmacytic lymphoma	J Clin Oncol	2013	31	3	301-307

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23	Chakhachiro ZI, Saliba RM, Okoroji GJ, Korbling M, Alousi AM, *et al.*	12-year experience with high-dose rituximab-containing autologous stem cell transplantation for SOX11-positive mantle cell lymphoma patients in first remission: Emerging lymphoma-free survival plateau after 3 years	Blood	2011	118	21	
24	Decaudin D, Bosq J, Tertian G, Nedellec G, Bennaceur A, *et al.*	Phase II trial of fludarabine monophosphate in patients with mantle- cell lymphomas	Journal of Clinical Oncology	1998	16	2	579-583
25	Flinn IW, Byrd JC, Furman RR, Brown JR, Benson DM, *et al.*	Evidence to clinical activity in a phase 1 study of CAL-101, an oral p110(delta) isoform-selective inhibitor of phosphatidylinositol 3-kinase, in patients with relapsed or refractory b-cell malignancies	Blood	2009	114	22	
26	Lust JA, Barranco C, Usmani SZ, Van Rhee F, Hamadani M, *et al.*	Phase 1b/2a open-label, multiple-dose, dose-escalation study to evaluate the safety and tolerability of intravenous infusion of SNS01-T in patients with relapsed or refractory multiple myeloma, mantle cell lymphoma, or diffuse large B cell lymphoma	Blood	2013	122	21	
27	Winkler U, Jensen M, Manzke O, Schulz H, Diehl V, *et al.*	Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8)	Blood	1999	94	7	2217-2224
28	Ghobrial IMB, E. N.Chuma, S.Banwai, R.Hanlon, C.Leblebjian, H.Warren, D.Mostyn, P.Masood, F.Richardson, P. G.Treon, S. P.Matous, J.	Phase I/II trial of everolimus, bortezomib and rituximab in relapsed or relapsed or refractory Waldenstrom's macroglobulinemia [Abstract 4402]	55th American Society of Hematology Annual Meeting and Exhibition	2013			

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29	Treon SP, Tripsas CK, Meid K, *et al.*	Carfilzomib, rituximab and dexamethasone (CaRD) is highly active and offers a neuropathy sparing approach for proteasome-inhibitor based therapy in Waldenstrom's macroglobulinemia [Abstract 757]	55th American Society of Hematology Annual Meeting and Exhibition	2013			
30	Treon SP, Tripsas CK, Meid K, *et al.*	Prospective, multicenter study of the Mtor inhibitor everolimus (RAD001) as primary therapy in Waldenstrom's macroglobulinemia [Abstract 1822]	55th American Society of Hematology Annual Meeting and Exhibition	2013			
31	Le Gouill SM, E.Callanan, M.Bodet-Milin, C.Meignan, M.Moreau, A.Traverse-Glehen, A.Bene, M.Maisonneuve, H.Solal-Celigny, P.Zerazhi, H.Bologna, S.De le Chapelle, T.Tilly, H.Delfau-Larue, M.Hermine, O.	Response rates using standard criteria, FDG-PET and MRD measurement after 4 courses of R-DHAP and after autologous stem cell transplantation in MCL, results from the Lyma trial [Abstract S1158]	18th Congress of the European Hematology Association	2013			
32	Treon SP, Christina K. Tripsas M, *et al.*	A prospective multicenter study of the Bruton's tyrosine kinase inhibitor ibrutinib in patients with relapsed or refractory Waldenstrom's macroglobulinemia [Abstract 251]	55th American Society of Hematology Annual Meeting and Exhibition	2013			

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33	Thomas SK, Haygood TM, Qazilbash MH, *et al.*	A phase II trial of bortezomib-rituximab followed by autologous stem cell harvest (SCH) and cladribine-cyclophosphamide-rituximab (2CdA-Cy-Rit) consolidation as primary therapy of Waldenström's macroglobulinemia (WM) [Abstract 4396]	55th American Society of Hematology Annual Meeting and Exhibition	2013			
34	Rule S, Briones J, Carella AM, *et al.*	A randomized comparison of maintenance therapy with subcutaneous rituximab for 2 years versus until progression in patients with indolent non-Hodgkin's lymphoma: interim safety data from the Mabcute study [Abstract 3052]	55th American Society of Hematology Annual Meeting and Exhibition	2013			
35	Oki, Y.,Fanale, M. A.,Romaguera, J. E.,Fayad, L.,Fowler, N.,Copeland, A. R. M.,Samaniego, F.,Kwak, L. W.,Neelapu, S. S.,Wang, M.,Feng, L.,Younes, A.	Phase II study of an akt inhibitor MK2206 in patients with relapsed or refractory lymphoma	Blood	2014	124	21	
36	Rule, S., Wang, M., Martin, P., Auer, R., Kahl, B., *et al.*	Updated interim results of an international, multicenter, phase 2 study of ibrutinib (PCI-32765) in relapsed or refractory mantle cell lymphoma	EHA 2013	2013			
37	Goy A, Sinha R, Williams ME, Besisik SK, Drach J, *et al.*	Phase II multicenter study of single-agent lenalidomide in subjects with mantle cell lymphoma who relapsed or progressed after or were refractory to bortezomib: The mcl-001 "Emerge" study	Blood	2012	120	21	
38	Herbrecht, R.,Romaguera, J.,Verhoef, G.,Crump, M.,Coiffier, B.,Strahs, A.	Treatment of patients with relapsed, refractory mantle cell lymphoma with temsirolimus: adverse event profiles of high and low dose regimens are similar [Abstract No. 728PD]	Annals of oncology	2009	19	Supplement 8	229

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39	McBride NC, Cavenagh JD, Ward MC, Grant I, Schey S, *et al.*	Liposomal daunorubicin (DaunoXome) in combination with cyclophosphamide, vincristine and prednisolone (COP-X) as salvage therapy in poor-prognosis non-Hodgkins lymphoma	Leuk Lymphoma	2001	42	1-2	89-98
40	Ghielmini M, Rufibach K, Salles G, Leoncini-Franscini L, Leger-Falandry C, *et al.*	Single agent rituximab in patients with follicular or mantle cell lymphoma: clinical and biological factors that are predictive of response and event-free survival as well as the effect of rituximab on the immune system: a study of the Swiss Group for Clinical Cancer Research (SAKK)	Ann Oncol	2005	16	10	1675-1682
41	Gladstone DE, Bolanos-Meade J, Huff CA, Zahurak M, Flinn I, *et al.*	High-dose cyclophosphamide and rituximab without stem cell transplant: a feasibility study for low grade B-cell, transformed and mantle cell lymphomas	Leuk Lymphoma	2011	52	11	2076-2081
42	Cervetti G, Galimberti S, Cecconi N, Caracciolo F and Petrini M	Role of low-dose 2-CdA in refractory or resistant lymphoplasmocytic lymphoma	J Chemother	2004	16	4	388-391
43	Ahmadi T, Chong EA, Gordon A, Aqui NA, Xu Y, *et al.*	Phase II trial to lenalidomide-rituximab +/- dexamethasone in relapsed or refractory indolent b-cell or mantle cell lymphomas resistant to rituximab	Blood	2011	118	21	
44	Aqui N, Leinbach L, Chong EA, Ahmadi T, Svoboda J, *et al.*	Changes in regulatory T-cells in responding and non-responding patients with indolent B-cell or mantle cell lymphomas during treatment with lenalidomide, dexamethasone, and rituximab	Journal of Clinical Oncology	2010	28	15	
45	Aqui N, Gordon A, Xu Y, Chong EA, Leinbach L, *et al.*	Differences in regulatory T cells (Tregs) in responding and non-responding patients with indolent B-cell or mantle cell lymphoma during treatment with lenalidomide and rituximab (plus or minus) dexamethasone	Journal of Clinical Oncology	2011	29	15	

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46	Coiffier B, Haioun C, Ketterer N, Engert A, Tilly H, *et al.*	Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: A multicenter phase II study	Blood	1998	92	6	1927-1932
47	Corradini P, Sarina B, Carniti C, Patriarca F, Carella A, *et al.*	High-dose rituximab in the conditioning regimen before allogeneic stem cell transplantation for relapsed lymphomas: Protective role of the antibody on GvHD incidence	Bone Marrow Transplantation	2012	47		S421
48	Czerwinski DK, Brody J, Kohrt HE, Faham M, Gabriel E, *et al.*	Immunotransplant expands vaccine-induced memory T cell responses in patients with mantle cell lymphoma	Blood	2013	122	21	
49	Foran JM, Rohatiner AZS, Cunningham D, Popescu RA, Solal-Celigny P, *et al.*	European phase II study of rituximab (chimeric anti-CD20 monoclonal antibody) for patients with newly diagnosed mantle-cell lymphoma and previously treated mantle-cell lymphoma, immunocytoma, and small B-cell lymphocytic lymphoma	Journal of Clinical Oncology	2000	18	2	317-324
50	Ghielmini M, Hsu Schmitz SF, Burki K, Pichert G, Betticher DC, *et al.*	The effect of Rituximab on patients with follicular and mantle-cell lymphoma	Annals of Oncology	2000	11	SUPPL. 1	S123-S126
51	Hess G, Keller U, Witzens-Harig M, Atta J, Medler C, *et al.*	Temsirolimus added to bendamustine and rituximab (BERT): Phase I results of a phase I/II-trial in patients with relapsed follicular lymphoma (FL) and mantle cell lymphoma (MCL)	Hematological Oncology	2013	31		146
52	Hess G, Romaguera J, Herbrecht R, Verhoef G, Crump M, *et al.*	Temsirolimus for the treatment of patients with relapsed or refractory mantle cell lymphoma: Supportive efficacy analyses from the phase 3 study	Haematologica	2009	94		391-392
53	Holkova B, Perkins EB, Sokol L, Richards KL, Parekh S, *et al.*	A phase II trial of bortezomib and vorinostat in mantle cell lymphoma and diffuse large b-cell lymphoma	Blood	2011	118	21	

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54	Lachaine J, Beauchemin C, Mathurin K and Aissa F	Cost-effectiveness of bendamustine+rituximab versus fludarabine+rituximab in the treatment of relapsed indolent non-hodgkin's and mantle cell lymphomas in Canada	Value in Health	2013	16	3	A141
55	Meneses-Lorente G, Carlile D, Birkett J, Wenger MK, Cartron G, *et al.*	Pharmacokinetics of RO5072759 (GA101) in patients with relapsed or refractory CD20+ malignant disease (phase I/II study BO20999)	Blood	2010	116	21	
56	Morrison VA, Fisher RI, Goy A, De Vos S, Bernstein SH, *et al.*	Herpes Zoster (HZ) complicating bortezomib therapy of relapsed or refractory indolent B-cell and mantle cell lymphoma: An analysis of two phase II trials	Blood	2010	116	21	
57	Padmanabhan S, Shea TC, Vose JM, Reeder CB, Berdeja JG, *et al.*	Phase I study of an investigational Aurora a kinase inhibitor MLN8237 in patients with advanced hematologic malignancies	Blood	2010	116	21	
58	Park B, Kim W, Eom H, Kim J, Oh S, *et al.*	A phase II trial of gemcitabine, ifosfamide, dexamethasone, and oxaliplatin (GIDOX) for patients with refractory or relapsed non-Hodgkin's lymphoma	Journal of Clinical Oncology	2009	27	15	8559
59	Park BB, Kim WS, Eom HS, Kim JS, Oh SJ, *et al.*	A phase II trial of gemcitabine, ifosfamide, dexamathasone, and oxaliplatin (GIDOx) for patients with refractory or relapsed non-hodgkin's lymphoma	Haematologica	2009	94		652
60	Pittaluga S, Bijnens L, Teodorovic I, Hagenbeek A, Meerwaldt JH, *et al.*	Clinical analysis of 670 cases in two trials of the European Organization for the Research and Treatment of Cancer Lymphoma Cooperative Group subtyped according to the revised European-American Classification of Lymphoid Neoplasms: A comparison with the working formulation	Blood	1996	87	10	4358-4367
61	Rummel MJ, Kaiser U, Balser C, Stauch MB, Brugger W, *et al.*	Bendamustine plus rituximab versus fludarabine plus rituximab in patients with relapsed follicular, indolent and mantle cell lymphomas - Final results of the randomized phase III study NHL 2-2003 on behalf of	Blood	2010	116	21	

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62	Sauter CS, Papadopoulos EB, Perales MA, Jakubowski AA, Goldberg JD, *et al.*	Non-myeloablative allogeneic hematopoietic stem cell transplantation with low-dose total body irradiation and peri-transplant rituximab for B cell non-Hodgkin lymphoma: Favorable disease control in chemosensitive patients	Blood	2011	118	21	
63	Sorror ML, Storer B, Sandmaier BM, Franke GN, Laport GG, *et al.*	Outcomes following relapse of non-hodgkin lymphoma (NHL) or chronic lymphocytic leukemia (CLL) after nonmyeloablative conditioning and allogeneic hematopoietic cell transplantation (HCT) from HLA-matched related or unrelated donors	Blood	2010	116	21	
64	Wang M, Popplewell LL, Collins RH, Winter JN, Goy A, *et al.*	Everolimus for patients with mantle cell lymphoma refractory to or intolerant of bortezomib: Multicentre, single-arm, phase 2 study	British Journal of Haematology	2014	165	4	510-518
65	Wang M, Popplewell L, Collins RH, Winter JN, Goy A, *et al.*	Pillar-1: Multicenter phase 2 study of everolimus for patients with mantle cell lymphoma who are refractory or intolerant to bortezomib	Blood	2012	120	21	
66	Younes A, Ayoub JP, Sarris A, Hagemeister F, North L, *et al.*	Paclitaxel activity for the treatment of non-Hodgkin's lymphoma: Final report of a phase II trial	British Journal of Haematology	1997	96	2	328-332

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67	Kohara TS, H.Uoshima, N.Terada, Y.Nakatani, E.Yoshida, H.Ishikawa, J.Masaie, H.Mugitani, A.Kumura, T.Okamoto, S.Kamitsuji, Y.Sugahara, H.Nakagawa, M.Kawakami, M.Ishiko, J.Take, H.Kosugi, S.Nakata, S.Nagate, Y.Kida, T.Moriyama, Y.Kataoka, Y.Tominaga, N.Mor	Evaluation of efficacy and safety of bendamustine treatment in Osaka Lymphoma Study Group (OLSG) of Japan [Abstract B1630]	18th Congress of the European Hematology Association	2013			
68	Witzens-Harig, M.,Benner, A.,Rieger, M.,McClanahan, F.,Hensel, M.,Neben, K.,Dreger, P.,Lengfelder, E.,Schmidt-Wolf, I.,Kramer, A.,Ho, A.	Rituximab maintenance therapy in Cd20+ B-cell non-hodgkinlymphoma-final results of a multicenter prospective randomised phase ii study	Haematologica	2011	96		396
69	Hiddemann, W.,Dreyling, M.,Forstpointner, R.,Gramatzki, M.,BÑ?ck, H.,Haenel, M.,Seymour, J.,Unterhalt, M.	Rituximab-maintenance after a combined immunochemotherapy significantly improves response duration in patients with relapsed follicular and mantle cell lymphoma [Abstract No. 449]	Annals of oncology	2005		12	169
70	Hiddemann, W.,Forstpointner, R.,Dreyling, M.,Gramatzki, M.,Bock, H.,Hanel, M.	Rituximab maintenance prolongs response duration after salvage therapy with FCRM in patients with relapsed follicular lymphomas and mantle cell lymphomas: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG)	Blood	2005	106	11	

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71	Forstpointner, R.,Dreyling, M.,Gramatzki, M.,Bock, H. P.,Hanel, M.,Seymour, J. F.,Planker, M.,Duhrsen, U.,Wilms, K.,Clemens, M. R.,Harder, H.,Wandt, H.,Rothmann, F.,Unterhalt, M.,Hiddemann, W.	Rituximab maintenance following a combined immuno-chemotherapy induction significantly prolongs the response duration in patients with relapsed follicular and mantle cell lymphomas: Results of a prospective randomized trial of the German Low Grade Lymphoma Study Group	Onkologie	2005	28	Suppl 3	37
72	Maddocks, K.,Christian, B.,Jaglowski, S.,Flynn, J.,Jones, J. A.,Porcu, P.,Wei, L.,Jenkins, C.,Lozanski, G.,Byrd, J. C.,Blum, K. A.	A phase 1/1b study of rituximab, bendamustine, and ibrutinib in patients with untreated and relapsed or refractory non-Hodgkin lymphoma	Blood	2015	125	2	242-8
73	Bair A, Hess G, Boni J and Offner F	Randomized phase IV trial comparing efficacy and tolerability of temsirolimus with and without an elevated starting dose in patients with relapsed, refractory mantle cell lymphoma	Journal of Clinical Oncology	2011	29	15	
74	Dreyling M, Hermine O, Ribrag V, Sun S, Rizo A, *et al.*	A phase 3 study of ibrutinib versus temsirolimus in patients with relapsed or refractory mantle cell lymphoma (MCL) who have received at least 1 prior therapy	Hematological Oncology	2013	31		274
75	Ito K, Okamoto M, Ando Y, Ando M, Kumazawa S, *et al.*	Influence to rituximab plus bendamustine chemotherapy on the immune system in lymphoma patients	Annals to Oncology	2013	24		ix37
76	Morrison VA, Jung S, Johnson JL, Leonard J and Cheson BD	A phase II trial of bortezomib plus lenalidomide for relapsed or refractory mantle cell lymphoma (MCL) (CALGB 50501)	Journal of Clinical Oncology	2011	29	15	

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77	Spurgeon SE, Okada CY, Huang J, Phillips J and Epner EE	Targeting the epigenome: A phase I/II study of vorinostat (SAHA), cladribine (2-CdA), and rituximab in relapsed B-cell malignancies	Journal of Clinical Oncology	2010	28	15	
78	Intragumtornchai T, Bunworasate U, Nakorn TN and Rojnuckarin P	Rituximab-CHOP-ESHAP vs CHOP-ESHAP-high-dose therapy vs conventional CHOP chemotherapy in high-intermediate and high-risk aggressive non-Hodgkin's lymphoma	Leuk Lymphoma	2006	47	7	1306-1314
79	Wang M, Fayad L, Wagner-Bartak N, Zhang L, Hagemeister F, *et al.*	Lenalidomide in combination with rituximab for patients with relapsed or refractory mantle-cell lymphoma: a phase 1/2 clinical trial	Lancet Oncol	2012	13	7	716-723
80	Furman RR, Byrd JC, Flinn IW, Coutre SE, Benson DM, *et al.*	Interim results from a phase I study of CAL-101, a selective oral inhibitor of phosphatidylinositol 3-kinase p110d isoform, in patients with relapsed or refractory hematologic malignancies	Journal of Clinical Oncology	2010	28	15	
81	Gerecitano J, Portlock CS, Hamlin PA, Moskowitz CH, Noy A, *et al.*	Rituximab, cyclophosphamide, bortezomib and prednisone (R-CBorP): Final results of a phase I trial evaluating two dosing schedules and the safety of overlapping pegfilgrastim in patients with relapsed or refractory indolent and mantle cell lymphomas	Blood	2009	114	22	
82	Gironella M, Lopez A, Merchan B, Abrisqueta P, Jaramillo A, *et al.*	Rituximab plus gemcitabine and oxaliplatin as salvage therapy in patients with relapsed or refractory mantle-cell lymphoma	Blood	2012	120	21	
83	Gironella M, Lopez A, Pau A, Anny J, Noelia P, *et al.*	Rituximab plus gemcitabine and oxaliplatin as salvage therapy in patients with relapsed or refractory mantle-cell lymphoma	Blood	2010	116	21	
84	Goy A, Hernandez-Ilzaliturri F, Kahl B, Ford P, Protomastro E, *et al.*	A phase I/II study of the pan Bcl-2 inhibitor obatoclax mesylate plus bortezomib for relapsed or refractory mantle cell lymphoma	Leuk Lymphoma	2014			

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85	Liliemark J, Porwit A and Juliusson G	Intermittent infusion to cladribine (CdA) in previously treated patients with low-grade non-Hodgkin's lymphoma	Leukemia and Lymphoma	1997	25	4-Mar	313-318
86	Longo DL, Duffey PL, Gribben JG, Jaffe ES, Curti BD, *et al.*	Combination chemotherapy followed by an immunotoxin (anti-B4-blocked ricin) in patients with indolent lymphoma: Results to a phase II study	Cancer Journal	2000	6	3	146-150
87	Romaguera JE, Fanale MA, Samaniego F, Fayad LE, Hagemeister FB, *et al.*	Phase II trial of bortezomib in combination with fractionated cyclophosphamide and rituximab (BCR) for relapsed or refractory mantle cell lymphoma (MCL)	Blood	2013	122	21	
88	Veliz M, Santana R, Lancet JE, Komrokji RS, Kharfan-Dabaja MA, *et al.*	Phase II study of lenalidomide in combination with rituximab for patients with CD5+/CD20+ hematologic malignancies who relapse or progress after rituximab. interim analysis	Blood	2009	114	22	
89	Lefebvre M, Kotb R, Larouche JF, *et al.*	Efficacy, safety, and cost efficiency of rituximab, gemcitabine, dexamethasone, and oxaliplatin (RGDOx) in B-cell NHL: Report of the prospective multicentric trial NCT01019863 [Abstract 8581]	American Society of Clinical Oncology 50th Annual Meeting	2014			
90	Morrison VAJ, S. H.Johnson, J.La Casce, A.Blum, K. A.Bartlett, N. L.Cheson, B. D.	Salvage therapy with bortezomib plus lenalidomide for relapsed or refractory mantle cell lymphoma: Initial results of a phase II trial (alliance/CALGB 50501)	Blood	2012	120	21	

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91	Spurgeon SEFW-J, N. D.Furman, R. R.Flinn, I.Coutre, S. E.Brown, J. R.Benson, D. M.Byrd, J. C.Leonard, J.Peterman, S.Johnson, D. M.Gu, J.Dansey, R. D.Godfrey, W. R.Kahl, B. S.	Final results of a phase I study of idelalisib, a selective inhibitor of phosphatidylinositol 3-kinase P110{delta} (PI3K{delta}), in patients with relapsed or refractory mantle cell lymphoma (MCL)	Journal of Clinical Oncology	2013	31	15	
92	Morrison VAJ, S. H.Johnson, J.La Casce, A.Blum, K. A.Bartlett, N. L.Cheson, B. D.	Salvage therapy with bortezomib plus lenalidomide for relapsed or refractory mantle cell lymphoma: Initial results of a phase II trial (alliance/CALGB 50501)	Blood	2012	120	21	
93	Martin P, DiLiberto M, Mason CE, *et al.*	The combination of palbociclib plus bortezomib is safe and active in patients with previously treated mantle cell lymphoma: final results of a phase I trial [4393]	55th American Society of Hematology Annual Meeting and Exhibition	2013			
94	Hess, G.,Keller, U.,Scholz, C. W.,Witzens-Harig, M.,Atta, J.,Buske, C.,Kirschey, S.,Ruckes, C.,Medler, C.,van Oordt, C.,Klapper, W.,Theobald, M.,Dreyling, M.	Safety and efficacy of Temsirolimus in combination with Bendamustine and Rituximab in relapsed mantle cell and follicular lymphoma	Leukemia	2015			

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95	Dodero, A.,Sarina, B.,Milone, G.,Patriarca, F.,Bosi, A.,Dominietto, A.,Farina, L.,Foa, R.,Terruzzi, E.,Onida, F.,Rambaldi, A.,Corradini, P.	Reduced-intensity conditioning (RIC) with high-dose rituximab and allogeneic stem cell transplantation for relapsed CD20+ lymphomas: Good disease control with low incidence of chronic GVHD	Bone Marrow Transplantation	2015	50		S162
96	Morrison, V. A.,Jung, S. H.,Johnson, J.,Lacasce, A.,Blum, K. A.,Bartlett, N. L.,Pitcher, B. N.,Cheson, B. D.	Therapy with bortezomib plus lenalidomide for relapsed or refractory mantle cell lymphoma: Final results of a phase II trial (CALGB 50501)	Leukemia and Lymphoma	2015	56	4	958-964
97	Noesslinger, T.,Moestl, M.,Tinchon, C.,Koller, E.,Linkesch, W.,Keil, F.	Autologous stem cell transplantation with benda-BEAM (Bendamustine, etoposide, cytarabine, melphalan) in aggressive non hodgkin and Hodgkin's lymphoma	Blood	2014	124	21	
98	Furtado, M.,Johnson, R.,Kruger, A.,Turner, D.,Rule, S.	Addition of bortezomib to standard dose chop chemotherapy improves response and survival in relapsed mantle cell lymphoma	Br J Haematol	2015	168	1	55-62
99	O'Connor OA, Portlock C, Moskowitz C, Straus D, Hamlin P, *et al.*	A multicentre phase II clinical experience with the novel aza-epothilone Ixabepilone (BMS247550) in patients with relapsed or refractory indolent non-Hodgkin lymphoma and mantle cell lymphoma	Br J Haematol	2008	143	2	201-209
100	Robak T, Smolewski P, Cebula B, Szmigielska-Kaplon A, Chojnowski K, *et al.*	Rituximab combined with cladribine or with cladribine and cyclophosphamide in heavily pretreated patients with indolent lymphoproliferative disorders and mantle cell lymphoma	Cancer	2006	107	7	1542-1550

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101	Weide R, Pandorf A, Heymanns J and Koppler H	Bendamustine/Mitoxantrone/Rituximab (BMR): a very effective, well tolerated outpatient chemoimmunotherapy for relapsed and refractory CD20-positive indolent malignancies. Final results of a pilot study	Leuk Lymphoma	2004	45	12	2445-2449
102	O'Connor OA, Portlock C, Moskowitz C, Hamlin P, Straus D, *et al.*	Time to treatment response in patients with follicular lymphoma treated with bortezomib is longer compared with other histologic subtypes	Clin Cancer Res	2010	16	2	719-726
103	Van Den Neste E, Michaux L, Layios N, Costantini S, Francart J, *et al.*	High incidence of complications after 2-chloro-2'-deoxyadenosine combined with cyclophosphamide in patients with advanced lymphoproliferative malignancies	Ann Hematol	2004	83	6	356-363
104	Ansell SM, Tang H, Kurtin PJ, Koenig PA, Inwards DJ, *et al.*	Temsirolimus and rituximab in patients with relapsed or refractory mantle cell lymphoma: a phase 2 study	Lancet Oncol	2011	12	4	361-368
105	Borchmann P, Herbrecht R, Wilhelm M, Morschhauser F, Hess G, *et al.*	Phase I/II study of pixantrone in combination with cyclophosphamide, vincristine, and prednisone in patients with relapsed aggressive non-Hodgkin lymphoma	Leuk Lymphoma	2011	52	4	620-628
106	Coleman M, Martin P, Ruan J, Furman R, Niesvizky R, *et al.*	Prednisone, etoposide, procarbazine, and cyclophosphamide (PEP-C) oral combination chemotherapy regimen for recurring/refractory lymphoma: low-dose metronomic, multidrug therapy	Cancer	2008	112	10	2228-2232
107	Garbo LE, Flynn PJ, MacRae MA, Rauch MA, Wang Y, *et al.*	Results of a Phase II trial of gemcitabine, mitoxantrone, and rituximab in relapsed or refractory mantle cell lymphoma	Invest New Drugs	2009	27	5	476-481
108	Gerecitano J, Portlock C, Hamlin P, Moskowitz CH, Noy A, *et al.*	Phase I trial of weekly and twice-weekly bortezomib with rituximab, cyclophosphamide, and prednisone in relapsed or refractory non-Hodgkin lymphoma	Clin Cancer Res	2011	17	8	2493-2501

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109	Gopal AK, Rajendran JG, Petersdorf SH, Maloney DG, Eary JF, *et al.*	High-dose chemo-radioimmunotherapy with autologous stem cell support for relapsed mantle cell lymphoma	Blood	2002	99	9	3158-3162
110	Gopal AK, Guthrie KA, Rajendran J, Pagel JM, Oliveira G, *et al.*	(9)(0)Y-Ibritumomab tiuxetan, fludarabine, and TBI-based nonmyeloablative allogeneic transplantation conditioning for patients with persistent high-risk B-cell lymphoma	Blood	2011	118	4	1132-1139
111	Inwards DJ, Fishkin PA, Hillman DW, Brown DW, Ansell SM, *et al.*	Long-term results of the treatment of patients with mantle cell lymphoma with cladribine (2-CDA) alone (95-80-53) or 2-CDA and rituximab (N0189) in the North Central Cancer Treatment Group	Cancer	2008	113	1	108-116
112	Kaufmann H, Raderer M, Wohrer S, Puspok A, Bankier A, *et al.*	Antitumor activity of rituximab plus thalidomide in patients with relapsed or refractory mantle cell lymphoma	Blood	2004	104	8	2269-2271
113	Kouroukis CT, Fernandez LA, Crump M, Gascoyne RD, Chua NS, *et al.*	A phase II study of bortezomib and gemcitabine in relapsed mantle cell lymphoma from the National Cancer Institute of Canada Clinical Trials Group (IND 172)	Leuk Lymphoma	2011	52	3	394-399
114	Lamm W, Kaufmann H, Raderer M, Hoffmann M, Chott A, *et al.*	Bortezomib combined with rituximab and dexamethasone is an active regimen for patients with relapsed and chemotherapy-refractory mantle cell lymphoma	Haematologica	2011	96	7	1008-1014
115	Mangel J, Buckstein R, Imrie K, Spaner D, Franssen E, *et al.*	Pharmacokinetic study of patients with follicular or mantle cell lymphoma treated with rituximab as 'in vivo purge' and consolidative immunotherapy following autologous stem cell transplantation	Ann Oncol	2003	14	5	758-765
116	Maris MB, Sandmaier BM, Storer BE, Chauncey T, Stuart MJ, *et al.*	Allogeneic hematopoietic cell transplantation after fludarabine and 2 Gy total body irradiation for relapsed and refractory mantle cell lymphoma	Blood	2004	104	12	3535-3542

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117	Morschhauser F, Seymour JF, Kluin-Nelemans HC, Grigg A, Wolf M, *et al.*	A phase II study of enzastaurin, a protein kinase C beta inhibitor, in patients with relapsed or refractory mantle cell lymphoma	Ann Oncol	2008	19	2	247-253
118	Ohmachi K, Ando K, Ogura M, Uchida T, Itoh K, *et al.*	Multicenter phase II study of bendamustine for relapsed or refractory indolent B-cell non-Hodgkin lymphoma and mantle cell lymphoma	Cancer Sci	2010	101	9	2059-2064
119	Renner C, Zinzani PL, Gressin R, Klingbiel D, Dietrich PY, *et al.*	A multicenter phase II trial (SAKK 36/06) of single-agent everolimus (RAD001) in patients with relapsed or refractory mantle cell lymphoma	Haematologica	2012	97	7	1085-1091
120	Rodriguez J, Gutierrez A, Palacios A, Navarrete M, Blancas I, *et al.*	Rituximab, gemcitabine and oxaliplatin: an effective regimen in patients with refractory and relapsing mantle cell lymphoma	Leuk Lymphoma	2007	48	11	2172-2178
121	Ruan J, Martin P, Coleman M, Furman RR, Cheung K, *et al.*	Durable responses with the metronomic rituximab and thalidomide plus prednisone, etoposide, procarbazine, and cyclophosphamide regimen in elderly patients with recurrent mantle cell lymphoma	Cancer	2010	116	11	2655-2664
122	Smalley RV, Weller E, Hawkins MJ, Oken MM, O'Connell MJ, *et al.*	Final analysis of the ECOG I-COPA trial (E6484) in patients with non-Hodgkin's lymphoma treated with interferon alfa (IFN-alpha2a) plus an anthracycline-based induction regimen	Leukemia	2001	15	7	1118-1122
123	Visco C, Finotto S, Zambello R, Paolini R, Menin A, *et al.*	Combination of rituximab, bendamustine, and cytarabine for patients with mantle-cell non-hodgkin lymphoma ineligible for intensive regimens or autologous transplantation	J Clin Oncol	2013	31	11	1442-1449
124	Wang M, Oki Y, Pro B, Romaguera JE, Rodriguez MA, *et al.*	Phase II study of yttrium-90-ibritumomab tiuxetan in patients with relapsed or refractory mantle cell lymphoma	J Clin Oncol	2009	27	31	5213-5218

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125	Weide R, Hess G, Koppler H, Heymanns J, Thomalla J, *et al.*	High anti-lymphoma activity of bendamustine/mitoxantrone/rituximab in rituximab pretreated relapsed or refractory indolent lymphomas and mantle cell lymphomas. A multicenter phase II study of the German Low Grade Lymphoma Study Group (GLSG)	Leuk Lymphoma	2007	48	7	1299-1306
126	Witzig TE, Reeder CB, LaPlant BR, Gupta M, Johnston PB, *et al.*	A phase II trial of the oral mTOR inhibitor everolimus in relapsed aggressive lymphoma	Leukemia	2011	25	2	341-347
127	Chow KU, Kim SZ, von Neuhoff N, Schlegelberger B, Stilgenbauer S, *et al.*	Clinical efficacy of immunochemotherapy with fludarabine, epirubicin and rituximab in the treatment for chronic lymphocytic leukaemia and prolymphocytic leukaemia	Eur J Haematol	2011	87	5	426-433
128	Dumontet C, Morschhauser F, Solal-Celigny P, Bouafia F, Bourgeois E, *et al.*	Gemcitabine as a single agent in the treatment of relapsed or refractory low-grade non-Hodgkin's lymphoma	Br J Haematol	2001	113	3	772-778
129	Evens, A. Vose, J. Harb, W., Gordon, L., Langdon, R., Grant, B., *et al.*,	A Phase II Multicenter Study of the Histone Deacetylase Inhibitor (HDACi) Abexinostat (PCI-24781) in Relapsed/ Refractory Follicular Lymphoma (FL) and Mantle Cell Lymphoma (MCL)	2012 ASH Annual Meeting	2012			Abstract No. 55
130	Gironella, M., Lopez, A., Merchan, B., Abrisqueta, P. Jaramillo, A., Bosch, F.	Rituximab Plus Gemcitabine and Oxaliplatin As Salvage Therapy in Patients with elapsed/Refractory Mantle-Cell Lymphoma	2012 ASH Annual Meeting	2012			Abstract No. 1627
131	Morrison, V.A., Jung, S.H., Johnson, J., LaCasce, A., Blum, K.A., Bartlett, N.L., Cheson, B.D.	Salvage Therapy with Bortezomib Plus Lenalidomide for Relapsed/Refractory Mantle Cell Lymphoma: Initial Results of a Phase II Trial (Alliance/CALGB 50501)	2012 ASH Annual Meeting	2012			Abstract No. 3696

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132	Wang, M., Popplewell, L., Collins Jr., R.H., Winter, J.N., Goy, A., *et al.*	Pillar-1: Multicenter Phase 2 Study of Everolimus for Patients with Mantle Cell Lymphoma Who Are Refractory or Intolerant to Bortezomib	2012 ASH Annual Meeting	2013			Abstract No. 2751
133	Hitz F, Martinelli G, Zucca E, von Moos R, Mingrone W, *et al.*	A multicentre phase II trial of gemcitabine for the treatment of patients with newly diagnosed, relapsed or chemotherapy resistant mantle cell lymphoma: SAKK 36/03	Hematol Oncol	2009	27	3	154-159
134	Kouroukis CT, Belch A, Crump M, Eisenhauer E, Gascoyne RD, *et al.*	Flavopiridol in untreated or relapsed mantle-cell lymphoma: results of a phase II study of the National Cancer Institute of Canada Clinical Trials Group	J Clin Oncol	2003	21	9	1740-1745
135	Lin TS, Howard OM, Neuberg DS, Kim HH and Shipp MA	Seventy-two hour continuous infusion flavopiridol in relapsed and refractory mantle cell lymphoma	Leuk Lymphoma	2002	43	4	793-797
136	Morschhauser F, Depil S, Jourdan E, Wetterwald M, Bouabdallah R, *et al.*	Phase II study of gemcitabine-dexamethasone with or without cisplatin in relapsed or refractory mantle cell lymphoma	Ann Oncol	2007	18	2	370-375
137	Orciuolo E, Buda G, Pelosini M and Petrini M	Fludarabine, Bortezomib, Myocet and rituximab chemotherapy in relapsed and refractory mantle cell lymphoma	Br J Haematol	2010	148	5	810-812
138	Zaja F, De Luca S, Vitolo U, Orsucci L, Levis A, *et al.*	Salvage treatment with lenalidomide and dexamethasone in relapsed or refractory mantle cell lymphoma: clinical results and effects on microenvironment and neo-angiogenic biomarkers	Haematologica	2012	97	3	416-422
139	Levy V, Porcher R, Leblond V, Fermand JP, Cazin B, *et al.*	Evaluating treatment strategies in advanced Waldenstrom macroglobulinemia: use of quality-adjusted survival analysis	Leukemia	2001	15	9	1466-1470
140	Ansell SM, Tang H, Kurtin P, Koenig P, Inwards DJ, *et al.*	A phase II study of temsirolimus (CCI-779) in combination with rituximab in patients with relapsed or refractory mantle cell lymphoma	Blood	2009	114	22	

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141	Brown J, Byrd J, Furman R, Flinn I, Benson D, *et al.*	Clinical activity in a phase 1 study of cal-101, an isoform-selective inhibitor of phosphatidylinositol 3-kinase P110delta, in patients with B-cell malignancies	Haematologica	2010	95		466
142	Cartron G, Thieblemont C, Solal-Celigny P, Morschhhauser F, Haioun C, *et al.*	Promising efficacy with the new anti-CD20 antibody GA101 in heavily pre-treated NHL patients - First results from a phase II study in patients with relapsed or refractory DLBCL and MCL	Blood	2010	116	21	
143	Churpek JE, Pro B, Van Besien K, Kline J, Conner K, *et al.*	A phase 2 study of epothilone B analog BMS-247550 (NSC 710428) in patients with relapsed aggressive non-Hodgkin lymphomas	Cancer	2013	119	9	1683-1689
144	Corradini P, Dodero A, Farina L, Fanin R, Patriarca F, *et al.*	Allogeneic stem cell transplantation (ALLO-SCT) following a reduced-intensity conditioning (RIC) regimen in relapsed lymphomas: 5-year follow-up of the phase II study of the Gruppo Italiano Trapianto di Midollo Osseo (GITMO)	Haematologica	2009	94		21
145	Corradini P, Sarina B, Carniti C, Patriarca F, Carella AM, *et al.*	High-dose rituximab in the conditioning regimen before allogeneic stem cell transplantation reduces the incidence to acute gvhd in b-cell lymphomas	Blood	2011	118	21	
146	Corradini P, Ladetto M, Zallio F, Astolfi M, Rizzo E, *et al.*	Long-term follow-up to indolent lymphoma patients treated with high-dose sequential chemotherapy and autografting: evidence that durable molecular and clinical remission frequently can be attained only in follicular subtypes	J Clin Oncol	2004	22	8	1460-1468
147	Evens AM, Vose JM, Harb W, Gordon LI, Langdon R, *et al.*	A phase II multicenter study of the histone deacetylase inhibitor (HDACI) abexinostat (PCI-24781) in relapsed or refractory follicular lymphoma (FL) and mantle cell lymphoma (MCL)	Blood	2012	120	21	

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148	Freedman AS, Kuruvilla J, Assouline SE, Engert A, Heo D, *et al.*	Clinical activity to lucatumumab (HCD122) in patients (pts) with relapsed or refractory hodgkin or non-hodgkin lymphoma treated in a phase Ia/II clinical trial (NCT00670592)	Blood	2010	116	21	
149	Friedberg J, Mahadevan D, Jung J, Persky DO, Lossos IS, *et al.*	Phase 2 trial of alisertib (MLN8237), an investigational, potent inhibitor of Aurora A Kinase (AAK), in Patients (pts) with aggressive B-and T-Cell Non-Hodgkin Lymphoma (NHL)	Blood	2011	118	21	
150	Friedberg JW, Mahadevan D, Cebula E, Persky D, Lossos I, *et al.*	Phase II study of alisertib, a selective Aurora A kinase inhibitor, in relapsed and refractory aggressive B- and T-cell non-Hodgkin lymphomas	Journal of clinical oncology : official journal of the American Society of Clinical Oncology	2014	32	1	44-50
151	Furtado M, Dyer MJS, Johnson R, Berrow M and Rule S	Ofatumumab monotherapy in relapsed or refractory mantle cell lymphoma - a phase II trial	British Journal of Haematology	2014	165	4	575-578
152	Ganti AK, Bierman PJ, Lynch JC, Bociek RG, Vose JM, *et al.*	Hematopoietic stem cell transplantation in mantle cell lymphoma	Ann Oncol	2005	16	4	618-624
153	Gill H, Au WY, Cheung WW, Lee EY and Kwong YL	Oral arsenic trioxide based regimen as salvage treatment for relapsed or refractory mantle cell lymphoma	Ann Oncol	2014			
154	Gill H, Au WY, Cheung WWW and Kwong YL	Oral arsenic trioxide based regimen as salvage treatment for relapsed or refractory mantle cell lymphoma	Blood	2013	122	21	

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155	Gopal AK, Gooley T, Rajendran J, Pagel JM, Fisher DR, *et al.*	A phase i study of myeloablative I-131-anti CD-20 (Tositumomab) radioimmunotherapy with escalating doses of fludarabine followed by Autologous Hematopoietic Stem Cell Transplantation (ASCT) for adults (greater-than or equal to) 60 years of age	Blood	2011	118	21	
156	Haas R, Brittinger G, Meusers P, Murea S, Goldschmidt H, *et al.*	Myeloablative therapy with blood stem cell transplantation is effective in mantle cell lymphoma	Leukemia	1996	10	12	1975-1979
157	Holkova B, Kmieciak M, Bose P, Barr PM, Tombes MB, *et al.*	Phase I trial of carfilzomib in combination with vorinostat (saha) in patients with relapsed or refractory B-cell lymphomas	Blood	2013	122	21	
158	Hotte SJ, Chen EX, McIntosh L, Hirte HW, Turner S, *et al.*	NCIC CTG IND.177: Phase I study of AT7519M given as a short infusion twice weekly	European Journal of Cancer, Supplement	2010	8	7	157
159	Jones JA, Rupert AS, Poi M, Phelps MA, Andritsos L, *et al.*	Flavopiridol can be safely administered using a pharmacologically derived schedule and demonstrates activity in relapsed and refractory non-Hodgkin's lymphoma	American Journal of Hematology	2014	89	1	19-24
160	Jones JA, Andritsos L, Baiocchi R, Benson DM, Blum KA, *et al.*	Flavopiridol can be safely administered using a pharmacologically derived schedule and demonstrates activity in relapsed and refractory non-hodgkin's lymphoma	Blood	2010	116	21	
161	Kahl B, Byrd JC, Flinn IW, Wagner-Johnston N, Spurgeon S, *et al.*	Clinical safety and activity in a phase 1 study to cal-101, an isoform-selective inhibitor of phosphatidylinositol 3-kinase p110(delta), in patients with relapsed or refractory non-hodgkin lymphoma	Blood	2010	116	21	

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162	Kahl BS, Bailey HH, Smith EP, Turman N, Smith J, *et al.*	Phase II study to weekly low-dose paclitaxel for relapsed and refractory non-Hodgkin's lymphoma: A Wisconsin Oncology Network Study	Cancer Investigation	2005	23	1	13-18
163	Kahl BS, Spurgeon SE, Furman RR, Flinn IW, Coutre SE, *et al.*	Results of a phase I study of idelalisib, a PI3Kdelta inhibitor, in patients with relapsed or refractory mantle cell lymphoma (MCL)	Blood	2014			
164	Kruger WH, Hirt C, Basara N, Sayer HG, Behre G, *et al.*	Allogeneic stem cell transplantation for mantle cell lymphoma-final report from the prospective trials of the East German Study Group Haematology/Oncology (OSHO)	Ann Hematol	2014			
165	Lanasa MC, Glenn M, Mato AR, Allgood SD, Wong S, *et al.*	First-in-human study of AMG 319, a highly selective, small molecule inhibitor of PI3K(delta), in adult patients with relapsed or refractory lymphoid malignancies	Blood	2013	122	21	
166	Leonard JP, Kahl BS, Furman RR, Flinn IW, Wagner-Johnston ND, *et al.*	Final report of a phase I study of idelalisib, a selective inhibitor of phosphatidylinositol 3-kinase P110D, in patients with relapsed or refractory mantle cell lymphoma	Hematological Oncology	2013	31		194-195
167	Leonard JP, LaCasce AS, Smith MR, Noy A, Chirieac LR, *et al.*	Selective CDK4/6 inhibition with tumor responses by PD0332991 in patients with mantle cell lymphoma	Blood	2012	119	20	4597-4607
168	Martin P, Di Liberto M, Ely S, Huang X, Furman R, *et al.*	Cell cycle inhibition with PD0332991 sensitizes MCL to kill by bortezomib: A phase I trial	Hematological Oncology	2013	31		145
169	Martin P, DiLiberto M, Mason CE, Ely SA, Ruan J, *et al.*	The combination of palbociclib plus bortezomib is safe and active in patients with previously treated mantle cell lymphoma: Final results of a phase I trial	Blood	2013	122	21	

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170	Morrison VA, Johnson JL, Jung S, Leonard JP and Cheson BD	A phase II trial of bortezomib plus lenalidomide for relapsed or refractory mantle cell lymphoma (MCL) (CALGB 50501): Results of a planned interim analysis	Journal of Clinical Oncology	2010	28	15	
171	Morrison VA, Jung SH, Johnson J, La Casce A, Blum KA, *et al.*	Salvage therapy with bortezomib plus lenalidomide for relapsed or refractory mantle cell lymphoma: Initial results of a phase II trial (alliance/CALGB 50501)	Blood	2012	120	21	
172	Morschhauser F, Cartron G, Thieblemont C, Solal-Celigny P, Haioun C, *et al.*	Encouraging activity of Obinutuzumab (GA101) monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma: Results from a phase II study (BO20999)	Blood	2011	118	21	
173	Morschhauser FA, Cartron G, Thieblemont C, Solal-Celigny P, Haioun C, *et al.*	Obinutuzumab (GA101) monotherapy in relapsed or refractory diffuse large b-cell lymphoma or mantle-cell lymphoma: results from the phase II GAUGUIN study	Journal of clinical oncology : official journal of the American Society of Clinical Oncology	2013	31	23	2912-2919
174	Noesslinger T, Keil F, Mostl M, Tinchon C, Koller E, *et al.*	Autologous stem cell transplantation with BeEAM (bendamustine, etoposide, cytarabine, melphalan) in aggressive NHL and Hodgkin Lymphoma	Onkologie	2013	36		6
175	O'Connor OA, Popplewell L, Winter JN, Yuan R, Robeva A, *et al.*	Pillar-1: Preliminary results of a phase II study of mtor inhibitor everolimus in patients with mantle cell lymphoma (MCL) who are refractory or intolerant to bortezomib	Blood	2010	116	21	
176	Ogura M, Uchida T, Ando K, Ohmachi K, Itoh K, *et al.*	Bendamustine is highly effective for relapsed or refractory indolent B-cell non-Hodgkin lymphoma (B-NHL) and mantle cell lymphoma (MCL): Final results of a japanese multicenter phase II study	Blood	2009	114	22	
177	Renner C, Zinzani PL, Gressin R, Klingbiel D,	A multi-center phase II study (SAKK 36/06) of single agent everolimus (RAD001) in patients with relapsed	Blood	2010	116	21	

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178	Renner C, Zinzani PL, Gressin R, Klingbiel D, Favet L, *et al.*	A multicenter phase II study (SAKK 36/06) of single-agent everolimus (RAD001) in patients with relapsed or refractory mantle cell lymphoma	Onkologie	2011	34		97
179	Rolland D, Ribrag V, Haioun C, Ghesquieres H, Jardin F, *et al.*	Phase II trial and prediction of response of single agent tipifarnib in patients with relapsed or refractory mantle cell lymphoma: A Groupe d'Etude des Lymphomes de l'Adulte trial	Cancer Chemotherapy and Pharmacology	2010	65	4	781-790
180	Sarris AH, Romaguera J, Hagemeister FB, Rodriguez MA, McLaughlin P, *et al.*	Irinotecan in relapsed or refractory non-Hodgkin's lymphoma	Oncology (Williston Park, N.Y.)	2001	15	7 Suppl 8	53-56
181	Shah BD, Tao J, Sokol L, Chervenick PA, Tomblyn MR, *et al.*	Bystander vaccine therapy in mantle cell lymphoma (MCL): Phase II clinical results	Journal of Clinical Oncology	2010	28	15	
182	Shah BD, Tao J, Sokol L, Chervenick PA, Tomblyn M, *et al.*	Long term followup of bystander vaccine therapy in mantle cell lymphoma (MCL)	Blood	2011	118	21	
183	Smith SM, Van Besien K, Karrison T, Dancey J, McLaughlin P, *et al.*	Temsirolimus has activity in non-mantle cell non-Hodgkin's lymphoma subtypes: The University of Chicago phase II consortium	Journal to Clinical Oncology	2010	28	31	4740-4746
184	Spurgeon SEF, Wagner-Johnston ND, Furman RR, Flinn I, Coutre SE, *et al.*	Final results of a phase I study of idelalisib, a selective inhibitor of phosphatidylinositol 3-kinase P110{delta} (PI3K{delta}), in patients with relapsed or refractory mantle cell lymphoma (MCL)	Journal of Clinical Oncology	2013	31	15	

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185	Visco C, Zambello R, Paolini R, Finotto S, Zanotti R, *et al.*	Rituximab, bendamustine and cytarabine (R-BAC) is a very active regimen in patients with mantle cell lymphoma not eligible for intensive chemotherapy or autologous transplant	Blood	2011	118	21	
186	Vose J and Sneller V	Outpatient regimen rituximab plus ifosfamide, carboplatin and etoposide (R-ICE) for relapsed non-Hodgkin's lymphoma	Annals of Oncology	2003	14	SUPPL. 1	i17-i20
187	Wagner-Johnston ND, De Vos S, Leonard J, Sharman JP, Schreeder MT, *et al.*	Preliminary results of PI3K{delta} inhibitor idelalisib (GS-1101) treatment in combination with everolimus, bortezomib, or bendamustine/rituximab in patients with previously treated mantle cell lymphoma (MCL)	Journal of Clinical Oncology	2013	31	15	
188	Wagner-Johnston ND, De Vos S, Leonard J, Sharman JP, Schreeder MT, *et al.*	Preliminary results of pi3kd inhibitor idelalisib (GS-1101) treatment in combination with everolimus, bortezomib, or bendamustine/rituximab in patients with previously treated mantle cell lymphoma (MCL)	Hematological Oncology	2013	31		266
189	William BM, Allen MS, Loberiza FR, Bociek RG, Bierman PJ, *et al.*	Phase I/II study of Velcade(registered trademark)-beam (V-beam) and autologous hematopoietic stem cell transplantation (ASCT) for relapsed indolent non-hodgkin's lymphoma (NHL), transformed or mantle cell lymphoma (MCL)	Biology of Blood and Marrow Transplantation	2012	18	2	S246-S247
190	Witzens-Harig M, Benner A, Rieger M, McClanahan F, Hensel M, *et al.*	Rituximab maintenenance therapy in CD20+ B-cell Non-Hodgkin-Lymphoma - Final results of a multicenter prospective randomised phase II study	Onkologie	2010	33	6	204
191	Witzens-Harig M, Benner A, Rieger M, McClanahan F, Hensel M, *et al.*	Rituximab maintenenance therapy in CD20+ B-cell non-hodgkin-lymphoma - final results of a multicenter prospective randomised phase II study	Blood	2009	114	22	
192	Zaja F, De Luca S, Vitolo U, Orsucci L, Levis A, *et al.*	Salvage treatment with lenalidomide and dexamethasone in patients with relapsed refractory mantle cell lymphoma	Haematologica	2010	95		115

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193	Zaja F, De Luca S, Vitolo U, Orsucci L, Levis A, *et al.*	Salvage treatment with lenalidomide and dexamethasone in patients with relapsed refractory mantle cell lymphoma	Blood	2009	114	22	
194	Zaja F, De Luca S, Vitolo U, Orsucci L, Levis A, *et al.*	Salvage treatment with lenalidomide and dexamethasone in patients with relapsed refractory mantle cell lymphoma: Clinical results and modifications of angiogenic biomarkers	Blood	2010	116	21	
195	Barr PM, Briehl MM, Bernstein SH, *et al.*	Redox associated gene expression predicts for responses to the pro-oxidant molecule imexon in relapsed and refractory B-cell non-Hodgkin lymphoma: results of a multi-center phase II study [Abstract 89]	55th American Society of Hematology Annual Meeting and Exhibition	2013			
196	Porter DL, Kalos M, Frey NV, *et al.*	Chimeric antigen receptor modified T cells directed against CD19 (CTL019 cells) have long-term persistence and induce durable responses in relapsed, refractory CLL [Abstract 4162]	55th American Society to Hematology Annual Meeting and Exhibition	2013			
197	Davids MSS, J. F.Gerecitano, J. F.Kahl, B. S.Pagel, J. M.Wierda, W.Anderson, M. A.Rudersdorf, N. K.Gressick, L.A.Montalvo, N. P.Yang, J.Busman, T. A.Dunbar, M.Cerri, S. H.Humerickhouse, R. A. Roberts, A. W.	The single-agent Bcl-2 inhibitor ABT-199 (GDC-0199) in patients with relapsed or refractory (R/R) non-Hodgkin lymphoma (NHL): responses observed in all mantle cell lymphoma (MCL) patients [Abstract 1789]	55th American Society of Hematology Annual Meeting and Exhibition	2013			

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198	Dreyling MM, F.Bron, D.Bouabdallah, K.Vitolo, U.Linton, K.Van Den Neste, E.Mappa, S.Giurescu, M.Childs, B. H.Zinzani, P. L.	Preliminary results of a Phase II study of single agent bay 80-6946, a novel PI3K inhibitor, in patients with relapsed or refractory, indolent or aggressive lymphoma	Blood	2013	122	21	
199	Evens AMV, J. M.Harb, W. A.Gordon, L. I.Langdon, R.Grant, B.Sprague, J.Plasencia, C.Sirisawad, M.Yue, J.Luan, Y.Siek, A.Zhou, L.Balasubramanian, S.Bartlett, N. L.	A phase II multicenter study of the histone deacetylase inhibitor (HDACi) abexinostat (PCI-24781) in relapsed/ refractory follicular lymphoma (FL) and mantle cell lymphoma (MCL) [Abstract 55]	54th American Society of Hematology Annual Meeting and Exposition	2012			
200	Sangha R, Davies A, Dang, NH, *et al.*	Phase I study of inotuzumab ozogamicin (InO) combined with R-GDP for relapsed or refractory CD22+ B-Cell non-Hodgkin lymphoma (B-NHL) [Abstract 1821]	55th American Society of Hematology Annual Meeting and Exhibition	2013			
201	Gopal AK, B. S.De Vos, S.Wagner-Johnston, N. D.Schuster, S. J.Blum, K. A.Jurczak, W. J.Flinn, I. W.Flowers, C. R.Martin, P.Viardot, A.Goy, A.Davies, A.Zinzani, P. L.Dreyling, M. H.Holes, L. M.Li, D.Dansey, R.Godfrey, W. R.Salles, G. A.	Mature response data from a phase 2 study to PI3K-delta inhibitor idelalisib in patients with double (Rituximab and Alkylating Agent)-refractory indolent B-cell non-hodgkin lymphoma (iNHL)	Blood	2013	122	21	

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202	Lanasa MC, Glenn M, Mato AR, *et al.*	First-in-human study of AMG 319, a highly selective, small molecule inhibitor of PI3Kδ, in adult patients with relapsed or refractory lymphoid malignancies [Abstract 678]	55th American Society of Hematology Annual Meeting and Exhibition	2013			
203	Kater AP, Tonino SH, Kersten MJ, *et al.*	Interim analysis of dose-escalation stage of a phase 1b study evaluating safety and pharmacology of GS-9820, a second-generation, selective, PI3Kd-inhibitor in recurrent lymphoid malignancies [Abstract 2881]	55th American Society of Hematology Annual Meeting and Exhibition	2013			
204	Kohrt HEG, J. E.Lossos, I. S.Williams, M. E.Timmerman, J.Link, B. K.Goldberg, S. M.McGirr, A.Kurland, J. F.Wigginton, J. M.Cohen, L. J.Levy, R.	A phase Ib, open-label, multicenter study of urelumab (BMS-663513) in combination with rituximab in subjects with relapsed or refractory B-cell malignancies [Poster TPS3108]	2013 Annual Meeting of the American Society of Clinical Oncology	2013			
205	Montes AA, M.Murillo, I.Lopez-Gomez, L.Baringo, T.Giraldo, P.	RIT with 90Y ibritumomab tiuxetan in agressive non-hodgkin lymphoma. Evaluation of recent outcomes in a single institution	Blood	2012	120	21	
206	Kaplan LD, Deitcher SR, Silverman JA, Morgan GJ.	Vincristine sulfate liposome injection (Marqibo®) and rituximab for patients with relapsed and refractory diffuse large B-cell lymphoma or mantle cell lymphoma in need of palliative therapy [Abstract 4355]	55th American Society of Hematology Annual Meeting and Exhibition	2013			

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207	Gill HA, Au WY, Cheung WW, *et al.*	Oral arsenic trioxide based regimen as salvage treatment for relapsed or refractory mantle cell lymphoma [Abstract 4346]	55th American Society of Hematology Annual Meeting and Exhibition	2013			
208	Ferrero SP, A.Forstpointner, R.Scholz, C. W.Pezzutto, A.Bergmann, L.Truemper, L.Finke, J.Keller, U.Ladetto, M.Hiddemann, W.Weigert, O.Unterhalt, M.Dreyling, M.	Radioimmunotherapy in relapsed or refractory mantle cell lymphoma patients: final results of a European MCL Network phase II trial [Abstract 4384]	55th American Society of Hematology Annual Meeting and Exhibition	2013			
209	Weigert, O.,Jurczak, W.,Schilling, C.,Giza, A.,Rummel, M.,Hubalewska, A.,Pezzutto, A.,Unterhalt, M.,Hiddemann, W.,Skotnicki, A.,Dreyling, M.,Sr,	Efficacy of radioimmunotherapy with (90Y) ibritumomab tiuxetan is superior as consolidation in relapsed or refractory mantle cell lymphoma: Results of two phase II trials of the European MCL Network and the PLRG	Journal of Clinical Oncology: ASCO annual meeting proceedings	2006	24	18s	7533
210	Morschhauser, F.,Wetterwald, M.,Jourdan, D.,Solal Celigny, P.,Coso, D.,Rose, C.,Dumontet, C.	Gemcitabine with dexamethasone +/- cisplatin in patients with previously treated CLL and mantle cell lymphoma	Proceedings of the American Society of Clinical Oncology	2002			206b, Abstract 2644
211	Cassaday, R. D.,Goy, A.,Advani, S.,Chawla, P.,Nachankar, R.,Gandhi, M.,Gopal, A. K.	A Phase II, Single-Arm, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of P276-00, a Cyclin-Dependent Kinase Inhibitor, in Patients With Relapsed or Refractory Mantle Cell Lymphoma	Clinical Lymphoma, Myeloma and Leukemia	2015			

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212	Blum, K. A.,Maddocks, K.,Nagy, Z.,Zinzani, P. L.,Goy, A.,Provencio, M.,Robak, T.,Buske, C.,Korolkiewicz, R. P.,Winderlich, M.,Jurczak, W.	A phase IIA, open-label, multicenter study of single-agent MOR00208, an FC-optimized anti-CD19 antibody, in patients with relapsed or refractory B-cell Non-Hodgkin's lymphoma	Blood	2014	124	21	
213	Younes, A.,Salles, G.,Bociek, R. G.,Martinelli, G.,Caballero, D.,Barca, E. G.,Mukherjee, N.,Williams, L.,Herbst, F.,Tavorath, R.,Kim, W. S.	An open-label phase II study of buparlisib (BKM120) in patients with relapsed and refractory diffuse large B-cell lymphoma, mantle cell lymphoma or follicular lymphoma	Blood	2014	124	21	
214	Shah, B. D.,Tao, J.,Chervenick, P. A.,Riches, M. L.,Pinilla-Ibarz, J.,Moscinski, L. C.,Antonia, S.,Sotomayor, E. M.,Dessureault, S.	Seven year followup for bystander vaccine therapy in mantle cell lymphoma (MCL)	Blood	2014	124	21	
215	Pagel, J. M.,Spurgeon, S. E.,Byrd, J. C.,Awan, F. T.,Flinn, I. W.,Lanasa, M. C.,Eisenfeld, A. J.,Stromatt, S. C.,Gopal, A. K.	Otlertuzumab (TRU-016), an anti-CD37 monospecific ADAPTIR(trademark) therapeutic protein, for relapsed or refractory NHL patients	British Journal of Haematology	2014			

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216	Monica, M.,Martin, A.,Gayoso, J.,Briones, J.,Jarque, I.,Arranz, R.,Heras, I.,Conde, E.,Bernal, T.,Grande, C.,Lopez, J.,Caballero, D.	Phase ii study of yttrium-90-ibritumomab tiuxetan in reduced intensity conditioning (RIC) allogeneic transplant in relapsed or refractory aggressive b-cell lymphoma: A gel/tamo phase ii clinical trial	Haematologica	2011	96		413-414
217	Urbano-Ispizua, A.,Pavletic, S. Z.,Flowers, M. E.,Klein, J. P.,Zhang, M. J.,Carreras, J.,Montoto, S.,Perales, M. A.,Aljurf, M. D.,Akpek, G.,Bredeson, C. N.,Costa, L. J.,Dandoy, C.,Freytes, C. O.,Fung, H. C.,Gale, R. P.,Gibson, J.,Hamadani, M.,Hayashi, R.	The Impact of Graft Versus Host Disease on Relapse Rate in Patients with Lymphoma Depends on the Histological Sub-Type and the Intensity of the Conditioning Regimen	Biol Blood Marrow Transplant	2015			
218	Pagel, J. M.,Spurgeon, S. E.,Byrd, J. C.,Awan, F. T.,Flinn, I. W.,Lanasa, M. C.,Eisenfeld, A. J.,Stromatt, S. C.,Gopal, A. K.	Otlertuzumab (TRU-016), an anti-CD37 monospecific ADAPTIR() therapeutic protein, for relapsed or refractory NHL patients	Br J Haematol	2015	168	1	38-45
219	Kahl, B. S.,Spurgeon, S. E.,Furman, R. R.,Flinn, I. W.,Coutre, S. E.,Brown, J. R.,Benson, D. M.,Byrd, J. C.,Peterman, S.,Cho, Y.,Yu, A.,Godfrey, W. R.,Wagner-Johnston, N. D.	A phase 1 study of the PI3Kdelta inhibitor idelalisib in patients with relapsed or refractory mantle cell lymphoma (MCL)	Blood	2014	123	22	3398-405

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220	Gopal, A. K.,Gooley, T. A.,Rajendran, J. G.,Pagel, J. M.,Fisher, D. R.,Maloney, D. G.,Appelbaum, F. R.,Cassaday, R. D.,Shields, A.,Press, O. W.	Myeloablative I-131-tositumomab with escalating doses of fludarabine and autologous hematopoietic transplantation for adults age >/= 60 years with B cell lymphoma	Biol Blood Marrow Transplant	2014	20	6	770-5
221	Jurczak W, Rule S, Martin P, Auer R, Kahl BS, *et al.*	Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma - Results of an international, multicenter, phase 2 study of Ibrutinib (PCI-32765) - EHA Encore	Acta Haematologica Polonica	2013	44	3	314-318
222	Galimberti S, Nagy B, Benedetti E, Pacini S, Brizzi S, *et al.*	Evaluation of the MDR1, ABCG2, Topoisomerases IIalpha and GSTpi gene expression in patients affected by aggressive mantle cell lymphoma treated by the R-Hyper-CVAD regimen	Leuk Lymphoma	2007	48	8	1502-1509
223	Kluin-Nelemans HC, van Marwijk Kooy M, Lugtenburg PJ, van Putten WL, Luten M, *et al.*	Intensified alemtuzumab-CHOP therapy for peripheral T-cell lymphoma	Ann Oncol	2011	22	7	1595-1600
224	Kluin-Nelemans HC, Hoster E, Hermine O, Walewski J, Trneny M, *et al.*	Treatment of older patients with mantle-cell lymphoma	N Engl J Med	2012	367	6	520-531
225	Mangel J, Leitch HA, Connors JM, Buckstein R, Imrie K, *et al.*	Intensive chemotherapy and autologous stem-cell transplantation plus rituximab is superior to conventional chemotherapy for newly diagnosed advanced stage mantle-cell lymphoma: a matched pair analysis	Ann Oncol	2004	15	2	283-290
226	Romaguera JE, Fayad L, Rodriguez MA, Broglio KR, Hagemeister FB, *et al.*	High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine	J Clin Oncol	2005	23	28	7013-7023

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227	Buske C, Hoster E, Dreyling M, Eimermacher H, Wandt H, *et al.*	The addition of rituximab to front-line therapy with CHOP (R-CHOP) results in a higher response rate and longer time to treatment failure in patients with lymphoplasmacytic lymphoma: results of a randomized trial of the German Low-Grade Lymphoma Study Group (GLSG)	Leukemia	2009	23	1	153-161
228	Dreyling M, Lenz G, Hoster E, Van Hoof A, Gisselbrecht C, *et al.*	Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL Network	Blood	2005	105	7	2677-2684
229	Saven A, Emanuele S, Kosty M, Koziol J, Ellison D, *et al.*	2-Chlorodeoxyadenosine activity in patients with untreated, indolent non- Hodgkin's lymphoma	Blood	1995	86	5	1710-1716
230	Rosenthal AC, Dueck AC, Gano K, *et al.*	A phase 2 study of lenalidomide, rituximab, cyclophosphamide and dexamethasone (LR-CD) for untreated low grade non-Hodgkin lymphoma requiring therapy: Waldenström's macroglobulinemia cohort results [Abstract 4352]	55th American Society of Hematology Annual Meeting and Exhibition	2013			
231	Dreyling, M.,Lenz, G.,Schiegnitz, E.,Wormann, B.,Duehrsen, U.,Metzner, B.,Eimermacher, H.,Neubauer, A.,Wandt, H.,Steinhauer, H.,Parwaresch, R.,Hasford, J.,Unterhalt, M.,Hiddemann, W.	Combined immuno-chemotherapy (R-CHOP) significantly improves response and time to treatment failure in patients with advanced mantle cell lymphoma - results of a randomized trial of the German Low Grade Lymphoma Study Group (GLSG)	Onkologie	2004	27	Suppl 3	15

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232	Koch P, Probst A, Berdel WE, Willich NA, Reinartz G, *et al.*	Treatment results in localized primary gastric lymphoma: data of patients registered within the German multicenter study (GIT NHL 02/96)	J Clin Oncol	2005	23	28	7050-7059
233	Tateishi U, Tatsumi M, Terauchi T, Ishizawa K, Ogura M, *et al.*	Relevance of monitoring metabolic reduction in patients with relapsed or refractory follicular and mantle cell lymphoma receiving bendamustine: a multicenter study	Cancer Sci	2011	102	2	414-418
234	Gobbi PG, Ferreri AJ, Ponzoni M and Levis A	Hodgkin lymphoma	Crit Rev Oncol Hematol	2013	85	2	216-237
235	Lefrere F, Delmer A, Levy V, Delarue R, Varet B, *et al.*	Sequential chemotherapy regimens followed by high-dose therapy with stem cell transplantation in mantle cell lymphoma: an update of a prospective study	Haematologica	2004	89	10	1275-1276
236	Arai S and Miklos DB	Rituximab in hematopoietic cell transplantation	Expert Opinion on Biological Therapy	2010	10	6	971-982
237	Burger JA	Bruton's tyrosine kinase (BTK) inhibitors in clinical trials	Current Hematologic Malignancy Reports	2014	9	1	44-49
238	Chavez JC, Sahakian E and Pinilla-Ibarz J	Ibrutinib: An evidence-based review of its potential in the treatment of advanced chronic lymphocytic leukemia	Core Evidence	2013	8		37-45
239	Cortelazzo S, Ponzoni M, Ferreri AJM and Dreyling M	Mantle cell lymphoma	Critical Reviews in Oncology/Hematology	2012	82	1	78-101
240	Hoy SM and McKeage K	Temsirolimus in relapsed andor refractory mantle cell lymphoma	BioDrugs	2011	25	3	193-195

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241	Hoy SM and McKeage K	Temsirolimus: In relapsed and/or refractory mantle cell lymphoma	Drugs	2010	70	14	1819-1829
242	Lenz G, Dreyling M and Hiddemann W	Mantle cell lymphoma: Established therapeutic options and future directions	Annals of Hematology	2004	83	2	71-77
243	Marcus R and Hagenbeek A	The therapeutic use of rituximab in non-Hodgkin's lymphoma	Eur J Haematol	2007	78	SUPPL. 67	5-14
244	Marcus R	Current treatment options in aggressive lymphoma	Leukemia and Lymphoma	2003	44	SUPPL. 4	S15-S27
245	Mato AR, Feldman T and Goy A	Proteasome inhibition and combination therapy for non-Hodgkin's lymphoma: From bench to bedside	Oncologist	2012	17	5	694-707
246	Ogura M	Current treatment strategy and new agents in mantle cell lymphoma	International Journal of Hematology	2010	92	1	25-32
247	Podar K	Efficacy of subcutaneous bortezomib in the management of patients with multiple myeloma or relapsed mantle cell lymphoma	Clinical Medicine Insights: Therapeutics	2014	6		15-23
248	Rivera-Rodriguez N and Cabanillas F	Recent advances in the management of mantle cell lymphoma	Curr Opin Oncol	2013	25	6	716-721
249	Andorsky DJ, Cataruozolo PE, Mouro JL, *et al.*	MAGNIFY: A phase 3B, randomized trial of lenalidomide plus rituximab induction and maintenance therapy followed by lenalidomide single-agent versus rituximab maintenance in patients with relapsed or refractory indolent non-Hodgkin lymphoma (NHL) [Abstact TPS8617]	American Society of Clinical Oncology 50th Annual Meeting	2014			
250	Nagai, S.	Comprehensive analysis of clinically relevant improvement in progression-free survival in hematologic malignancy from the viewpoint of revised EMA's guideline on anticancer medicinal products	Haematologica	2013	98		450

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251	Vidal L, Gafter-Gvili A, Gurion R, Raanani P, Dreyling M, *et al.*	Bendamustine for patients with indolent B cell lymphoid malignancies including chronic lymphocytic leukaemia	Cochrane Database Syst Rev	2012	9		CD009045
252	Bouabdallah K, Ribrag V, Terriou L, Soria JC and Delarue R	Temsirolimus in the treatment of mantle cell lymphoma: frequency and management of adverse effects	Curr Opin Oncol	2013	25 Suppl 2		S1-12
253	Cohen BJ, Moskowitz C, Straus D, Noy A, Hedrick E, *et al.*	Cyclophosphamide/fludarabine (CF) is active in the treatment of mantle cell lymphoma	Leuk Lymphoma	2001	42	5	1015-1022
254	Lee J, Cho SG, Chung SM, Ryu MR, Kim SH, *et al.*	Retrospective analysis of treatment outcomes for extranodal NK/T-cell lymphoma (ENKL), nasal type, stage I-IIE: single institute experience of combined modality treatment for early localized nasal extranodal NK/T-cell lymphoma (ENKL)	Ann Hematol	2013	92	3	333-343
255	Schulz H, Bohlius JF, Trelle S, Skoetz N, Reiser M, *et al.*	Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis	J Natl Cancer Inst	2007	99	9	706-714
256	Schulz H, Bohlius J, Skoetz N, Trelle S, Kober T, *et al.*	Chemotherapy plus Rituximab versus chemotherapy alone for B-cell non-Hodgkin's lymphoma	Cochrane Database Syst Rev	2007	4		CD003805
257	O'Connor SR and Rana SK	Selective loss of lymphoid component simulating myeloma in lymphoplasmacytic lymphoma treated with rituximab	Br J Haematol	2013	161	4	460
258	Nabhan, C. Villines, D., Chiu, B., Ollberding, N.J., Valdex, T., *et al.*	Meta Analysis of Grade 3 and/or 4 Toxicities in Follicular (FL) and Mantle Cell (MCL) Non-Hodgkin Lymphoma (NHL) Patients Receiving Maintenance Rituximab (MR): Impact of Schedule, Histology, and Induction Regimen	2012 ASH Annual Meeting	2012			Abstract No. 3654

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259	Witzig TE, Vose J, Zinzani PL, Habermann TM, Tuscano JM, *et al.*	Combined analysis of single-agent lenalidomide in relapsed or refractory mantle cell lymphoma	2013 ASCO Annual Meeting	2013			
260	Witzig, T., Vose, J., Zinzani, P., Habermann, T., Tuscano, J. *et al.*	Single-agent lenalidomide in relapsed or refractory mantle cell lymphoma: a combined analysis from the MCL-001, NHL- 002, and NHL-003 studies	EHA 2013	2013			
261	Aksoy S, Dizdar O, Hayran M and Harputluoglu H	Infectious complications of rituximab in patients with lymphoma during maintenance therapy: A systematic review and meta-analysis	Leukemia and Lymphoma	2009	50	3	357-365
262	Cai Q, Chen Y, Zou D, Badillo M, Zhou S, *et al.*	Novel combination of lenalidomide-rituximab provides an effective bridge to stem cell transplantation in relapsed and/or refractory aggressive b-cell non-hodgkin's lymphomas: A single center experience	Blood	2013	122	21	
263	Cao L, Fan L, Xu W and Li J	Reports on research progress of mantle cell lymphoma in the 55th ASH annual meeting	Journal of Leukemia and Lymphoma	2014	23	2	70-72
264	Coiffier B	Clinical efficacy and management of temsirolimus in patients with relapsed or refractory mantle cell lymphoma	Clinical Lymphoma, Myeloma and Leukemia	2013	13	4	351-359
265	Cunningham S, Muneer S, Ranganathan A, Shivakumar L, Lonial S, *et al.*	Phase II trial for lenalidomide alone in relapsed or refractory aggressive non-Hodgkin lymphoma	Clinical Lymphoma and Myeloma	2007	7	5	339

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266	Dabaja B, Voong R, Shihadeh F, Arzu I, Pinnix C, *et al.*	Radiation therapy is a very effective modality in the treatment of mantle cell lymphoma,>80% complete disappearance of disease site in heavily pretreated patients	International Journal of Radiation Oncology Biology Physics	2013	87	2	S555
267	Dabaja BS, Tsang R, Qi S, Allen P, Hodgson DC, *et al.*	Either combined-modality or radiotherapy alone provide favorable outcome in stage I-II mantle cell lymphoma: A report of 82 patients from the international lymphoma radiation oncology group (ILROG)	Blood	2013	122	21	
268	Dreyling M, Thieblemont C, Gallamini A, Arcaini L, Campo E, *et al.*	ESMO consensus conferences: Guidelines on malignant lymphoma. Part 2: Marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma	Annals of Oncology	2013	24	4	857-877
269	Kennedy D, Mwamburi M, Ranganathan G, Mayo D, Tremmel L, *et al.*	Bendamustine-r2ituximab combination treatment in relapsed NHL: Combined experience from two phase 2 trials and exploration to response predictors	Haematologica	2010	95		117-118
270	Khouri IF, Wei W, Valverde R, Korbling M, Turturro F, *et al.*	Bfr (bendamustine, fludarabine, rituximab) nonmyeloablative allogeneic conditioning: A novel regimen inducing immunosuppression without myelosuppression	Blood	2013	122	21	
271	Krekeler G, Herzberg C, Dreyling M, Hess G and Kalanovic D	Evaluation of safety, tolerability and efficacy of Temsirolimus in patients with relapsed or refractory mantle cell lymphoma (rel/refr MCL) in routine clinical practice	Onkologie	2013	36		139-140
272	Krekeler G, Herzberg C, Dreyling M, Hess G and Kalanovic D	Evaluation of safety, tolerability and efficacy of Temsirolimus in patients with relapsed or refractory mantle cell lymphoma (rel/refr MCL) in routine clinical	European Journal of Cancer	2013	49		S850-S851

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273	Laudi N, Arora M, Burns L, McGlave P, Miller J, *et al.*	Efficacy of high-dose therapy and hematopoietic stem cell transplantation for mantle cell lymphoma	Am J Hematol	2006	81	7	519-524
274	Lubanski PM and Czuczman MS	Lenalidomide for the treatment of B-cell lymphoma	Expert Opinion on Orphan Drugs	2013	1	8	651-659
275	Magnusson E, Cao Q, Linden MA, Frolich J, Anand V, *et al.*	Hematopoietic cell transplantation for mantle cell lymphoma: Predictive value of pretransplant positron emission tomography/computed tomography and bone marrow evaluations for outcomes	Clinical Lymphoma, Myeloma and Leukemia	2014	14	2	114-121
276	Njue A, Trask PC, Colosia A, Olivares R, Khan S, *et al.*	Efficacy and safety of treatments for relapsed or refractory mantle cell lymphoma (MCL): Results of a systematic literature review	Blood	2013	122	21	
277	Tan TD, Wu MC and Chiou LW	Long-term survival of mantle cell lymphoma - A single institution experience in Taiwan	Haematologica	2010	95		633
278	Weide R, Feiten S, Friesenhahn V, Heymanns J, Kleboth K, *et al.*	Retreatment with bendamustine-containing regimens in patients with relapsed or refractory chronic lymphocytic leukemia and indolent B-cell lymphomas achieves high response rates and some long lasting remissions	Leukemia and Lymphoma	2013	54	8	1640-1646
279	Cai QC, Y.Zou, D.Badillo, M.Zhou, S.Zhang, L.Lopez, E. R.Jiang, W.Huang, H. Q.Lin, T.Wang, M.	Novel combination of lenalidomide-rituximab provides an effective bridge to stem cell transplantation in relapsed and/or refractory aggressive b-cell non-hodgkin's lymphomas: A single center experience	Blood	2013	122	21	

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280	Krekeler GH, C.Dreyling, M. H.Hess, G.Kalanovic, D.	Evaluation of safety, tolerability and efficacy of temsirolimus in patients with relapsed or refractory mantle cell lymphoma (REL/REFR MCL) in the usual health care setting	European Cancer Organisation (ECCO) European Cancer Congress 2012	2012			
281	Lin PWAP, S. K.,Neumann, P. J.Cohen, J. T.	Cost-effectiveness analysis of innovation in hematologic malignancies [Abstract PCN98]	International Society for Pharmacoeconomics and Outcomes Research 19th Annual International Meeting	2014			
282	Senbetta M, Dandappanavar A, McKenzie RS, *et al.*	Ibrutinib therapy for patients with relapsed or refractory mantle cell lymphoma: A budget impact analysis from a U.S. payer perspective [Abstract e19553]	American Society of Clinical Oncology 50th Annual Meeting	2014			
283	Witzig TV, J.Zinzani, P.Habermann, T.Tuscano, J.Sinha, R.Williams, M.Drach, J.Ramchandren, R.Besisik, S.Zhang, L.Cicero, S.Fu, T.Goy, A.	Single-agent lenalidomide in relapsed or refractory mantle cell lymphoma: a combined analysis from the MCL-001, NHL-002, and NHL-003 studies [Abstract P305]	18th Congress of the European Hematology Association	2013			
284	Njue, A.,Colosia, A.,Trask, P. C.,Olivares, R.,Khan, S.,Abbe, A.,Police, R.,Wang, J.,Ruiz-Soto,	Clinical efficacy and safety in relapsed or refractory mantle dell lymphoma: a systematic literature review (Provisional abstract)	Database of Abstracts of Reviews of Effects	2014		2	epub

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	R.,Kaye, J. A.,Awan, F.						
285	Peng, L.,Ye, X.,Zhou, Y.,Zhang, J.,Zhao, Q.	Meta-analysis of incidence and risk of peripheral neuropathy associated with intravenous bortezomib	Supportive Care in Cancer	2015			
286	Vidal, L.,Gafter-Gvili, A.,Dreyling, M.,Ghielmini, M.,Unterhalt, M.,Raanani, P.,Shpilberg, O.,Ram, R.,Gurion, R.	Rituximab maintenance (MR) for patients with mantle cell lymphoma (MCL)-a systematic review and meta-analysis of randomized controlled trials (RCTs)	Blood	2014	124	21	
287	Hoster, E.,Unterhalt, M.,Pfreundschuh, M.,Hallek, M.,Forstpointner, R.,Metzner, B.,Einsele, H.,Krauter, J.,Duhrsen, U.,Ludwig, W. D.,Birkmann, J.,Peter, N.,Klapper, W.,Dreyling, M. H.,Hiddemann, W.	The addition of rituximab to CHOP improves failure-free and overall survival of mantle-cell lymphoma patients-a pooled trials analysis of the german low-grade lymphoma study group (GLSG)	Blood	2014	124	21	
288	Pott, C.,Macintyre, E.,Delfau-Larue, M. H.,Ribrag, V.,Unterhalt, M.,Kneba, M.,Hiddemann, W.,Dreyling, M.,Hermine, O.,Hoster, E.	MRD eradication should be the therapeutic goal in mantle cell lymphoma and may enable tailored treatment approaches: Results of the intergroup trials of the European MCL network	Blood	2014	124	21	
289	Sorensen, S.,Dorman, E.,Xu, Y.,Sallum, R.,Pan, F.,Szatkowski, A.,Gaudig, M.,Sengupta, N.	Systematic review of relapsed or refractory mantle cell lymphoma (MCL) clinical trials: Implications for decision modeling	Value in Health	2014	17	7	A615-A616

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290	Njue, A.,Colosia, A.,Trask, P. C.,Olivares, R.,Khan, S.,Abbe, A.,Police, R.,Wang, J.,Ruiz-Soto, R.,Kaye, J. A.,Awan, F.	Clinical Efficacy and Safety in Relapsed/Refractory Mantle Cell Lymphoma: A Systematic Literature Review	Clinical Lymphoma, Myeloma and Leukemia	2014			
291	Gaudig, M.,Erhardt, W.,Kempel, A.	Systematic review and assessment of outcomes in patients with the rare disease of mantle cell lymphoma (MCL)	Value in Health	2014	17	3	A96
292	Bachanova, V.,Burns, L. J.,Ahn, K. W.,Laport, G. G.,Akpek, G.,Kharfan-Dabaja, M. A.,Nishihori, T.,Agura, E.,Armand, P.,Jaglowski, S. M.,Cairo, M. S.,Cashen, A. F.,Cohen, J. B.,D'Souza, A.,Freytes, C. O.,Gale, R. P.,Ganguly, S.,Ghosh, N.,Holmberg, L. A.,In	Impact of Pretransplantation F-fluorodeoxy Glucose-Positron Emission Tomography Status on Outcomes after Allogeneic Hematopoietic Cell Transplantation for Non-Hodgkin Lymphoma	Biol Blood Marrow Transplant	2015			
293	Njue, A.,Colosia, A.,Trask, P. C.,Olivares, R.,Khan, S.,Abbe, A.,Police, R.,Wang, J.,Ruiz-Soto, R.,Kaye, J. A.,Awan, F.	Clinical efficacy and safety in relapsed or refractory mantle cell lymphoma: a systematic literature review	Clin Lymphoma Myeloma Leuk	2015	15	1	1-12 e7
294	Faderl S, Thomas DA, O'Brien S, Garcia-Manero G, Kantarjian HM, *et al.*	Experience with alemtuzumab plus rituximab in patients with relapsed and refractory lymphoid malignancies	Blood	2003	101	9	3413-3415
295	Budde LE, Zhang MM, Shustov AR, Pagel JM, Gooley TA, *et al.*	A phase I study of pulse high-dose vorinostat (V) plus rituximab (R), ifosphamide, carboplatin, and etoposide (ICE) in patients with relapsed lymphoma	Br J Haematol	2013	161	2	183-191

#	Author	Title	Journal	Year	Volume	Issue	Page
296	Crump M, Couban S, Meyer R, Rudinskas L, Zanke B, *et al.*	Phase II study of sequential topotecan and etoposide in patients with intermediate grade non-Hodgkin's lymphoma: a National Cancer Institute of Canada Clinical Trials Group study	Leuk Lymphoma	2002	43	8	1581-1587
297	Friedberg JW, Vose JM, Kelly JL, Young F, Bernstein SH, *et al.*	The combination of bendamustine, bortezomib, and rituximab for patients with relapsed or refractory indolent and mantle cell non-Hodgkin lymphoma	Blood	2011	117	10	2807-2812
298	Hess G, Flohr T, Kolbe K, Bonn S, Schuler M, *et al.*	Effect of rituximab on the long-term outcome after high-dose therapy for relapsed B-cell non-Hodgkin's lymphoma	Ann Hematol	2006	85	11	769-779
299	Koenigsmann M, Knauf W, Herold M, Pasold R, Muller G, *et al.*	Fludarabine and bendamustine in refractory and relapsed indolent lymphoma--a multicenter phase I/II trial of the East German Society of Hematology and Oncology (OSHO)	Leuk Lymphoma	2004	45	9	1821-1827
300	Kroschinsky F, Schleyer E, Renner U, Schimming C, Schimmelpfennig C, *et al.*	Increased myelotoxicity of idarubicin: is there a pharmacological basis? Results of a pharmacokinetic and an in vitro cytotoxicity study	Cancer Chemother Pharmacol	2004	53	1	61-67
301	Leonard JP, Link BK, Emmanouilides C, Gregory SA, Weisdorf D, *et al.*	Phase I trial of toll-like receptor 9 agonist PF-3512676 with and following rituximab in patients with recurrent indolent and aggressive non Hodgkin's lymphoma	Clin Cancer Res	2007	13	20	6168-6174
302	Macpherson N, Belch A, Taylor M, Sutherland J, Czaykowski P, *et al.*	Liposomal encapsulated doxorubicin (Caelyx) in the treatment of relapsed aggressive non-Hodgkin's lymphoma: a phase II study	Leuk Lymphoma	2006	47	7	1327-1332
303	Oki Y, Ogura M, Kato H, Kikuchi A, Taji H, *et al.*	Phase II study of a salvage regimen using cyclophosphamide, high-dose cytarabine, dexamethasone, etoposide, and rituximab in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma	Cancer Sci	2008	99	1	179-184

#	Author	Title	Journal	Year	Volume	Issue	Page
304	Orlowski RZ, Stinchcombe TE, Mitchell BS, Shea TC, Baldwin AS, *et al.*	Phase I trial of the proteasome inhibitor PS-341 in patients with refractory hematologic malignancies	J Clin Oncol	2002	20	22	4420-4427
305	Rigacci L, Mappa S, Nassi L, Alterini R, Carrai V, *et al.*	Liposome-encapsulated doxorubicin in combination with cyclophosphamide, vincristine, prednisone and rituximab in patients with lymphoma and concurrent cardiac diseases or pre-treated with anthracyclines	Hematol Oncol	2007	25	4	198-203
306	Rodriguez MA, Pytlik R, Kozak T, Chhanabhai M, Gascoyne R, *et al.*	Vincristine sulfate liposomes injection (Marqibo) in heavily pretreated patients with refractory aggressive non-Hodgkin lymphoma: report of the pivotal phase 2 study	Cancer	2009	115	15	3475-3482
307	Witzig TE, Geyer SM, Kurtin PJ, Colgan JP, Inwards DJ, *et al.*	Salvage chemotherapy with rituximab DHAP for relapsed non-Hodgkin lymphoma: a phase II trial in the North Central Cancer Treatment Group	Leuk Lymphoma	2008	49	6	1074-1080
308	Smith SM, Grinblatt D, Johnson JL, Niedzwiecki D, Rizzieri D, *et al.*	Thalidomide has limited single-agent activity in relapsed or refractory indolent non-Hodgkin lymphomas: a phase II trial of the Cancer and Leukemia Group B	Br J Haematol	2008	140	3	313-319
309	Pro B, Leber B, Smith M, Fayad L, Romaguera J, *et al.*	Phase II multicenter study of oblimersen sodium, a Bcl-2 antisense oligonucleotide, in combination with rituximab in patients with recurrent B-cell non-Hodgkin lymphoma	Br J Haematol	2008	143	3	355-360
310	Thomas DW, Owen RG, Johnson SA, Hillmen P, Seymour JF, *et al.*	Superior quality and duration of responses among patients with mantle-cell lymphoma treated with fludarabine and cyclophosphamide with or without rituximab compared with prior responses to CHOP	Leuk Lymphoma	2005	46	4	549-552
311	Barr PM, Briehl MM, Bernstein SH, Friedberg JW, Baran A, *et al.*	Redox associated gene expression predicts for responses to the pro-oxidant molecule imexon in relapsed and refractory B-cell non-hodgkin lymphoma: Results of a multi-center phase II study	Blood	2013	122	21	

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312	Bashey A, Medina B, Corringham S, Pasek M, Carrier E, *et al.*	CTLA4 blockade with ipilimumab to treat relapse of malignancy after allogeneic hematopoietic cell transplantation	Blood	2009	113	7	1581-1588
313	Bethge WA, Lange T, Von Harsdorf S, Bornhauser M, Federmann B, *et al.*	Phase II study of radioimmunotherapy with yttrium-90-ibritumomab tiuxetan as part of a reduced-intensity conditioning regimen for allogeneic haematopoietic cell transplantation in patients with advanced indolent non-Hodgkin lymphoma	Bone Marrow Transplantation	2010	45		S44
314	Chang JE, Voorhees PM, Kolesar JM, Ahuja HG, Sanchez FA, *et al.*	Phase II study of arsenic trioxide and ascorbic acid for relapsed or refractory lymphoid malignancies: A Wisconsin Oncology Network study	Hematological Oncology	2009	27	1	11-16
315	Chong EA, Ahmadi T, Aqui NA, Nasta SD, Svoboda J, *et al.*	High response rate to combination lenalidomide-rituximab in Fc(gamma)RIIIa-F carriers with indolent or mantle cell lymphomas previously refractory to rituximab	Blood	2013	122	21	
316	Dreyling M, Morschhauser F, Bron D, Bouabdallah K, Vitolo U, *et al.*	Preliminary results of a Phase II study of single agent bay 80-6946, a novel PI3K inhibitor, in patients with relapsed or refractory, indolent or aggressive lymphoma	Blood	2013	122	21	
317	Fanale M, Assouline S, Kuruvilla J, Solal-Celigny P, Heo DS, *et al.*	Phase IA/II, multicentre, open-label study of the CD40 antagonistic monoclonal antibody lucatumumab in adult patients with advanced non-Hodgkin or Hodgkin lymphoma	British Journal of Haematology	2014	164	2	258-265
318	Flinn IW, Mainwaring M, Peacock N, Shipley D, Arrowsmith E, *et al.*	Rituximab, lenalidomide, and bortezomib in the first-line or second-line treatment of patients with mantle cell lymphoma a phase I/II trial	Blood	2012	120	21	
319	Girinsky T, Lapusan S, Ribrag V, Koscielny S, Ferme C, *et al.*	Phase II study of concomitant chemoradiotherapy in bulky refractory or chemoresistant relapsed lymphomas	Int J Radiat Oncol Biol Phys	2005	61	2	476-479

#	Author	Title	Journal	Year	Volume	Issue	Page
320	Guidetti A, Carlo-Stella C, Locatelli SL, Malorni W, Pierdominici M, *et al.*	Phase II study to sorafenib in patients with relapsed or refractory lymphoma	British Journal to Haematology	2012	158	1	108-119
321	Kaplan LD, Deitcher SR, Silverman JA and Morgan G	Phase II study of vincristine sulfate liposome injection (Marqibo) and rituximab for patients with relapsed and refractory diffuse large B-cell lymphoma or mantle cell lymphoma in need of palliative therapy	Clinical Lymphoma, Myeloma and Leukemia	2014	14	1	37-42
322	Kaplan LD, Deitcher SR, Silverman JA and Morgan GJ	Vincristine sulfate liposome injection (Marqibo(registered trademark)) and rituximab for patients with relapsed and refractory diffuse large B-cell lymphoma or mantle cell lymphoma in need of palliative therapy	Blood	2013	122	21	
323	Kim SK, Song MK, Chung JS and Shin HJ	Phase II study of ifosfamide, etoposide, and oxaliplatin (IFETOX) chemotherapy for relapsed or refractory non-hodgkin's lymphoma	International Journal of Hematology	2013	98	5	543-548
324	Kirschbaum M, Frankel P, Popplewell L, Zain J, Delioukina M, *et al.*	Phase II study of vorinostat for treatment of relapsed or refractory indolent non-hodgkin's lymphoma and mantle cell lymphoma	Journal of Clinical Oncology	2011	29	9	1198-1203
325	Koenigsmann M, Mohren M, Jentsch-Ullrich K, Franke A, Becker E, *et al.*	High-dose treosulfan in patients with relapsed or refractory high-grade lymphoma receiving tandem autologous blood stem cell transplantation	Bone Marrow Transplantation	2004	34	6	477-483
326	Kornblit B, Maloney DG, Storb R, Storek J, Hari P, *et al.*	Fludarabine and 2-Gy TBI is superior to 2Gy TBI as conditioning for HLA-Matched related hematopoietic cell transplantation: A phase III randomized trial	Biology to Blood and Marrow Transplantation	2013	19	9	1340-1347
327	Krishnan A, Raubitschek A, Palmer J, Nademanee AP, Kogut N, *et al.*	Y90 plus high dose beam with autologous stem cell transplantation for chemorefractory non hodgkin lymphoma	Blood	2009	114	22	

#	Author	Title	Journal	Year	Volume	Issue	Page
328	Larsen JT, Hogan WJ, Micallef IN, Dispenzieri A, Gertz MA, *et al.*	A phase I/II trial of reduced intensity allogeneic hematopoietic cell transplant for hematologic malignancies using cladribine, thiotepa and rabbit antithymocyte globulin	Leukemia and Lymphoma	2013	54	8	1713-1718
329	Ma SY, Au WY, Chim CS, Lie AKW, Lam CCK, *et al.*	Fludarabine, mitoxantrone and dexamethasone in the treatment to indolent B- and T-cell lymphoid malignancies in Chinese patients	British Journal to Haematology	2004	124	6	754-761
330	Morschhauser F, Leonard JP, Fayad L, Coiffier B, Petillon MO, *et al.*	Humanized anti-CD20 antibody, veltuzumab, in refractory/recurrent non-Hodgkin's lymphoma: Phase I/II results	Journal of Clinical Oncology	2009	27	20	3346-3353
331	Nguyen DT, Amess JA, Doughty H, Hendry L and Diamond LW	IDEC-C2B8 anti-CD20 (Rituximab) immunotherapy in patients with low- grade non-Hodgkin's lymphoma and lymphoproliferative disorders: Evaluation to response on 48 patients	Eur J Haematol	1999	62	2	76-82
332	Noesslinger T, Keil F, Moestl M, Tinchon C, Koller E, *et al.*	Autologous stem cell transplantation with beeam (bendamustine, etoposide, cytarabine, melphalan) in aggressive nhl and hodgkin lymphoma	Hematological Oncology	2013	31		260
333	Noesslinger T, Moestl M, Koller E, Tinchon C, Mulabecirovic A, *et al.*	Autologous stem cell transplantation with beeam (bendamustine, etoposide, cytarabine, melphalan) in aggressive NHL and hodgkin's lymphoma	Bone Marrow Transplantation	2014	49		S167-S168
334	Ogura M, Hatake K, Ando K, Tobinai K, Tokushige K, *et al.*	Phase I study of anti-CD22 immunoconjugate inotuzumab ozogamicin plus rituximab in relapsed or refractory B-cell non-Hodgkin lymphoma	Cancer Science	2012	103	5	933-938
335	Oki Y, Buglio D, Fanale M, Fayad L, Copeland A, *et al.*	Phase i study of panobinostat plus everolimus in patients with relapsed or refractory lymphoma	Clinical Cancer Research	2013	19	24	6882-6890
336	Pregno P, Chiappella A, Zinzani PL, Orsucci L,	Activity and safety of Bortezomib and Rituximab in relapsed or refractory indolent non follicular and mantle-cell non hodgkin lymphoma: A phase II	Haematologica	2009	94		167

#	Author	Title	Journal	Year	Volume	Issue	Page
	Stefoni V, *et al.*	multicenter study by intergruppo italiano linfomi					
337	Pregno P, Chiappella A, Evangelista A, Balzarotti M, Fabbri A, *et al.*	Bortezomib (B) and Rituximab (R) combination is effective and safe in the treatment of relapsed or refractory indolent non follicular and mantle-cell non Hodgkin lymphoma: A phase II multicenter study by Intergruppo Italiano Linfomi (IIL)	Haematologica	2009	94		8
338	Rizzieri DA, Sand GJ, McGaughey D, Moore JO, DeCastro C, *et al.*	Low-dose weekly paclitaxel for recurrent or refractory aggressive non-Hodgkin lymphoma	Cancer	2004	100	11	2408-2414
339	Rummel MJ, Chow KU, Jager E, Leimer L, Hossfeld DK, *et al.*	Intermittent 2-hour-infusion of cladribine as first-line therapy or in first relapse of progressive advanced low-grade and mantle cell lymphomas	Leukemia and Lymphoma	1999	35	2-Jan	129-138
340	Savage DG, Rule SAJ, Tighe M, Garrett TJ, Oster MW, *et al.*	Gemcitabine for relapsed or resistant lymphoma	Annals of Oncology	2000	11	5	595-597
341	Stopeck AT, Unger JM, Rimsza LM, Bellamy WT, Iannone M, *et al.*	A phase II trial of single agent bevacizumab in patients with relapsed, aggressive non-Hodgkin lymphoma: Southwest oncology group study S0108	Leukemia and Lymphoma	2009	50	5	728-735
342	Tobinai K, Kobayashi Y, Narabayashi M, Ogura M, Kagami Y, *et al.*	Feasibility and pharmacokinetic study of a chimeric anti-CD20 monoclonal antibody (IDEC-C2B8, rituximab) in relapsed B-cell lymphoma. The IDEC-C2B8 Study Group	Ann Oncol	1998	9	5	527-534
343	William BM, Allen MS, Loberiza FR, Bociek RG, Bierman PJ, *et al.*	Phase I/II study to bortezomib-beam and autologous hematopoietic stem cell transplantation for relapsed indolent non-hodgkin lymphoma, transformed, or mantle cell Lymphoma	Biology to Blood and Marrow Transplantation	2014	20	4	536-542

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344	Witzig TE, White CA, Wiseman GA, Gordon LI, Emmanouilides C, *et al.*	Phase I/II trial of IDEC-Y2B8 radioimmunotherapy for treatment of relapsed or refractory CD20+ B-cell non-Hodgkin's lymphoma	Journal of Clinical Oncology	1999	17	12	3793-3803
345	Younes A, Flinn I, Berdeja J, Friedberg J, Alberti S, *et al.*	Phase 1b study combining ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-chop) in patients with CD20-positive bcell nonhodgkin lymphoma (NHL)	Hematological Oncology	2013	31		119-120
346	Younes A, Sarris A, Melnyk A, Romaguera J, McLaughlin P, *et al.*	Three-hour paclitaxel infusion in patients with refractory and relapsed non-Hodgkin's lymphoma	Journal of Clinical Oncology	1995	13	3	583-587
347	Zain JM, Foss FM, Diefenbach CS, Petrylak D, Narwal A, *et al.*	Preliminary results of an ongoing phase i trial of oral belinostat, a novel histone deacetylase inhibitor in patients with lymphoid malignancies	Blood	2011	118	21	
348	Harb WA, Lakhani N, Logsdon A, *et al.*	The BCL2 targeted deoxyribonucleic acid inhibitor (DNAi) PNT2258 is active in patients with relapsed or refractory non-Hodgkin’s lymphoma [Abstract 88]	55th American Society of Hematology Annual Meeting and Exhibition	2013			
349	Chong EAA, T.Aqui, N. A.Nasta, S. D.Svoboda, J.Walsh, K. M.Gordon, A. Schuster, S. J.	High response rate to combination lenalidomide-rituximab in FcγRIIIa-F carriers with indolent or mantle cell lymphomas previously refractory to rituximab [Abstract 250]	55th American Society of Hematology Annual Meeting and Exhibition	2013			
350	Fenske TSK, K. M.Zhang, C.Farnen, J. P.Onitilo, A. A.Blank, J. H.Ahuja, H.Wassenaar, T.Oamar, R.Mansky, P.Traynor, A.Mattison, R. J.Kahl, B. S.	Weekly temsirolimus and bortezomib for relapsed or refractory B-cell non-Hodgkin lymphoma: a Wisconsin Oncology Network phase II study [Abstract 3035]	55th American Society of Hematology Annual Meeting and Exhibition	2013			

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351	Holkova, B.,Kmieciak, M.,Perkins, E. B.,Bose, P.,Baz, R. C.,Roodman, G. D.,Stuart, R. K.,Ramakrishnan, V.,Wan, W.,Peer, C. J.,Dawson, J.,Kang, L.,Honeycutt, C.,Tombes, M. B.,Shrader, E.,Weir-Wiggins, C.,Wellons, M.,Sankala, H.,Hogan, K. T.,Colevas, A. D.,	Phase I trial of bortezomib (PS-341; NSC 681239) and "nonhybrid" (Bolus) infusion schedule of alvocidib (Flavopiridol; NSC 649890) in patients with recurrent or refractory indolent B-cell neoplasms	Clinical cancer research	2014	20	22 // () *National Cancer Institute *	5652-62
352	Matsumoto, K.,Takayama, N.,Aisa, Y.,Ueno, H.,Hagihara, M.,Watanabe, K.,Nakaya, A.,Chen, K.,Shimizu, T.,Tsukada, Y.,Yamada, Y.,Nakazato, T.,Ishida, A.,Miyakawa, Y.,Yokoyama, K.,Nakajima, H.,Masuda, Y.,Yano, T.,Okamoto, S.	A phase II study of bendamustine plus rituximab in Japanese patients with relapsed or refractory indolent B-cell non-Hodgkin lymphoma and mantle cell lymphoma previously treated with rituximab: BRB study	Int J Hematol	2015			
353	Rule, A., Furtado, M., Eve, H., Johnson, R. Kruger, A., *et al.*	The addition of bortezomib to standard dose chop chemotherapy significantly improves survival in relapsed mantle cell lymphoma	EHA 2012	2012			Abstract No. 0247

Appendix 5: Quality Assessment of the relevant RCTs

The quality assessment of the RAY (MCL3001) RCT is presented in Table 109.

Table 109: Quality assessment of RAY (MCL3001)

RAY(MCL3001)	Response	Rationale
Was randomisation carried out appropriately?	Yes	Patients were randomly assigned to ibrutinib or TEM based on a computer-generated randomisation schedule. Randomisation was balanced by using randomly permuted blocks.
Was the concealment of treatment allocation adequate?	No	Patients and investigators were unmasked to treatment assignment. Ibrutinib is an orally administered therapy, whilst TEM is administered intravenously.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Baseline characteristics such as age and gender where equally balanced between the study arms. Disease characteristics, such as stage of MCL at study entry or previous LOTs, were also similar between arms.
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	Patients and investigators were unmasked to treatment assignment. Endpoints (including the primary endpoint) were, however, assessed by an independent review committee that was masked to study treatment and by the investigator.
Were there any unexpected imbalances in drop-outs between groups?	No	124 patients (87.9%) on TEM and 74 patients (53.2%) on ibrutinib discontinued treatment. There are a notably higher proportion of patients on TEM that discontinued treatment due to AEs (n = 36, 25.5%) and treatment refusal (n = 16, 12.9%) compared to ibrutinib (n = 9, 12.2%, for discontinuation due to AEs and n = 4, 5.4%, due to refusal of treatment). However, these differences are not unexpected given the differing side-effect profiles of ibrutinib and TEM.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All measured outcomes are reported in the main trial publication or CSR.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Intention-to-treat population was clearly defined and appropriately labelled. No methods were defined for handling missing data, but dataset was complete (no patients lost to follow-up).

Appendix 6: Quality Assessment of the relevant non-RCTs

Quality assessments of the PCYC1104 and SPARK (MCL2001) non-RCTs are presented in Table 110. These quality assessments were performed based on the Downs and Black checklist for the methodological quality of randomised and non-randomised studies of health care interventions.

Table 110: Quality assessment of PCYC1104 and SPARK (MCL2001)

	PCYC1104	SPARK (MCL2001)
Is the hypothesis/aim/objective of the study clearly described?	Yes	Yes
Are the main outcomes to be measured clearly described in the introduction or methods section?	Yes	Yes
Are the characteristics of the patients included in the study clearly described?	Yes	Yes
Are the interventions of interest clearly described?	Yes	Yes
Are the main findings of the study clearly described?	Yes	Yes
Does the study provide estimates of the random variability in the data for the main outcomes?	Yes	Yes
Have all important adverse events that may be a consequence of the intervention been reported?	Yes	Yes
Have the characteristics of patients lost to follow-up been described?	No	No
If any of the results of the study were based on “data dredging”, was this made clear?	Yes	Yes
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	Yes
Were the statistical tests used to assess the main outcomes appropriate?	Yes	Yes
Was compliance with the intervention/s reliable?	Yes	Yes
Were the main outcome measures used accurate (valid and reliable)?	Yes	Yes
Were losses of patients to follow-up taken into account?	Yes	Yes

Appendix 7: Full list of subsequent anticancer therapy in RAY (MCL3001)

Table 111: Summary of antineoplastic therapy used in at least 2% of patients subsequent to ibrutinib or TEM

Analysis set: intent-to-treat	Ibrutinib (n = 139)	TEM (n =141)
Antineoplastic systemic therapy	44 (31·7)	82 (58·2)
Rituximab	21 (15·1)	36 (25·5)
Bendamustine	15 (10·8)	22 (15·6)
Cyclophosphamide	12 (8·6)	19 (13·5)
Cytarabine	10 (7·2)	16 (11·3)
Dexamethasone	9 (6·5)	17 (12·1)
Prednisolone	8 (5·8)	7 (5·0)
Etoposide	7 (5·0)	12 (8·5)
Vincristine	5 (3·6)	6 (4·3)
Bortezomib	4 (2·9)	13 (9·2)
Doxorubicin	4 (2·9)	3 (2·1)
TEM	4 (2·9)	0
Cisplatin	3 (2·2)	4 (2·8)
Lenalidomide	3 (2·2)	5 (3·5)
Fludarabine	2 (1·4)	5 (3·5)
Mitoxantrone	2 (1·4)	3 (2·1)
Prednisone	2 (1·4)	5 (3·5)
Investigational drug	1 (0·7)	5 (3·5)
Melphalan	1 (0·7)	3 (2·1)
Methylprednisolone	1 (0·7)	5 (3·5)
Chlorambucil	0	3 (2·1)
Ibrutinib	0	32 (22·7)
Ifosfamide	0	4 (2·8)
Stem cell transplant	1 (0·7)	4 (2·8)
TEM; Temsirolimus		

Appendix 8: Subgroup Analysis

Details of the covariate-adjusted analysis for PFS by IRC assessment can be found in Table 112 below.

Table 112: Covariate- adjusted analysis for PFS by IRC assessment

	HR	95% CI for HR	p-value
Treatment (ibrutinib *vs* TEM)	0.41	(0.30–0.57)	<0.0001
Sex (male vs female)	0.82	(0.57–1.18)	0.2812
Age group (≥65 vs <65 years)	1.08	(0.74–1.58)	0.6713
Race (Caucasian vs non-Caucasian)	1.05	(0.57–1.93)	0.8808
Baseline ECOG PS (1 vs 0)	1.56	(1.13–2.16)	0.0069
Region (Europe vs non-Europe)	0.84	(0.53–1.34)	0.4688
Baseline extranodal disease (yes vs no)	0.91	(0.62–1.33)	0.6225
MIPI score (intermediate vs low)*	1.36	(0.90–2.03)	0.1400
MIPI score (high vs low)*	2.51	(1.55–4.07)	0.0002
Prior lines of therapy (≥3 vs <3)*	1.58	(1.14–2.19)	0.0066
Stage of disease (IV vs I-III)	1.08	(0.61–1.91)	0.7902
Prior bortezomib (yes vs no)	1.03	(0.70–1.53)	0.8641
Tumour bulk (≥5 vs <5 cm)	0.96	(0.66–1.40)	0.8309
Tumour burden	1.00	(1.00–1.00)	0.8147
Histology (blastoid vs non-blastoid)	2.49	(1.60–3.86)	<0.0001
Refractory disease (yes vs no)	1.21	(0.86–1.71)	0.2680
Bone marrow involvement (yes vs no)	0.96	(0.67-1.40)	0.8509

HR: hazard ratio, CI: confidence interval, ECOG: Eastern Cooperative Oncology Group, PS: performance status, MIPI: Modified International Prognostic Index.
*From interactive web response system (IWRS) assignment.

Appendix 9: Additional searches for estimates of the efficacy of comparators reflective of current UK clinical practice

As described in Section 4.10, no data to inform the effectiveness of R-chemo in R/R MCL were identified by the clinical SLR. Therefore, additional searching was conducted in order to exhaust potential sources of relevant data. This included revisiting studies identified by the clinical SLR but not considered relevant to the decision problem, reviewing full-texts excluded from the clinical SLR and reviewing full texts of articles included and excluded from the SLR performed to support the findings on first line MCL in the draft NICE Clinical Guideline on NHL, as described in Section 4.10.

The following criteria were used to identify additional eligible studies:

- Patients receiving treatment for R/R MCL – first line MCL studies were not considered relevant as outcomes at first line are known to be vastly different to those of patients with R/R MCL, as shown within the available data from the HMRN audit (median OS = 2.1 years at first line compared to 8.4 months at second line)

- Patients receiving chemotherapy in combination with rituximab. All chemotherapies were considered at this stage and not only the ones included in the final NICE scope.

- Reported KM curves for either PFS or OS. This was a minimum requirement for the modelling

No restriction on sample size was applied and no studies were excluded on the base of reporting a mixed population (e.g. different types if lymphoma, including a MCL subgroup).

This process identified four additional studies that possessed some characteristics that merited consideration for use as proxy for effectiveness of R-chemo. However, on further assessment, all four studies were considered less suitable than the Hess, 2009 study for the reasons highlighted in Table 113.

Table 113: Summary of studies reconsidered as estimates of efficacy of current UK clinical practice (rituximab-based chemotherapy)

Study reference	Interventions	Population	Potential use as an estimate of effectiveness of R-chemo	Median PFS	Quality of evidence	Relevance to decision problem	Reason for ultimate rejection as an alternative to Hess, 2009
MCL002 (SPRINT) (Trneny 2014[119], Trneny 2016)[182]*	Lenalidomide vs PC	R/R MCL	PC as a proxy for current UK clinical practice	PC: 5.2 months	Phase II RCT 84 patients in the PC arm KM data available	As per Hess, 2009, the therapies used as PC were single-agent chemotherapies not reflective of current UK clinical practice. Patients in the PC arm were slightly older than in RAY (MCL3001); the gender balance was similar between studies. The median number of prior therapies was 2 in both studies. MIPI values are non-comparable as the Trneny, 2016 study used the MIPI whereas RAY (MCL3001) reported sMIPI.	No ITC could be performed. PC composition was no more relevant than in Hess, 2009. High crossover from PC to lenalidomide (46%)
German Low-Grade Lymphoma Study Group (Forstpointner, 2004)[60]	FCMR vs FCM	R/R FCL and R/R MCL Patients with MCL represented a subgroup of the full study population	FCMR as a proxy for FCR	FCMR: 8 months	Randomised, open-label, multicentre phase III trial 24 patients with MCL in the FCMR arm No KM data available	Neither FCM or FCMR are relevant comparators – they would have to act as a proxy for FCR, which itself is not the most prominent therapy in current clinical practice (R-CHOP is more prominent). Mitoxantrone is a very toxic therapy and therefore likely to influence outcomes and reduce appropriateness as a proxy. A higher proportion of patients had received only one or two	Limited value of comparator as a proxy given the toxicity of mitoxantrone. Very small sample size. Limited comparability to ibrutinib data (healthier population). No KM curves

Study reference	Interventions	Population	Potential use as an estimate of effectiveness of R-chemo	Median PFS	Quality of evidence	Relevance to decision problem	Reason for ultimate rejection as an alternative to Hess, 2009
						prior LOTs than in the RAY (MCL3001) study, suggesting a healthier cohort. Age and gender split were similar in the for the MCL patients who received FCMR in the Forstpointner, 2004 study and those receiving ibrutinib in the RAY (MCL3001) study	available
Rummel, 2016[183]	BR vs FR	Patients with relapse, indolent, NHL and MCL. Patients with MCL represented a subgroup of the full study population	FR arm could potentially be used as a proxy for FCR, one of the comparators defined in the NICE scope	FR: 4.7 months	Phase III RCT 23 patients in the FR arm with MCL KM data available	FR is not a relevant comparator – it would act as a proxy for FCR, which itself is not the most prominent therapy in current clinical practice (R-CHOP is more prominent). Patient population not comparable: • Patients refractory to regimens that included rituximab, bendamustine or purine analogue drugs were excluded, unlike in the RAY (MCL3001) study in which an inclusion criteria was receipt of a prior rituximab-containing regimen • Patients had received a median of only 1 prior LOT and therefore represented a healthier cohort	Critical difference in inclusion criteria. Very small sample size. Limited comparability to ibrutinib data (healthier population)
Furtado, 2014[184]	Bortezomib +	MCL patients	CHOP arm could	CHOP:	Randomised	CHOP is not a relevant	Critical

Study reference	Interventions	Population	Potential use as an estimate of effectiveness of R-chemo	Median PFS	Quality of evidence	Relevance to decision problem	Reason for ultimate rejection as an alternative to Hess, 2009
	CHOP vs CHOP	at first relapse; median of 3 prior cycles of therapy	be used as a proxy for R-CHOP, or adjusted to account for an additional rituximab effect	8.1 months	two-arm parallel group phase II, multicentre, open-label study 23 patients in the CHOP arm KM data available	comparator – it would act as a proxy for R-CHOP. There was a considerably higher proportion of male patients in the CHOP arm of the Furtado, 2014 study than the ibrutinib arm of the RAY (MCL3001) study. The Furtado study comprised patients at first relapse who had received a median of 3 prior cycles of therapy before relapse. In contrast, patients in RAY (MCL3001) had received a median of 2 prior LOTs	difference in patients' prognosis. Very small sample size

BR: bendamustine and rituximab, FR: fludarabine and rituximab, FCM: fludarabine, cyclophosphamide and mitoxantrone, FCMR: fludarabine, cyclophosphamide and mitoxantrone and rituximab, CHOP: cyclophosphamide, doxorubicin, vincristine and prednisolone, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone, PC: physician's choice, TEM: temsirolimus, FCL: follicular cell lymphoma, MCL: mantle cell lymphoma, NHL: non-Hodgkin's lymphoma, LOT: line of therapy, KM: Kaplan-Meier, RCT: randomised controlled trial, MIPI: mantle cell lymphoma international prognostic index, sMIPI: simplified mantle cell lymphoma international prognostic index, FR: fludarabine, rituximab, FCR: fludarabine, cyclophosphamide, rituximab

*Trneny 2014 was identified as part of the clinical SLR. Trneny 2016 represents the full publication on the MCL002 (SPRINT) study and was published after the SLR was run and hence not captured by the SLR. The Trneny 2016 publication was captured by the additional searching described in Section 4.10 and Appendix 9.

Appendix 10: Meta-analysis: Baseline characteristics

Details of the patient demographics and baseline characteristics of RAY (MCL3001), PCYC1104 and SPARK (MCL2001) can be found in Table 114 below.

Table 114: Patient demographics and baseline characteristics of RAY (MCL3001), PCYC1104 and SPARK (MCL2001)

Demographics	SPARK (MCL2001)	RAY (MCL3001)	PCYC1104	Pooled
Analysis set: intent-to-treat	120	139	111	370
Age				
N	120	139	111	370
Mean (SD)	66.69 (9.98)	66.73 (8.68)	67.14 (8.56)	66.84(9.07)
Median	67.5	67	68	67.5
Range	(35, 85)	(39, 84)	(40, 84)	(35, 85)
>=65 years	75 (62.5%)	86 (61.87%)	70 (63.06%)	231 (62.43%)
>=70 years	56 (46.67%)	58 (41.73%)	46 (41.44%)	160 (43.24%)
Sex				
N	120	139	111	370
Male	104 (86.67%)	100 (71.94%)	85 (76.58%)	289 (78.11%)
Female	16 (13.33%)	39 (28.06%)	26 (23.42%)	81 (21.89%)
Race				
N	120	139	111	370
White	113 (94.17%)	115 (82.73%)	102 (91.89%)	330 (89.19%)
Asian	0	16 (11.51%)	1 (0.9%)	17 (4.59)
Other	0	3 (2.16%)	2 (1.8%)	5 (1.35%)
Black or African American	2 (1.67%)	0	5 (4.5%)	7 (1.89%)
Native Hawaiian or other pacific island	0	0	1 (0.9%)	1 (0.27%)
Unknown	1 (0.83%)	1 (0.72%)	0	2 (0.54%)
Not reported	4 (3.33%)	4 (2.88%)	0	8 (2.16%)
Ethnicity				
N	120	139	111	370
Hispanic or Latino	4 (3.33%)	7 (5.04%)	5 (4.5%)	16 (4.32%)
Not Hispanic or Latino	97 (80.83%)	127 (91.37%)	106 (95.5%)	330 (89.19%)
Not reported	6 (5%)	4 (2.88%)	0	10 (2.7%)
Unknown	13 (10.83%)	1 (0.72%)	0	14 (3.78%)
ECOG performance status				
N	120	139	111	370
0	42 (35%)	67 (48.20%)	51 (45.95%)	160 (43.24%)
1	67 (55.83%)	71 (51.08%)	48 (43.24%)	186 (50.27%)
2	11 (9.17%)	1 (0.72%)	11 (9.91%)	23 (6.22%)
3	0	0	1 (0.9%)	1 (0.27%)
Height (cm)				
N	120	138	102	360

Mean (SD)	173.61 (8.35)	168.94 (9.48)	172.67 (10.02)	171.56 (9.49)
Median	173	168.5	175.15	172
Range	(145, 193)	(142, 204)	(149.2, 193)	(142, 204)
Weight (kg)				
N	118	139	108	365
Mean (SD)	85.40 (17.74)	75.85 (14.35)	80.83 (19.75)	80.41 (17.61)
Median	83.5	75	78.15	78
Range	(45.5, 145)	(47, 130)	(40.63, 146.2)	(40.63, 146.2)
Baseline characteristics	**SPARK (MCL2001)**	**RAY (MCL3001)**	**PCYC1104**	**Pooled**
Analysis set: intent-to-treat	120	139	111	370
Simplified MCL international prognostic index				
N	120	139	111	368
Low risk (1-3)	28 (23.73%)	44 (31.65%)	15 (13.51%)	87 (23.64%)
Intermediate risk (4-5)	57 (48.31%)	65 (46.76%)	42 (37.84%)	164 (44.57%)
High risk (6-11)	33 (27.97%)	30 (21.58%)	54 (48.65%)	117 (31.79%)
Prior lines of therapy				
N	120	139	111	370
1	20 (16.67%)	57 (41.01%)	22 (19.82%)	99 (26.76%)
2	43 (35.83%)	38 (27.34%)	28 (25.23%)	109 (29.46%)
3	29 (24.17%)	28 (20.14%)	24 (21.62%)	81 (21.89%)
4	17 (14.17%)	8 (5.76%)	15 (13.51%)	40 (10.81%)
5	10 (8.33%)	5 (3.6%)	22 (19.82%)	37 (10%)
7	0	2 (1.44%)	0	2 (0.54%)
8	1 (0.83%)	0	0	1 (0.27%)
9	0	1 (0.72%)	0	1 (0.27%)
>=3	57 (47.5%)	44 (31.65%)	61 (54.95%)	162 (43.78%)
Median	2	2	3	2
Blastoid history				
N	120	139	111	370
Non-blastoid	109 (90.83%)	123 (88.49%)	94 (84.68%)	326 (88.11%)
Blastoid	11 (9.17%)	16 (11.51%)	17 (15.32%)	44 (11.89%)
Extranodal disease				
N	120	139	111	370
No	48 (40%)	56 (40.29%)	51 (45.95%)	155 (41.89%)
Yes	72 (60%)	83 (59.71%)	60 (54.05%)	215 (58.11%)
Prior lenalidomide use				
N	120	139	111	370
No	97 (80.83%)	131 (94.24%)	84 (75.68%)	312 (84.32%)
Yes	23 (19.17%)	8 (5.76%)	27 (24.32%)	58 (15.68%)
Prior bortezomib use				
N	120	139	111	370
No	0	109 (78.42%)	63 (56.76%)	172 (46.49%)

Yes	120 (100%)	30 (21.58%)	48 (43.24%)	198 (53.51%)
Prior stem cell transplant				
N	120	139	111	370
No	80 (66.67%)	106 (76.26%)	99 (89.19%)	285 (77.03%)
Yes	40 (33.33%)	33 (23.74%)	12 (10.81%)	85 (22.97%)

ECOG: Eastern Cooperative Oncology Group, MCL: mantle cell lymphoma, SD: standard deviation
Source: Ibrutinib pooled analysis of three trials (data on file), March 2016[6]

Appendix 11: Supporting details for the ITC

A comparison of the RAY (MCL3001) and Hess, 2009 studies using the PICOS framework is provided in Table 115.

Table 115: Comparison of RAY (MCL3001) and Hess, 2009 using PICOS framework

PICOS criteria	Parameter	RAY (MCL3001) (17 June 2015 CSR)		Hess, 2009	
		Ibrutinib	TEM 175/75 mg	TEM 175/75 mg	PC
Population	**Median age (range)**	67 (39–84)	67 (37-88)	68 (44-87)	64.5 (39-88)
	≥65, n (%)	86 (61.9%)	87 (61.7%)	Not reported	Not reported
	Histological grade: blastoid	16 (11.5%)	17 (12.1%)	0 (0%)	4 (7%)
	Median # of prior therapies (range)	2 (1–9)	2 (1–9)	3 (Not reported)	4 (Not reported)
	≥3	44 (31.7%)	48 (34.0%)	19 (35%)	15 (28%)
	Bulky disease (≥5cm)	74 (53.6%)	75 (53.2%)	Not reported	Not reported
	Refractory disease	36 (25.9%)	47 (33.3%)	Not reported	Not reported
	Stage				
	I, or II	10 (7.2%)	7 (4.9%)	0 (0%)	3 (6%)
	III or IV	129 (92.8%)	134 (95%)	54 (100%)	51 (94%)
Interventions		Ibrutinib, 560 mg daily		TEM IV 175 mg per week for 3 weeks followed by weekly 75 mg until disease progression or unacceptable toxicity	

Comparators			TEM IV 175 mg on day 1, 8, 15 of first cycle followed by 75 mg day 1, 8, 15 of each subsequent 21-day cycle		Single-agent treatment as chosen by the investigator.[a] gemcitabine (42%), fludarabine IV (23%), fludarabine oral (4%), chlorambucil oral (6%), cladribine (6%), etoposide (6%), cyclophosphamide oral (4%), thalidomide (4%), vinblastine (4%), alemtuzumab (2%), lenalidomide (2%)
Outcomes	**ORR**	71.9%	40.4%	22%	2%
	Median PFS	14.6 months	6.3 months	4.8 months	1.9 months
	Median OS	Not reached	21.3 months	11.1 months (2007) 12.8 months (2008)	9.5 months (2007) 9.7 months (2008)
Study design	**Sample size**	139	141	54[b]	54
	Trial design	RCT, phase III Median follow-up 20.2 month		RCT, phase III	

	Eligibility criteria	**Inclusion criteria** • MCL diagnosis confirmed by morphology and expression of either cyclin D1 in association with one B-cell marker • Received at least one prior rituximab-containing chemotherapy regimen. Separate lines of therapy are defined as single or combination therapies that are either separated by disease progression or by a > 6 month treatment-free interval. • ECOG score 0 or 1 • Absolute neutrophil count ≥1,000 cells per microlitre • Platelet count ≥75,000 or 50,000 cell per microlitre **Exclusion criteria** • Patients with CNS lymphoma, HIV or hepatitis B or C virus infections, and anticancer treatment within 3 weeks or major surgery with 4 weeks • Patients requiring warfarin or strong CYP3A4/5 inhibitors	**Inclusion criteria** • MCL had to be confirmed at the investigational site by histology, immunophenotype, and cyclin D1 analysis. • Active MCL requiring therapy after two to seven previous therapies • Prior therapy must have an alkylating agent, an anthracycline, and rituximab • Karnofsky score≥60 • Higher, measureable disease and adequate bone marrow and organ functions • Life expectancy of at least 3 months • Absolute neutrophil count ≥1,000 cells per microlitre • Platelet count ≥75,000 or 50,000 cell per microlitre **Exclusion criteria** • Active CNS lymphoma, HIV or hepatitis B or C virus infections, and anticancer treatment or major surgery within 3 weeks

a. The single agents were protocol specified or prospectively approved additions, which were selected after an extensive review of the literature and discussions with a large number of investigators.

b. There are 14% patients in the trial coded as unconfirmed MCL due to insufficient samples were insufficient or of poor quality for independent assessment.

TEM: temsirolimus, PC: Physicians' choice, IV: intravenous, RCT: randomised controlled trial, MCL: mantle cell lymphoma, ECOG: Eastern Cooperative Oncology Group, CNS: central nervous system, HIV: human immunodeficiency virus.

Appendix 12: Search strategy for cost-effectiveness studies

Embase (2014)

Table 116: Search terms for Embase (2014)

#	Embase RR-MCL Economic Evaluation Search String	Hits
Population		
#1	'mantle cell lymphoma'/exp	7,208
#2	'mantle cell lymphoma':ab,ti OR 'mantle-cell lymphoma':ab,ti	5,161
#3	'mantle cell':ab,ti OR 'mantle-cell':ab,ti AND (lymphoma:ab,ti OR lymphomas:ab,ti)	5,831
#4	#1 OR #2 OR #3	8,048
Intervention/comparators		
#5	'salvage chemotherapy':ab,ti OR 'salvage treatment':ab,ti OR 'salvage therapy'/exp OR 'resistant chemotherapy':ab,ti OR 'chemotherapy resistant':ab,ti OR 'treatment resistant':ab,ti	33,439
#6	'second line' OR '2nd line' OR (second:ab,ti AND line:ab,ti)	50,271
#7	'third line' OR 'third-line' OR '3rd line' OR (third:ab,ti AND line:ab,ti)	17,103
#8	refractory:ab,ti OR refractor*:ab,ti OR resistant:ab,ti OR relaps*:ab,ti OR recurrent:ab,ti OR 'previously treated' OR 'drug resistance':ab,ti	976,548
#9	failed:ab,ti OR failure:ab,ti AND (treatment:ab,ti OR therapy:ab,ti OR prior:ab,ti OR previous:ab,ti)	419,610
#10	chemotherapy:ab,ti OR treatmen*:ab,ti OR regime*:ab,ti OR medication*:ab,ti OR therap*:ab,ti AND (refractory:ab,ti OR recurrent:ab,ti OR resistant:ab,ti OR rescue:ab,ti OR salvage:ab,ti OR failed:ab,ti OR failure:ab,ti)	800,341
#11	#5 OR #6 OR #7 OR #8 OR #9 OR #10	1,452,515
Outcomes		
#12	budget*:ab,ti	26,184
#13	'cost'/exp OR cost*:ab,ti OR 'fee'/exp	682,552
#14	utility:ab,ti OR utilities:ab,ti	171,383
#15	'resource utilization':ab,ti OR 'resource utilisation':ab,ti	9,385
#16	'quality adjusted life year':ab,ti OR 'quality adjusted life years':ab,ti OR qaly:ab,ti	12,121
#17	'health resource':ab,ti OR 'health state' OR 'health care':ab,ti OR 'medical resource':ab,ti AND (use:ab,ti OR utilisation:ab,ti OR utilization:ab,ti OR utility:ab,ti OR value:ab,ti OR service:ab,ti OR consumption:ab,ti)	109,652
#18	qald*:ab,ti OR qale*:ab,ti OR qtime*:ab,ti	206
#19	'time trade off':ab,ti OR 'time tradeoff':ab,ti OR tto:ab,ti	1,728
#20	'hospital costs'/exp OR 'drug cost'/exp OR 'hospitalization cost'/exp OR 'health care cost'/exp OR 'cost of illness'/exp OR 'reimbursement'/exp	256,516
#21	'cost benefit analysis'/exp OR 'cost effectiveness analysis'/exp	165,980
#22	'biomedical technology assessment'/exp	11,479
#23	'cost utility analysis'/exp OR 'cost minimization analysis'/exp OR 'economic evaluation'/exp	225,777
#24	'health economics'/exp OR 'health economics' OR 'economic aspect'/exp OR economic*:ab,ti OR 'pharmacoeconomics'/exp OR pharmacoeconomic*:ab,ti	1,308,974
#25	expenditure*:ab,ti OR productivity:ab,ti OR burden*:ab,ti	251,160

Combined		
#26	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	1,941,678
#27	#4 AND #11 AND #26	223

Embase In Process(2014)

Table 117: Search terms for Embase In Process (2014)

#	Embase RR-MCL Economic Evaluation Search String	Hits
Population		
#1	'mantle cell lymphoma' OR 'mantle-cell lymphoma'	7,774
#2	'mantle cell' OR 'mantle-cell' AND (lymphoma OR lymphomas)	8,093
#3	#1 OR #2	8,093
Intervention/comparators		
#4	'salvage chemotherapy' OR 'salvage treatment' OR 'salvage therapy' OR 'resistant chemotherapy' OR 'chemotherapy resistant' OR 'treatment resistant'	29,117
#5	'second line' OR '2nd line' OR (second AND line)	68,965
#6	'third line' OR 'third-line' OR '3rd line' OR (third AND line)	24,823
#7	refractory OR refractor* OR resistant OR relaps* OR recurrent OR 'previously treated' OR 'drug resistance'	1,154,154
#8	failed OR failure AND (treatment OR therapy OR prior OR previous)	779,078
#9	chemotherapy OR treatmen* OR regime* OR medication* OR therap* AND (refractory OR recurrent OR resistant OR rescue OR salvage OR failed OR failure)	1,300,168
#10	#4 OR #5 OR #6 OR #7 OR #8 OR #9	1,956,489
Outcomes		
#11	budget*	38,237
#12	cost* OR fee	845,925
#13	utility OR utilities	175,299
#14	'resource utilization' OR 'resource utilisation'	10,226
#15	'quality adjusted life year' OR 'quality adjusted life years' OR qaly	17,960
#16	'health resource' OR 'health state' OR 'health care' OR 'medical resource' AND (use OR utilisation OR utilization OR utility OR value OR service OR consumption)	507,585
#17	qald* OR qale* OR qtime*	209
#18	'time trade off' OR 'time tradeoff' OR tto	1,773
#19	'hospital costs' OR 'drug cost' OR 'hospitalization cost' OR 'health care cost' OR 'cost of illness' OR 'reimbursement'	243,237
#20	'cost benefit analysis' OR 'cost effectiveness analysis'	167,512
#21	'biomedical technology assessment'	11,495
#22	'cost utility analysis' OR 'cost minimization analysis' OR 'economic evaluation'	22,383
#23	'health economics' OR 'economic aspect' OR economic* OR 'pharmacoeconomics' OR pharmacoeconomic*	627,372
#24	expenditure* OR productivity OR burden*	286,398
Combined		
#25	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	1,960,027

#26	#3 AND #10 AND #25	245
#27	#26 AND [in process]/lim	0

PubMed(2014)

Table 118: Search terms for PubMed (2014)

#	PubMed RR-MCL Economic Evaluation Search String	Hits
Population		
#1	("mantle cell"[tiab] OR "mantle-cell"[tiab]) AND (lymphoma[tiab])	3,454
#2	“mantle cell lymphoma” OR “mantle-cell lymphoma”	3,480
#3	"Lymphoma, Mantle-Cell"[Mesh]	2,054
#4	#1 OR #2 OR #3	3,736
Intervention/comparators		
#5	"salvage chemotherapy" OR "salvage treatment" OR "salvage therapy" OR “salvage therapy”[Mesh]	14,562
#6	"resistant chemotherapy" OR "chemotherapy resistant" OR "treatment resistant"	6,203
#7	“second line" OR “second-line” OR "2nd line" OR "2'nd line" OR (second[tiab] AND line[tiab])	34,479
#8	“third line” OR “third-line” OR “3rd line” OR "3'rd line" OR (third[tiab] AND line[TIAB])	11,690
#9	refractory[tiab] OR refractor*[tiab] OR resistant[tiab] OR relaps*[tiab] OR recurrent[tiab] OR “drug resistance, neoplasm”[MeSH] OR "previously treated"[tiab]	742,660
#10	(failed[tiab] OR failure[tiab]) AND (treatment[tiab] OR therapy[tiab] OR prior[tiab] OR previous[tiab])	295,112
#11	(chemotherapy[tiab] OR treatmen*[tiab] OR regime*[tiab] OR medication*[tiab] OR therap*[tiab]) AND (refractory[tiab] OR recurrent[tiab] OR resistant[tiab] OR rescue[tiab] OR salvage[tiab] OR failed[tiab] OR failure[tiab])	568,608
#12	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	1,081,636
Outcomes		
#13	"Health resources"[MesH] OR "drug costs"[MesH] OR "Hospital costs"[MesH] OR "direct service costs"[MesH] OR "health care costs"[MesH] OR "cost-benefit analysis"[MesH] OR "cost savings"[MesH] OR "costs and cost analysis"[MesH] OR "economics"[MesH] OR "cost of illness"[MesH] OR "Cost Sharing"[MesH]	514,118
#14	(“health resource”[tiab] OR "health state" OR “health care”[tiab] OR “medical resource”[tiab]) AND (use[tiab] OR utilisation[tiab] OR utilization[tiab] OR "utility"[tiab] OR value[tiab] OR service[tiab] OR consumption[tiab])	47,845
#15	cost*[tiab] OR costs[tiab] OR budget*[tiab] OR expenditure*[tiab] OR economic*[tiab] OR pharmacoeconomic*[tiab] OR productivity[tiab] OR burden*[tiab] OR “health economics”	692,317
#16	utility[tiab] OR utilities[tiab]	132,352
#17	“resource utilization”[tiab] OR “resource utilisation”[tiab]	5,716
#18	"quality adjusted life year"[tiab] OR "quality adjusted life years"[tiab] OR QALY[tiab]	7,757
#19	qald*[tiab] OR qale*[tiab] OR qtime*[tiab]	126
#20	"time trade off"[tiab] OR "time tradeoff"[tiab] OR tto[tiab]	1,298
#21	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	1,191,011
Study design/limits		
#22	Editorial[ptyp] OR "Published Erratum"[ptyp] OR Letter[ptyp] OR Comment[ptyp]	1,406,214
PICOS combined		

#23	(#4 AND #12 AND #21) NOT #22	40

PubMed In-Process(2014)

Table 119: Search terms for PubMed In-Process (2014)

#	PubMed RR-MCL Economic Evaluation Search String	Hits
Population		
#1	("mantle cell" OR "mantle-cell") AND (lymphoma)	3,785
#2	“mantle cell lymphoma” OR “mantle-cell lymphoma”	3,480
#3	"Lymphoma Mantle-Cell"	2,060
#4	#1 OR #2 OR #3	3,785
Intervention/comparators		
#5	"salvage chemotherapy" OR "salvage treatment" OR "salvage therapy"	14,562
#6	"resistant chemotherapy" OR "chemotherapy resistant" OR "treatment resistant"	6,203
#7	“second line" OR “second-line” OR "2nd line" OR "2'nd line" OR (second AND line)	53,313
#8	“third line” OR “third-line” OR “3rd line” OR "3'rd line" OR (third AND line)	19,218
#9	refractory OR refractor* OR resistant OR relaps* OR recurrent OR “drug resistance neoplasm” OR "previously treated"	751,001
#10	(failed OR failure) AND (treatment OR therapy OR prior OR previous)	565,532
#11	(chemotherapy OR treatmen* OR regime* OR medication* OR therap*) AND (refractory OR recurrent OR resistant OR rescue OR salvage OR failed OR failure)	714,418
#12	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	1,355,108
Outcomes		
#13	"Health resources" OR "drug costs" OR "Hospital costs" OR "direct service costs" OR "health care costs" OR "cost-benefit analysis" OR "cost savings" OR "costs and cost analysis" OR "economics" OR "cost of illness" OR "Cost Sharing"	464,171
#14	(“health resource” OR "health state" OR “health care” OR “medical resource”) AND (use OR utilisation OR utilization OR utility OR value OR service OR consumption)	265,781
#15	(cost* OR costs OR budget* OR expenditure* OR economic* OR pharmacoeconomic* OR productivity OR burden* OR “health economics”)	1,278,151
#16	utility OR utilities	132,606
#17	“resource utilization” OR “resource utilisation”	6,427
#18	"quality adjusted life year" OR "quality adjusted life years" OR QALY	11,326
#19	qald* OR qale* OR qtime*	127
#20	"time trade off" OR "time tradeoff" OR tto	1,304
#21	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	1,519,620
Study design/limits		
#22	Editorial[ptyp] OR "Published Erratum"[ptyp] OR Letter[ptyp] OR Comment[ptyp]	1,406,214
#23	“2014/12/01”[PDat] : “2015/12/31”[PDat]	652,549
PICOS combined		
#24	(#4 AND #12 AND #21 AND #23) NOT #22	2

CENTRAL/Cochrane Search(2014)

Table 120: Search terms for CENTRAL/Cochrane (2014)

#	CENTRAL/Cochrane RR-MCL Economic Evaluation Search String	Hits
Population		
#1	("mantle cell":ti,ab,kw or "mantle-cell":ti,ab,kw) and lymphoma:ti,ab,kw	172
#2	“mantle cell lymphoma” or "mantle-cell lymphoma"	163
#3	MeSH descriptor: [Lymphoma, Mantle-Cell] explode all trees	48
#4	#1 or #2 or #3	182
Intervention/comparators		
#5	“salvage chemotherapy” or "salvage treatment" or "salvage therapy"	1,021
#6	“resistant chemotherapy” or "chemotherapy resistant" or "treatment resistant"	1,315
#7	“second line” or “second-line” or "2nd line" or "2'nd line" or (second:ti,ab,kw and line:ti,ab,kw)	3,576
#8	“third line” or "third-line" or "3rd line" or "3'rd line" or (third:ti,ab,kw and line:ti,ab,kw)	860
#9	(refractory:ti,ab,kw or refractor*:ti,ab,kw or resistant:ti,ab,kw or relaps*:ti,ab,kw or recurrent:ti,ab,kw or "previously treated":ti,ab,kw)	44,963
#10	MeSH descriptor: [Drug Resistance, Neoplasm] explode all trees	346
#11	(failed:ti,ab,kw or failure:ti,ab,kw) and (treatment:ti,ab,kw or therapy:ti,ab,kw or prior:ti,ab,kw or previous:ti,ab,kw)	39,023
#12	(chemotherapy:ti,ab,kw or treatmen*:ti,ab,kw or regime*:ti,ab,kw or medication*:ti,ab,kw or therap*:ti,ab,kw) and (refractory:ti,ab,kw or recurrent:ti,ab,kw or resistant:ti,ab,kw or rescue:ti,ab,kw or salvage:ti,ab,kw or failed:ti,ab,kw or failure:ti,ab,kw)	64,218
Combined		
#13	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12	88,104
#14	#4 and #13	88
#15	#4 and #13 - *results for “Trials”*	78
#16	#4 and #13 - *results for “Cochrane Reviews”*	7
#17	#4 and #13 - *results for “Other Reviews”*	1
#18	#4 and #13 - *results for “Economic Evaluations”*	0
#19	#4 and #13 - *results for “Technology Assessments”*	2

DARE/NHS EED/HTA(2014)

Table 121: Search terms for DARE/NHS EED/HTA (2014)

#	DARE/NHS EED / HTA RR-MCL Cost Search String	Hits
Population		
#1	MeSH DESCRIPTOR Lymphoma, Mantle-Cell EXPLODE ALL TREES	8
#2	((mantle cell lymphoma) OR (mantle-cell lymphoma))	10
#3	(((mantle cell):ti OR (mantle-cell):ti) AND (lymphoma:ti OR lymphomas:ti))	7
#4	(#1 OR #2 OR #3)	12
Outcomes / Study design		
#5	(budget*:ti)	83
#6	MeSH DESCRIPTOR Cost Allocation EXPLODE ALL TREES	14
#7	MeSH DESCRIPTOR Cost of Illness EXPLODE ALL TREES	634

#8	MeSH DESCRIPTOR Cost Savings EXPLODE ALL TREES	653
#9	MeSH DESCRIPTOR Cost-Benefit Analysis EXPLODE ALL TREES	13,058
#10	MeSH DESCRIPTOR Costs and Cost Analysis EXPLODE ALL TREES	17,043
#11	MeSH DESCRIPTOR Direct Service Costs EXPLODE ALL TREES	126
#12	MeSH DESCRIPTOR Drug Costs EXPLODE ALL TREES	1,121
#13	MeSH DESCRIPTOR Economics EXPLODE ALL TREES	17,502
#14	MeSH DESCRIPTOR Health Care Costs EXPLODE ALL TREES	4,565
#15	MeSH DESCRIPTOR Hospital Costs EXPLODE ALL TREES	980
#16	MeSH DESCRIPTOR Economics, Hospital EXPLODE ALL TREES	1,166
#17	MeSH DESCRIPTOR Economics, Medical EXPLODE ALL TREES	45
#18	MeSH DESCRIPTOR Economics, Nursing EXPLODE ALL TREES	9
#19	MeSH DESCRIPTOR Economics, Pharmaceutical EXPLODE ALL TREES	189
#20	MeSH DESCRIPTOR Inflation, Economic EXPLODE ALL TREES	2
#21	MeSH DESCRIPTOR Models, Economic EXPLODE ALL TREES	1,770
#22	MeSH DESCRIPTOR Value of Life EXPLODE ALL TREES	117
#23	MeSH DESCRIPTOR Fee Schedules EXPLODE ALL TREES	13
#24	MeSH DESCRIPTOR Fee-for-Service Plans EXPLODE ALL TREES	70
#25	MeSH DESCRIPTOR Health Expenditures EXPLODE ALL TREES	185
#26	MeSH DESCRIPTOR Budgets EXPLODE ALL TREES	47
#27	MeSH DESCRIPTOR Quality-Adjusted Life Years EXPLODE ALL TREES	3,370
#28	(utility:ti OR utilities:ti)	832
#29	((resource utilization):ti OR (resource utilisation):ti)	71
#30	((quality adjusted life year):ti OR (quality adjusted life years):ti OR (QALY):ti)	29
#31	(((health resource):ti OR (health state) OR (health care):ti OR (medical resource):ti) AND (use:ti OR utilisation:ti OR utilization:ti OR utility:ti OR value:ti OR service:ti OR consumption:ti))	167
#32	(qald*:ti OR qale*:ti OR qtime*:ti)	0
#33	((time trade off):ti OR (time tradeoff):ti OR tto:ti)	1
#34	((health economics) OR economic*:ti OR pharmacoeconomic*:ti)	3,862
#35	(expenditure*:ti OR productivity:ti OR burden*:ti)	138
#36	((cost allocation) OR (cost of illness) OR (cost savings) OR (cost-benefit analysis) OR (cost and cost analysis) OR (direct service cost) OR (drug cost) OR economics OR (health care costs) OR (hospital costs) OR (economics) OR (economics and hospital) OR (economics AND medical) OR (economics AND nursing) OR (economics AND pharmaceutical) OR (economics AND inflation) OR (economics AND models) OR (value of life) OR (fee schedules) OR (fee-for-service plans) OR (health expenditures) OR budget OR (quality-adjusted life years) OR cost)	23,380
Combined		
#37	(#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36)	23,941
#38	(#4 AND #37)	1

EconLit (2014)

Table 122: Search terms for EconLit (2014)

#	EconLit RR-MCL Cost Search String	Search Options	Hits
#1	“mantle-cell” OR “mantle cell”	Expanders - Also search within the full text of the articles Search modes - Boolean/Phrase	0

Embase (2015)

Table 123: Search terms for Embase (2015)

Search Number	Embase RR-MCL Economic Evaluation Search String	Yield
Patient population		
1.	‘mantle cell lymphoma’/exp	6,592
2.	(‘mantle cell lymphoma’:ab,ti) OR (‘mantle-cell lymphoma’:ab,ti)	4,277
3.	(‘mantle cell’:ab,ti OR ‘mantle-cell’:ab,ti) AND (lymphoma:ab,ti OR lymphomas:ab,ti)	4,867
4.	#1 OR #2 OR #3	6,852
Intervention or comparators		
5.	'salvage chemotherapy':ab,ti OR 'salvage treatment':ab,ti OR 'salvage therapy'/exp OR 'resistant chemotherapy':ab,ti OR 'chemotherapy resistant':ab,ti OR 'treatment resistant':ab,ti	30,847
6.	'second line' OR '2nd line' OR ('second':ab,ti AND 'line':ab,ti)	43,756
7.	'third line' OR 'third-line' OR '3rd line' OR ('third':ab,ti AND 'line':ab,ti)	14,888
8.	refractory:ab,ti OR refractor*:ab,ti OR resistant:ab,ti OR relaps*:ab,ti OR recurrent:ab,ti OR 'previously treated' OR 'drug resistance':ab,ti OR 'previously treated':ab,ti	880,324
9.	failed:ab,ti OR failure:ab,ti AND (treatment:ab,ti OR therapy:ab,ti OR prior:ab,ti OR previous:ab,ti)	376,529
10.	chemotherapy:ab,ti OR treatmen*:ab,ti OR regime*:ab,ti OR medication*:ab,ti OR therap*:ab,ti AND (refractory:ab,ti OR recurrent:ab,ti OR resistant:ab,ti OR rescue:ab,ti OR salvage:ab,ti OR failed:ab,ti OR failure:ab,ti)	713,541
11.	#5 OR #6 OR #7 OR #8 OR #9 OR #10	1,307,615
Outcomes		
12.	budget*:ab,ti OR	23,979
13.	‘cost’/exp OR cost*:ab,ti OR ‘fee’/exp	691,292
14.	utility:ab,ti OR utilities:ab,ti	150,423
15.	‘resource utilization’:ab,ti OR ‘resource utilisation’:ab,ti	7,854
16.	‘quality adjusted life year’:ab,ti OR ‘quality adjusted life years’:ab,ti OR ‘QALY’:ab,ti	8,163
17.	(‘health resource’:ab,ti OR ‘health state’ OR ‘health care’:ab,ti OR ‘medical resource’:ab,ti) AND (use:ab,ti OR utilisation:ab,ti OR utilization:ab,ti OR ‘utility’:ab,ti OR value:ab,ti OR service:ab,ti OR consumption:ab,ti)	125,480
18.	qald*:ab,ti OR qale*:ab,ti OR qtime*:ab,ti	179
19.	‘time trade off’:ab,ti OR ‘time tradeoff’:ab,ti OR ‘tto’:ab,ti	1,529
20.	‘Hospital costs’/exp OR ‘drug cost’/exp OR ‘hospitalization cost’/exp OR ‘health care cost’/exp OR ‘cost of illness’/exp OR 'reimbursement’/exp	2,459,48
21.	‘cost benefit analysis’/exp OR ‘cost effectiveness analysis’/exp	154,805
22.	‘biomedical technology assessment’/exp	11,256
23.	‘cost utility analysis’/exp OR ‘cost minimization analysis’/exp OR ‘economic	210,854

	evaluation'/exp	
24.	'health economics'/exp OR 'health economics' OR 'economic aspect'/exp OR economic*:ab,ti OR 'pharmacoecomomics'/exp OR pharmacoeconomic*:ab,ti	1,210,854
25.	expenditure*:ab,ti OR productivity:ab,ti OR burden*:ab,ti	215,633
26.	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	1,794,635
PICO Combined		
27.	#4 AND #11 AND #26	189

Embase In Process (2015)

Table 124: Search terms for Embase In Process (2015)

Search Number	Embase RR-MCL Economic Evaluation Search String	Yield
Patient population		
1.	'mantle cell lymphoma'/exp	6,600
2.	('mantle cell lymphoma') OR ('mantle-cell lymphoma')	6,600
3.	('mantle cell' OR 'mantle-cell') AND (lymphoma OR lymphomas)	6,868
4.	#1 OR #2 OR #3	6,868
Intervention or comparators		
5.	'salvage chemotherapy' OR 'salvage treatment' OR 'salvage therapy'/exp OR 'resistant chemotherapy' OR 'chemotherapy resistant' OR 'treatment resistant'	31,338
6.	'second line' OR '2nd line' OR ('second' AND 'line')	59,834
7.	'third line' OR 'third-line' OR '3rd line' OR ('third' AND 'line')	21,593
8.	refractory OR refractor* OR resistant OR relaps* OR recurrent OR 'previously treated' OR 'drug resistance' OR 'previously treated'	1,111,007
9.	failed OR failure AND (treatment OR therapy OR prior OR previous)	801,350
10.	chemotherapy OR treatmen* OR regime* OR medication* OR therap* AND (refractory OR recurrent OR resistant OR rescue OR salvage OR failed OR failure)	1,179,413
11.	#5 OR #6 OR #7 OR #8 OR #9 OR #10	1,917,356
Outcomes		
12.	budget* OR	35,348
13.	'cost'/exp OR cost* OR 'fee'/exp	784,201
14.	utility OR utilities	154,359
15.	'resource utilization' OR 'resource utilisation'	8,563
16.	'quality adjusted life year' OR 'quality adjusted life years' OR 'QALY'	15,335
17.	('health resource' OR 'health state' OR 'health care' OR 'medical resource') AND (use OR utilisation OR utilization OR 'utility' OR value OR service OR consumption)	1,202,686
18.	qald* OR qale* OR qtime*	181
19.	'time trade off' OR 'time tradeoff' OR 'tto'	1,564
20.	'Hospital costs'/exp OR 'drug cost'/exp OR 'hospitalization cost'/exp OR 'health care cost'/exp OR 'cost of illness'/exp OR 'reimbursement'/exp	246,327
21.	'cost benefit analysis'/exp OR 'cost effectiveness analysis'/exp	155,017
22.	'biomedical technology assessment'/exp	11,257

23.	‘cost utility analysis’/exp OR ‘cost minimization analysis’/exp OR ‘economic evaluation’/exp	210,350
24.	‘health economics’/exp OR ‘health economics’ OR ‘economic aspect’/exp OR economic* OR ‘pharmacoecomomics’/exp OR pharmacoeconomic*	1,249,839
25.	expenditure* OR productivity OR burden*	248,726
26.	#4 AND #11 AND #26	439
Study design limits		
27.	[2013 -2014]/py	800,617
PICO Combined		
28.	#27 AND #28	51

PubMed (2015)

Table 125: Search terms for PubMed (2015)

Search Number	PubMed RR-MCL Economic Evaluation Search String	Yield
Patient population		
1.	("mantle cell"[tiab] OR "mantle-cell"[tiab]) AND (lymphoma[tiab])	14,532
2.	“mantle cell lymphoma” OR “mantle-cell lymphoma”	3,168
3.	"Lymphoma, Mantle-Cell"[Mesh]	3,190
4.	(#1 OR #2 OR #3)	1,949
Intervention or comparators		
5.	("salvage chemotherapy" OR "salvage treatment" OR "salvage therapy" OR “salvage therapy”[Mesh])	13,478
6.	"resistant chemotherapy" OR "chemotherapy resistant" OR "treatment resistant"	5,447
7.	(“second line" OR second-line OR "2nd line" OR "2'nd line" OR (second[tiab] AND line[tiab]))	31,702
8.	(“third line” OR “third-line” OR “3rd line” OR "3'rd line" OR ("third"[tiab] AND "line"[TIAB])	10,828
9.	(refractory[tiab] OR refractor*[tiab] OR resistant[tiab] OR relaps*[tiab] OR recurrent[tiab] OR “drug resistance, neoplasm”[MeSH] OR "previously treated"[tiab])	692,887
10.	((failed[tiab] OR failure[tiab]) AND (treatment[tiab] OR therapy[tiab] OR prior[tiab] OR previous[tiab]))	276,058
11.	(chemotherapy[tiab] OR treatmen*[tiab] OR regime*[tiab] OR medication*[tiab] OR therap*[tiab]) AND (refractory[tiab] OR recurrent[tiab] OR resistant[tiab] OR rescue[tiab] OR salvage[tiab] OR failed[tiab] OR failure[tiab])	527,559
12.	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)	1,008,985
Outcomes		
13.	"Health resources"[Mesh] OR "drug costs"[Mesh] OR "Hospital costs"[Mesh] OR "direct service costs"[Mesh] OR "health care costs"[Mesh] OR "cost-benefit analysis"[Mesh] OR "cost savings"[mesh] OR "costs and cost analysis"[Mesh] OR "economics"[Mesh] OR "cost of illness"[Mesh] OR "Cost Sharing"[Mesh]	503,249
14.	(“health resource” [tiab] OR "health state" OR “health care” [tiab] OR “medical resource” [tiab]) AND (use[tiab] OR utilisation[tiab] OR utilization[tiab] OR "utility"[tiab] OR value[tiab] OR service[tiab] OR consumption[tiab])	44,074

15.	(cost*[tiab] OR costs[tiab] OR budget*[tiab] OR expenditure*[tiab] OR economic*[tiab] OR pharmacoeconomic*[tiab] OR productivity[tiab] OR burden*[tiab] OR “health economics”)	634,318
16.	utility[tiab] OR utilities[tiab]	120,657
17.	“resource utilization”[tiab] OR “resource utilisation”[tiab]	5,153
18.	"quality adjusted life year"[tiab] OR "quality adjusted life years"[tiab] OR "QALY"[tiab]	6,822
19.	qald*[tiab] OR qale*[tiab] OR qtime*[tiab]	119
20.	"time trade off"[tiab] OR "time tradeoff"[tiab] OR "tto"[tiab]	1,197
21.	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	1,114,549
Study design limitation		
22.	(Editorial[ptyp] OR "Published Erratum"[ptyp] OR Letter[ptyp] OR Comment[ptyp])	1,317,442
PICO Combined		
23.	(#4 AND #12 AND #21) NOT #22	38

PubMed In-Process (2015)

Table 126: Search terms for PubMed In-Process (2015)

Search Number	PubMed RR-MCL Economic Evaluation Search String	Yield
Patient population		
1.	("mantle cell" OR "mantle-cell") AND (lymphoma)	3,439
2.	“mantle cell lymphoma” OR “mantle-cell lymphoma”	3,152
3.	"Lymphoma, Mantle-Cell"	1,860
4.	(#1 OR #2 OR #3)	3,439
Intervention or comparators		
5.	("salvage chemotherapy" OR "salvage treatment" OR "salvage therapy")	13,490
6.	"resistant chemotherapy" OR "chemotherapy resistant" OR "treatment resistant"	5,458
7.	(“second line" OR second-line OR "2nd line" OR "2'nd line" OR (second AND line))	48,966
8.	(“third line” OR “third-line” OR “3rd line” OR "3'rd line" OR ("third" AND "line")	17,689
9.	(refractory OR refractor* OR resistant OR relaps* OR recurrent OR “drug resistance, neoplasm” OR "previously treated")	700,789
10.	((failed OR failure) AND (treatment OR therapy OR prior OR previous))	533,103
11.	(chemotherapy OR treatmen* OR regime* OR medication* OR therap*) AND (refractory OR recurrent OR resistant OR rescue OR salvage OR failed OR failure)	665,552
12.	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)	1,268,609
Outcomes		
13.	"Health resources" OR "drug costs" OR "Hospital costs" OR "direct service costs" OR "health care costs" OR "cost-benefit analysis" OR "cost savings" OR "costs and cost analysis" OR "economics" OR "cost of illness" OR "Cost Sharing"	439,666
14.	(“health resource” OR "health state" OR “health care” OR “medical resource”) AND (use OR utilisation OR utilization OR "utility" OR value OR service OR consumption)	249,472
15.	(cost* OR costs OR budget* OR expenditure* OR economic* OR pharmacoeconomic* OR productivity OR burden* OR “health economics”)	1,173,235
16.	utility OR utilities	119,716

17.	“resource utilization” OR “resource utilisation”	5,631
18.	"quality adjusted life year" OR "quality adjusted life years" OR "QALY"	9,920
19.	qald* OR qale* OR qtime*	119
20.	"time trade off" OR "time tradeoff" OR "tto"	1,190
21.	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	1,395,558
Study design limitation		
22.	(Editorial[ptyp] OR "Published Erratum"[ptyp] OR Letter[ptyp] OR Comment[ptyp])	1,317,442
23.	"2013/01 /01"[PDat] : "2014/12/31"[PDat]	621,182
PICO Combined		
24.	(#4 AND #12 AND #21 AND #23) NOT #22	2

CENTRAL/Cochrane Search(2015)

Table 127: Search terms for CENTRAL/Cochrane (2015)

ID	CENTRAL/Cochrane Search	Yield
Patient population		
#1	("mantle cell":ti,ab,kw or "mantle-cell":ti,ab,kw) and lymphoma:ti,ab,kw	0
#2	mantle cell lymphoma or "mantle-cell lymphoma"	133
#3	Lymphoma, Mantle-Cell	0
#4	#1 or #2 or #3	133
Intervention or comparator		
#5	salvage chemotherapy or "salvage treatment" or "salvage therapy"	917
#6	resistant chemotherapy or "chemotherapy resistant" or "treatment resistant"	1,106
#7	second line or second-line or "2nd line" or "2'nd line" or (second:ti,ab,kw and line:ti,ab,kw)	3,217
#8	third line or "third-line" or "3rd line" or "3'rd line" or ("third":ti,ab,kw and "line":ti,ab,kw)	682
#9	(refractory:ti,ab,kw or refractor*:ti,ab,kw or resistant:ti,ab,kw or relaps*:ti,ab,kw or recurrent:ti,ab,kw or "Drug Resistance, Neoplasm" or "previously treated":ti,ab,kw)	39,259
#10	((failed:ti,ab,kw or failure:ti,ab,kw) and (treatment:ti,ab,kw or therapy:ti,ab,kw or prior:ti,ab,kw or previous:ti,ab,kw))	37,221
#11	(chemotherapy:ti,ab,kw or treatmen*:ti,ab,kw or regime*:ti,ab,kw or medication*:ti,ab,kw or therap*:ti,ab,kw) and (refractory:ti,ab,kw or recurrent:ti,ab,kw or resistant:ti,ab,kw or rescue:ti,ab,kw or salvage:ti,ab,kw or failed:ti,ab,kw or failure:ti,ab,kw)	58,572
#12	#5 or #6 or #7 or #8 or #9 or #10 or #11	79,704
PICO Combined		
#13	#4 and #12	58

DARE/ NHS EED / HTA(2015)

Table 128: Search terms for DARE/NHSEED/HTA (2015)

Search Number	DARE/NHS EED / HTA RR-MCL Cost Search String	Yield
Patient population		
1.	MeSH DESCRIPTOR lymphoma, mantle-cell EXPLODE ALL TREES	6
2.	(mantle cell lymphoma) OR (mantle-cell lymphoma)	10
3.	((mantle cell):ab,ti OR (mantle-cell):ab,ti) AND (lymphoma:ab,ti OR lymphomas:ab,ti)	6
4.	#1 OR #2 OR #3	10
Outcomes		
5.	budget*:ab,ti	23,979
6.	(MeSH DESCRIPTOR cost allocation EXPLODE ALL TREES) (MeSH DESCRIPTOR cost of illness EXPLODE ALL TREES) (MeSH DESCRIPTOR cost savings EXPLODE ALL TREES) (MeSH DESCRIPTOR cost-benefit analysis EXPLODE ALL TREES) (MeSH DESCRIPTOR cost and cost analysis EXPLODE ALL TREES) (MeSH DESCRIPTOR direct service cost EXPLODE ALL TREES) (MeSH DESCRIPTOR drug cost EXPLODE ALL TREES) (MeSH DESCRIPTOR economics EXPLODE ALL TREES) (MeSH DESCRIPTOR health care costs EXPLODE ALL TREES) (MeSH DESCRIPTOR hospital costs EXPLODE ALL TREES) (MeSH DESCRIPTOR economics EXPLODE ALL TREES) (MeSH DESCRIPTOR economics, hospital EXPLODE ALL TREES) (MeSH DESCRIPTOR economics, medical EXPLODE ALL TREES) (MeSH DESCRIPTOR economics, nursing EXPLODE ALL TREES) (MeSH DESCRIPTOR economics, pharmaceutical EXPLODE ALL TREES) (MeSH DESCRIPTOR economics, inflation EXPLODE ALL TREES) (MeSH DESCRIPTOR economics, models EXPLODE ALL TREES) (MeSH DESCRIPTOR value of life EXPLODE ALL TREES)	691,202
7.	(MeSH DESCRIPTOR fee schedules EXPLODE ALL TREES) OR (MeSH DESCRIPTOR fee-for-service plans EXPLODE ALL TREES)	12
8.	(MeSH DESCRIPTOR health expenditures EXPLODE ALL TREES)	174
9.	(MeSH DESCRIPTOR budget EXPLODE ALL TREES)	0
10.	(MeSH DESCRIPTOR quality-adjusted life years EXPLODE ALL TREES)	0
11.	utility:ab,ti OR utilities:ab,ti	731
12.	(resource utilization):ab,ti OR (resource utilisation):ab,ti	66
13.	(quality adjusted life year):ab,ti OR (quality adjusted life years):ab,ti OR (QUALY):ab,ti	18
14.	((health resource):ab,ti OR (health state) OR (health care):ab,ti OR (medical resource):ab,ti) AND (use:ab,ti OR utilisation:ab,ti OR utilization:ab,ti OR (utility):ab,ti OR value:ab,ti OR service:ab,ti OR consumption:ab,ti)	159
15.	qald*:ab,ti OR qale*:ab,ti OR qtime*:ab,ti	0
16.	(time trade off):ab,ti OR (time tradeoff):ab,ti OR (tto):ab,ti	1
17.	-(health economics) OR economic*:ab,ti OR pharmacoeconomic*:ab,ti	3,631

18.	expenditure*:ab,ti OR productivity:ab,ti OR burden*:ab,ti	126
19.	(cost allocation) OR (cost of illness) OR (cost savings) OR (cost-benefit analysis) OR (cost and cost analysis) OR (direct service cost) OR (drug cost) OR (economics) OR (health care costs) OR (hospital costs) OR (economics) OR (economics, hospital) OR (economics, medical) OR (economics, nursing) OR (economics, pharmaceutical) OR (economics, inflation) OR (economics, models) OR (value of life) OR (fee schedules) OR (fee-for-service plans) OR (health expenditures) OR (budget) OR (quality-adjusted life years) OR (cost)	22,663
20.	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	22,319
PICO Combined		
21.	#4 AND #20	0

EconLit (2015)

Table 129: Search terms for EconLit (2015)

Search Number	EconLit RR-MCL Cost Search String	Hits
Patient population		
1.	"mantle cell" OR "mantle-cell" AND lymphoma	0
2.	“mantle cell lymphoma” OR “mantle-cell lymphoma”	2
3.	“mantle-cell” OR “mantle cell”	0
Combined		
4.	(#1 OR #2 OR #3)	2

Appendix 13 : Summary of cost-effectiveness / cost studies found within the SLR

Table 130: Summary of included cost-effectiveness studies identified within the SLR

Citation	Year	Country(ies)	Summary of Model	Patient Population (Average Age in Years)	QALYs (Intervention, Comparators)	Costs (Currency; Intervention, Comparator)	ICER (per QALY gained)
Lachaine J *et al.* 2013[85]	2013	Canada	The objective of this study was to assess the economic impact of BR compared to FR in the treatment of relapsed iNHL and MCL in Canada Time horizon: Lifetime Time dependent Markov model Markov model composed of three health states: progression-free, PD and death. The length of each Markov cycle is one month Analyses were conducted from both a Canadian Ministry of Health and a societal perspective	NR	NR	NR	Compared with FR, BR is associated with ICERs of $38,821 per QALY and $45,809 per QALY, from a Ministry of Health and societal perspective respectively PSA indicated that, according to a WTP of $50,000, BR remains a cost-effective strategy in 100% and 90.2% of the simulations
Yoong K *et al.* 2009[84]	2009	Canada	The objective was to evaluate the cost-effectiveness of bortezomib versus FCM. Five-year time horizon Costs and benefits were discounted by 5% and a provincial Ministry of Health perspective was taken.	NR	The discounted QALYs were 1.47 (bortezomib) and 0.86 (FCM)	The total cost was Canadian (CAN) $27,886 (bortezomib) and $5,059 (FCM)	ICER (bortezomib vs FCM) was $37,253 per QALY

Table 131: Summary of included cost studies identified within the SLR

Citation	Geographic Location of Study	Date of Study	Applicability to UK Clinical Practice	Cost Valuations Used in Study	Costs for Use In Economic Analysis (Including Drug/Technology Costs, Administration Costs, Monitoring Costs, AE Costs, Costs of Other Medical Resource Use)
Feinberg *et al.* 2015[105]	US	2013	The resource use estimates are based on US based healthcare practise and hence would not be applicable for the UK clinical setting	NR	50% had ER visits, and 53% had hospitalizations throughout their treatment history. Significant increases in ER visits and hospitalizations were associated with the following factors (OR/p-value): chemotherapy duration (ER: 1.001/.046, hospitalization: 1.001/.01), supportive care (ER: 2.249/.014, hospitalization: 2.56/.004), number of MCL related adverse events (ER: 10.571/<.000, hospitalization: 39.282/<.000), and treatment following relapse (ER: 1.771/.005, hospitalization: 2.012/.001). Significant variables associated with a decrease in ER visits were male gender (0.576/.008) and having commercial insurance (0.548/.009). Age was associated with ER increase (1.024/.024). Patients treated in the Northeast region of the US were more likely to be hospitalized (1.897/.005).

Citation	Geographic Location of Study	Date of Study	Applicability to UK Clinical Practice	Cost Valuations Used in Study	Costs for Use In Economic Analysis (Including Drug/Technology Costs, Administration Costs, Monitoring Costs, AE Costs, Costs of Other Medical Resource Use)
Senbetta *et al.* 2014[104]	US		The costs are based on US based healthcare practise and hence would not be applicable for the UK clinical setting	Estimate the budget impact of adding ibrutinib to a US health plan formulary over a 1-year to a hypothetical 1-million member US health plan	The incremental budget impact of adopting ibrutinib for R/R MCL patients treated with ibrutinib for duration of 8.3 months and 12 months is estimated to be $0.010 and $0.027 per member per month, respectively

Citation	Geographic Location of Study	Date of Study	Applicability to UK Clinical Practice	Cost Valuations Used in Study	Costs for Use In Economic Analysis (Including Drug/Technology Costs, Administration Costs, Monitoring Costs, AE Costs, Costs of Other Medical Resource Use)
Wade *et al.* 2015[106]	US	2015	The costs are based on US based healthcare practise and hence would not be applicable for the UK clinical setting	NR	For patients receiving ASCT, the mean monthly cost between diagnosis and the start of 2L treatment was $12,565 with the highest mean monthly cost occurring between months 4 and 6 ($43,703). Pharmacy, inpatient, and outpatient costs accounted for approximately 26%, 47%, and 27%, respectively. For non-ASCT patients, the mean monthly cost following diagnosis to the next line treatment was $5,964, with the highest mean monthly cost occurring in the first 3 months ($24,363). For these patients, pharmacy, inpatient, and outpatient costs accounted for approximately 43%, 27%, and 30%, respectively. For all patients, monthly 1L costs stabilized at about 16 months to approximately $4,000. Upon initiating 2L and 3L therapy, monthly costs rose to $21,660 and $22,718 over the first three months, respectively, then followed by a pattern of reduction similar to what was seen in 1L treatment. For 2L and 3L therapy, pharmacy costs made up approximately 45% of all costs, with inpatient and outpatient costs each accounting for 25%>30% of remaining costs. Inpatient costs rose to 47% of total costs during months 4-6 after the initiation of 3L therapy.

Appendix 14 : Data informing subgroup analysis based on prior lines of therapy (1 line vs >1 line of therapy)

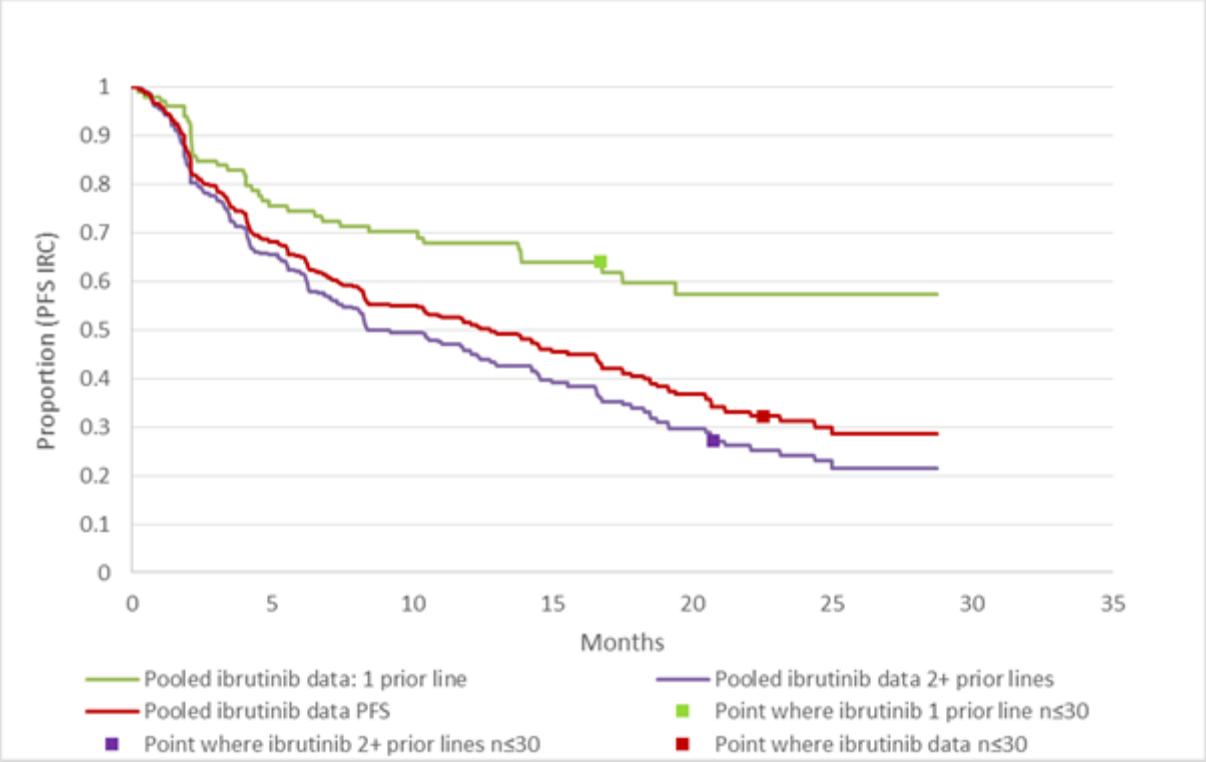
Subgroup analysis has been conducted that assesses the cost-effectiveness of ibrutinib compared to R-chemo in two different treatment populations, those that have only received one prior LOT or those that have received two or more prior LOTs. The information used to inform this analysis are presented within this section and the results are show in Section 5.8.5 for ibrutinib at list price and in Appendix 20 using the discounted price of ibrutinib.

In all cases the curve fit selected for use within the model base case was kept consistent with that selected for ITT analysis.

Progression free survival data

Figure 41 shows the KM curves of the pooled ibrutinib PFS data. The data show that there is a large difference in PFS between the two subgroups, with patients receiving 1 prior LOT performing substantially better than those that have received more than one prior LOT). This is consistent with the findings of the *post-hoc* analysis of RAY (MCL3001) presented in Section 4.8.2, clearly demonstrating that an increased benefit is observed when ibrutinib is used early in the treatment pathway for R/R MCL, which were also confirmed in the pooled dataset (Section 4.12.2).

Figure 41: Observed PFS (IRC-assessed) of ibrutinib patients from the pooled dataset split by number of prior LOTs



Investigator-assessed PFS was used for PCYC1104 as was the only available.

Parametric curves were fit to the data with a covariate adjustment for those patients having only received one prior LOT, the following curves were fitted:

- Exponential

- Weibull
- Log-normal
- Log-logistic

Figure 42 and Figure 43 show the parametric curve fit to the KM PFS data for the 1 prior LOT and 2+ prior LOTs respectively. Shape and scale parameters of the parametric curves are shown in

Table 132 with AIC and BIC statistics reported in Table 133.

Figure 42: PFS parametric curve fits to ibrutinib data: 1 prior LOT

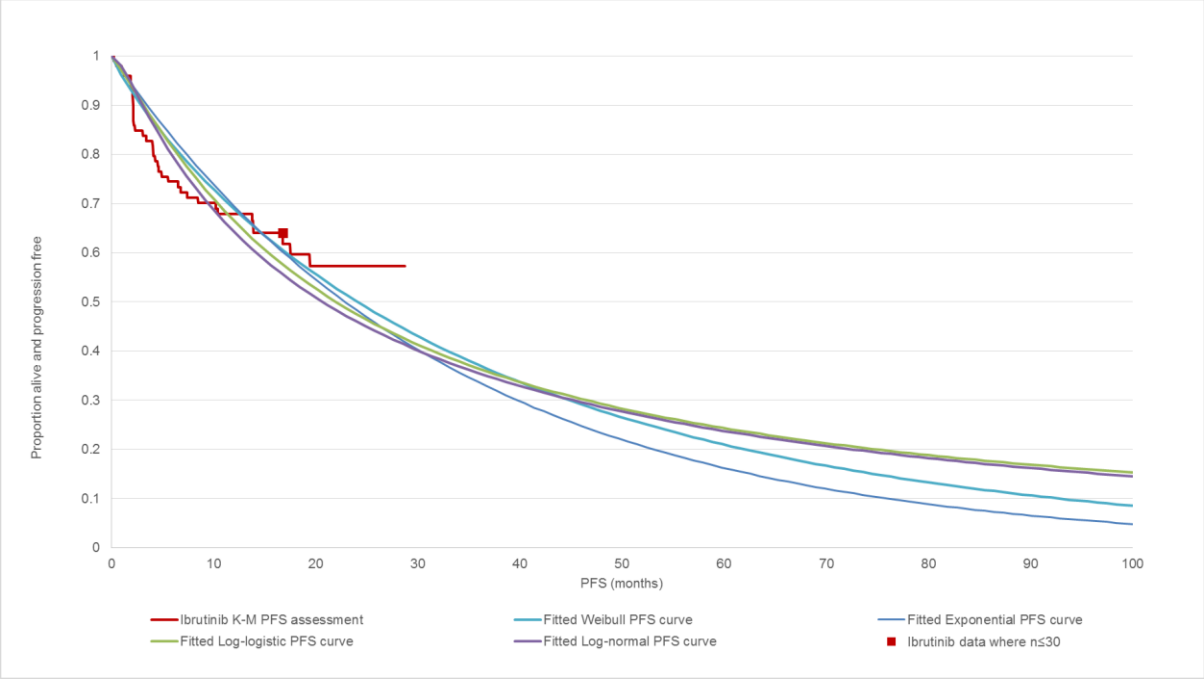


Figure 43: PFS parametric curve fits to ibrutinib data: 2+ prior LOTs

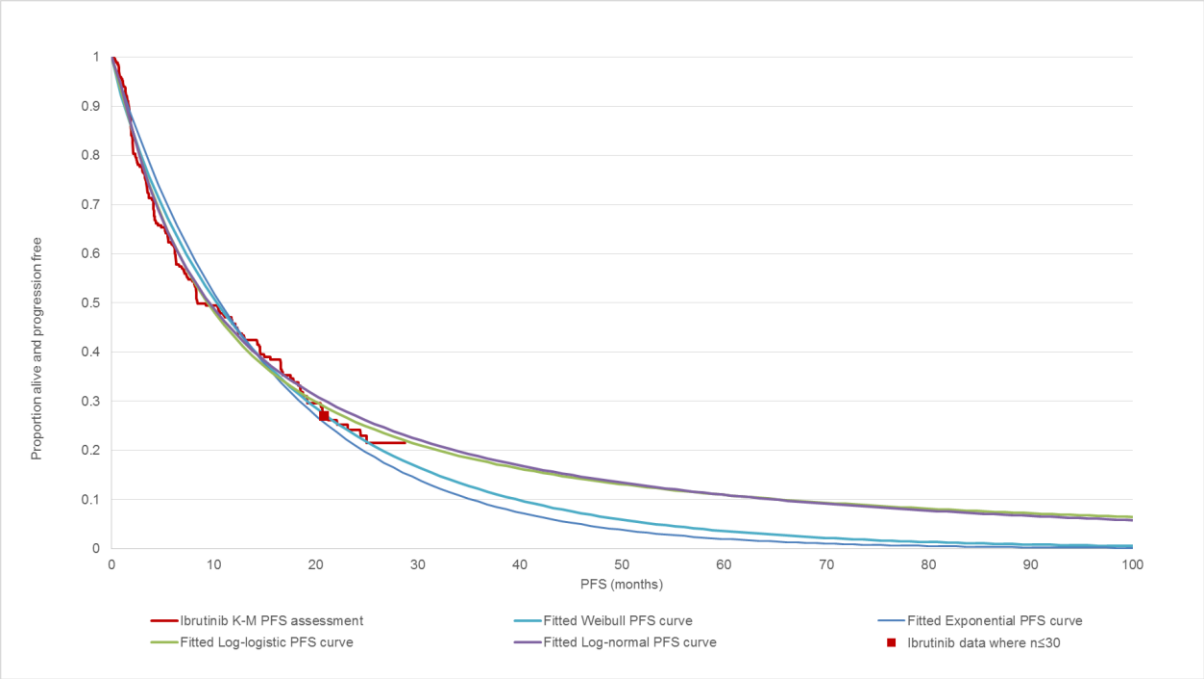


Table 132: Shape and scale parameters with covariate adjustment for ibrutinib PFS

Parameter	Weibull		Log-normal		Exponential		Log-logistic	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Intercept	6.159	0.084	5.676	0.0983	6.144	0.0743	5.656	0.0965
1 prior LOT	0.85	0.2072	0.768	0.2013	0.768	0.1804	0.85	0.2087
Scale	1.123	0.0655	1.492	0.0775	1	0	0.884	0.0502
SE; standard error								

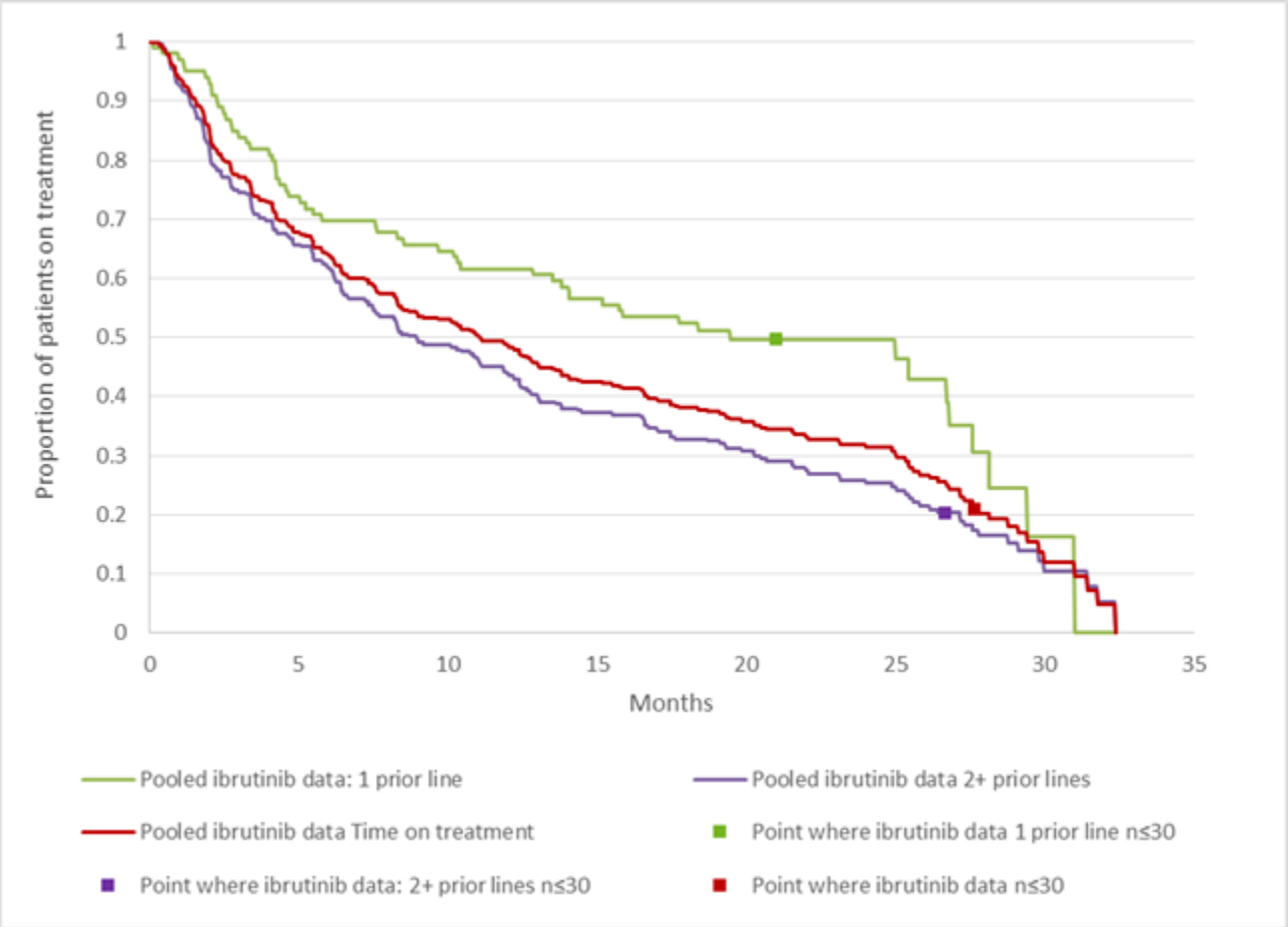
Table 133: AIC / BIC statistics for PFS covariate adjusted analysis

Parameter	Weibull	Log Normal	Exponential	Log Logistic
AIC	1039.81	1020.797	1041.987	1029.516
BIC	1051.55	1032.537	1049.814	1041.256

Time on treatment data

Figure 44 shows the KM curve for the pooled ibrutinib TOT data.

Figure 44: Observed TOT KM curve for ibrutinib split by number of prior LOTs



Parametric curves were fit to the data with a covariate adjustment for those patients having only received one prior line, the following curves were fitted:

- Exponential
- Weibull
- Log-normal
- Log-logistic

Figure 45 and Figure 46 show the parametric curve fit to the KM TOT data for the 1 prior LOT and 2+ prior LOTs respectively. Shape and scale parameters of the parametric curves are shown in Table 134 with AIC and BIC statistics reported in Table 135.

Figure 45: Parametric curve fits to TOT data for ibrutinib: 1 prior LOT

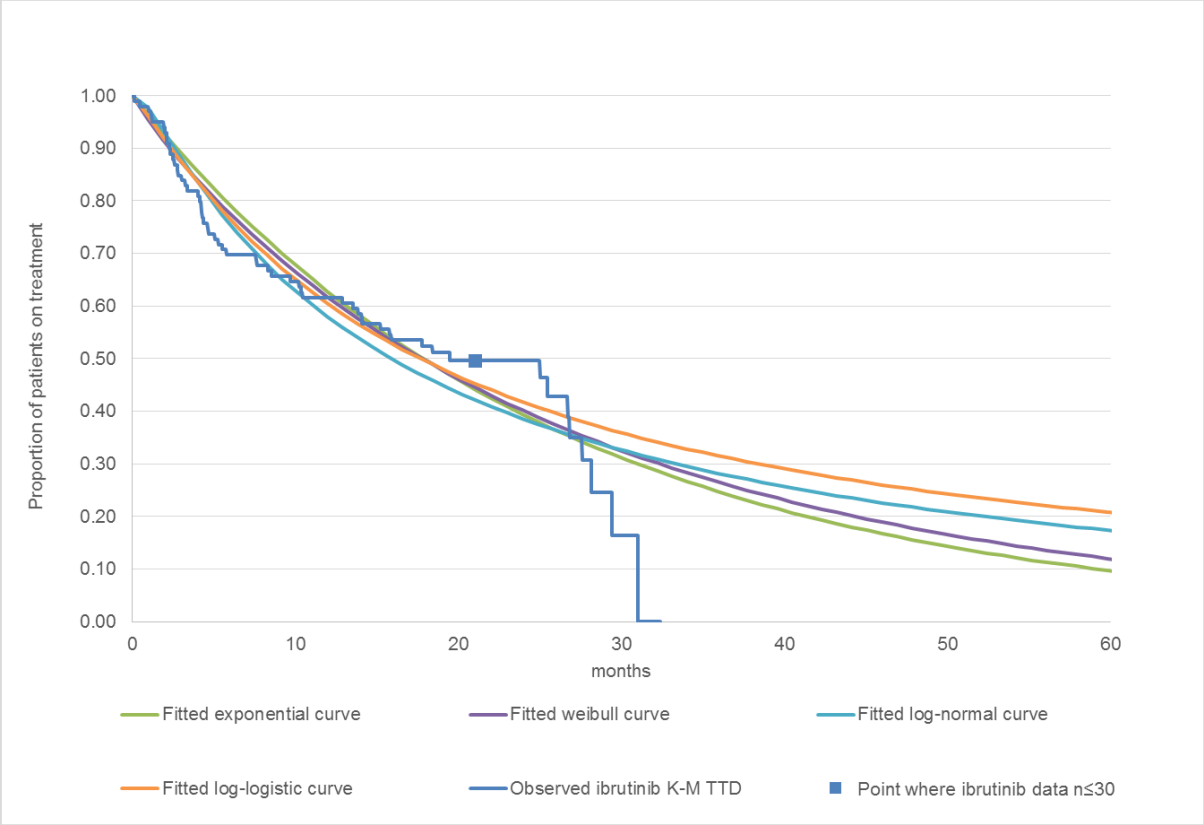


Figure 46: Parametric curve fits to TOT data for ibrutinib: 2+ prior LOTs

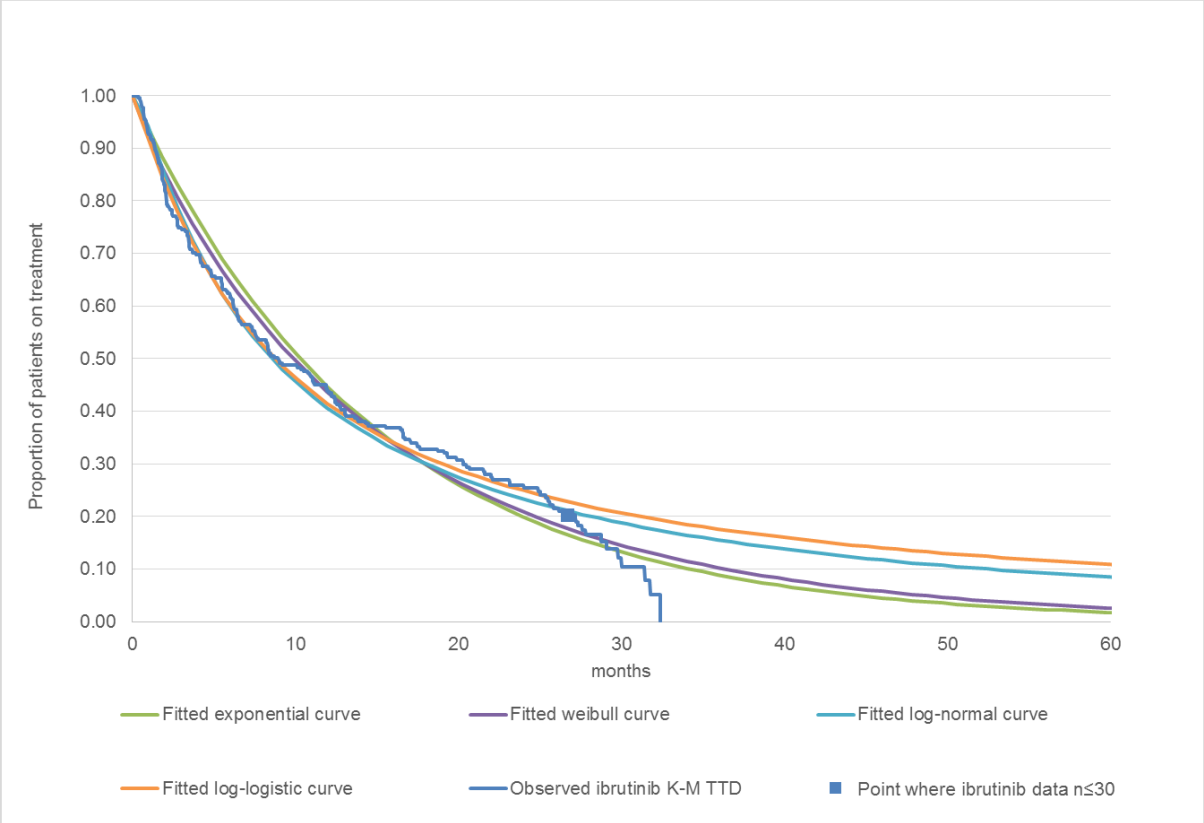


Table 134: Shape and scale parameters with covariate adjustment for ibrutinib TOT

Parameter	Weibull		Log-normal		Exponential		Log-logistic	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Intercept	6.104	0.0736	5.564	0.0884	6.114	0.0676	5.584	0.0895
1 prior LOT	0.587	0.1634	0.618	0.177	0.549	0.1487	0.703	0.1805
Scale	1.086	0.0557	1.413	0.0633	1	0	0.916	0.0418
SE; standard error								

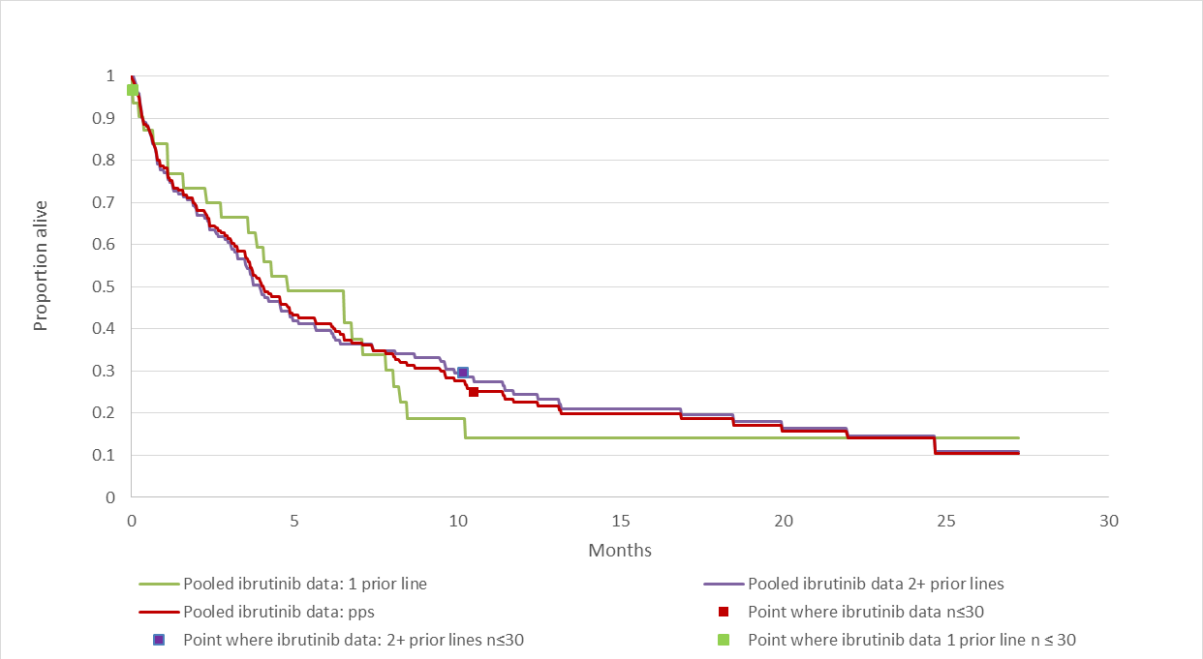
Table 135: AIC / BIC statistics for TOT covariate adjusted analysis

Parameter	Weibull	Log Normal	Exponential	Log Logistic
AIC	1152.752	1146.212	1153.436	1156.048
BIC	1164.492	1157.952	1161.263	1167.789

Post-progression survival data

PPS split by number of prior LOTs is shown in Figure 47. It is noteworthy that the n=20 for patients that have received only one prior LOT.

Figure 47: Observed PPS (IRC-assessed) of ibrutinib patients from pooled data split by number of prior LOTs

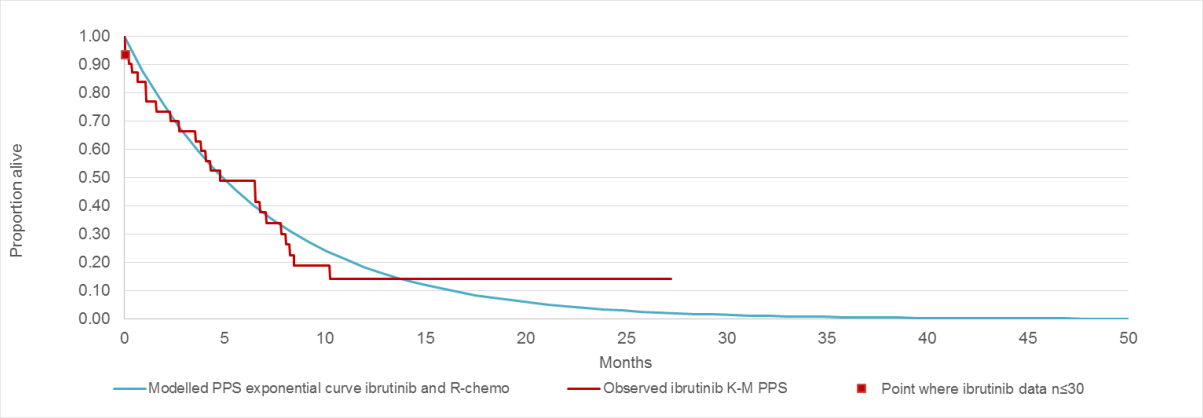


Parametric curves were fit to the data with a covariate adjustment for those patients having only received one prior LOT, the following curves were fitted:

- Exponential
- Weibull
- Log-normal
- Log-logistic

Figure 48 and Figure 49 show the parametric curve fit to the KM PPS data for the 1 prior LOT and 2+ prior LOTs respectively. Shape and scale parameters of the parametric curves are shown in Table 136. As PPS estimates was based on a fixed probability of death while patients are in the PPS state, only an exponential curve was used (see 5.3 for details).

Figure 48: PPS ibrutinib parametric curve fit: 1 prior LOT



*note that n<30 within this subgroup

Figure 49: PPS ibrutinib parametric curve fit: 2+ prior LOTs

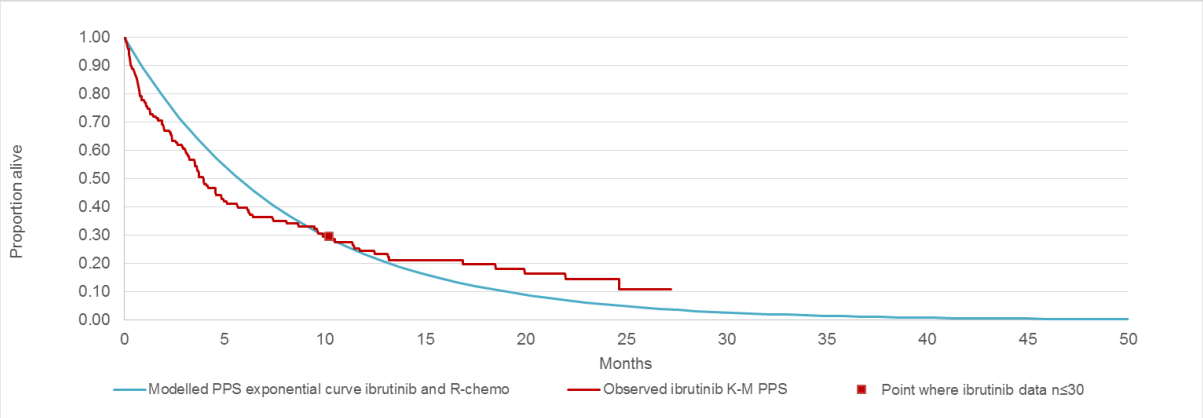


Table 136: Intercept parameter of exponential distribution used to derive PPS curve for ibrutinib with covariate adjustment

Parameter	Exponential	
	Estimate	SE
Intercept	5.524	0.0962
1 Prior Line	-0.152	0.2257
SE: standard error		

Appendix 15: Log cumulative – hazard plots & parametric curve statistics for ibrutinib data

PFS: pooled ibrutinib data

Figure 50: Log-cumulative hazard plot for PFS in the pooled ibrutinib data

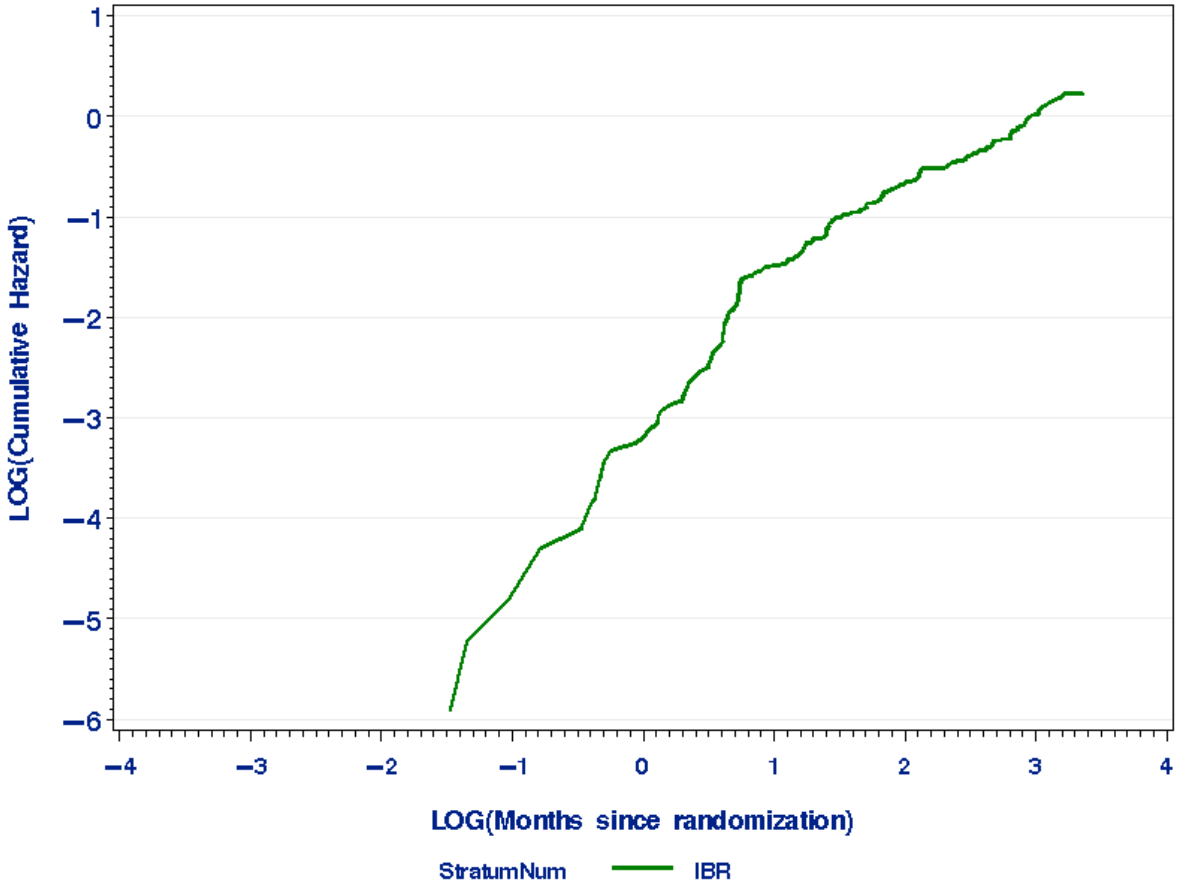
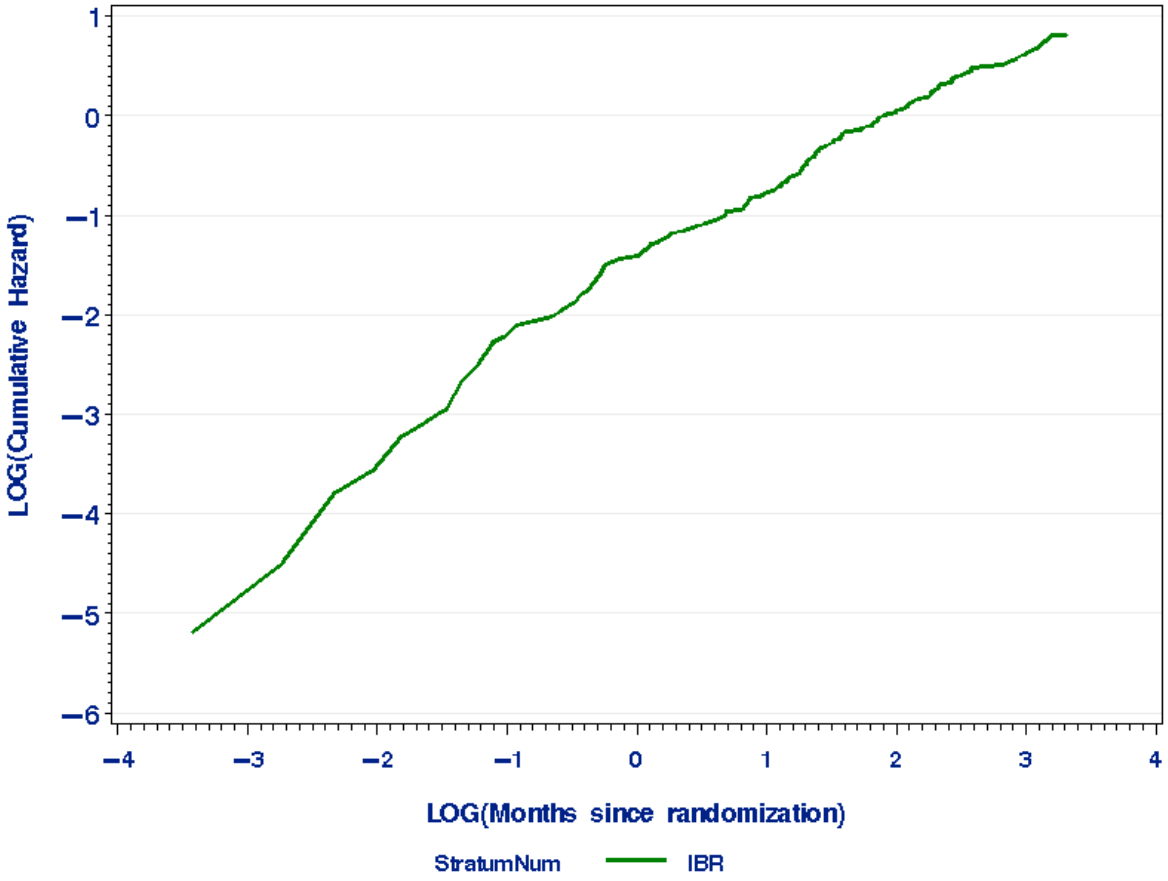


Table 137: PFS by IRC AIC / BIC statistics

Statistic	Weibull	Log-normal	Exponential	Log-logistic
AIC	1058.355	1033.88	1061.221	1044.983
BIC	1066.182	1041.707	1065.134	1052.81

PPS: pooled ibrutinib data

Figure 51: Log-cumulative hazard plot for PPS in the pooled ibrutinib data



Constant rate of death assumed (exponential curve)

Time on Treatment (TOT): pooled ibrutinib data

Figure 52: Log-cumulative hazard plot for TOT in the pooled ibrutinib data

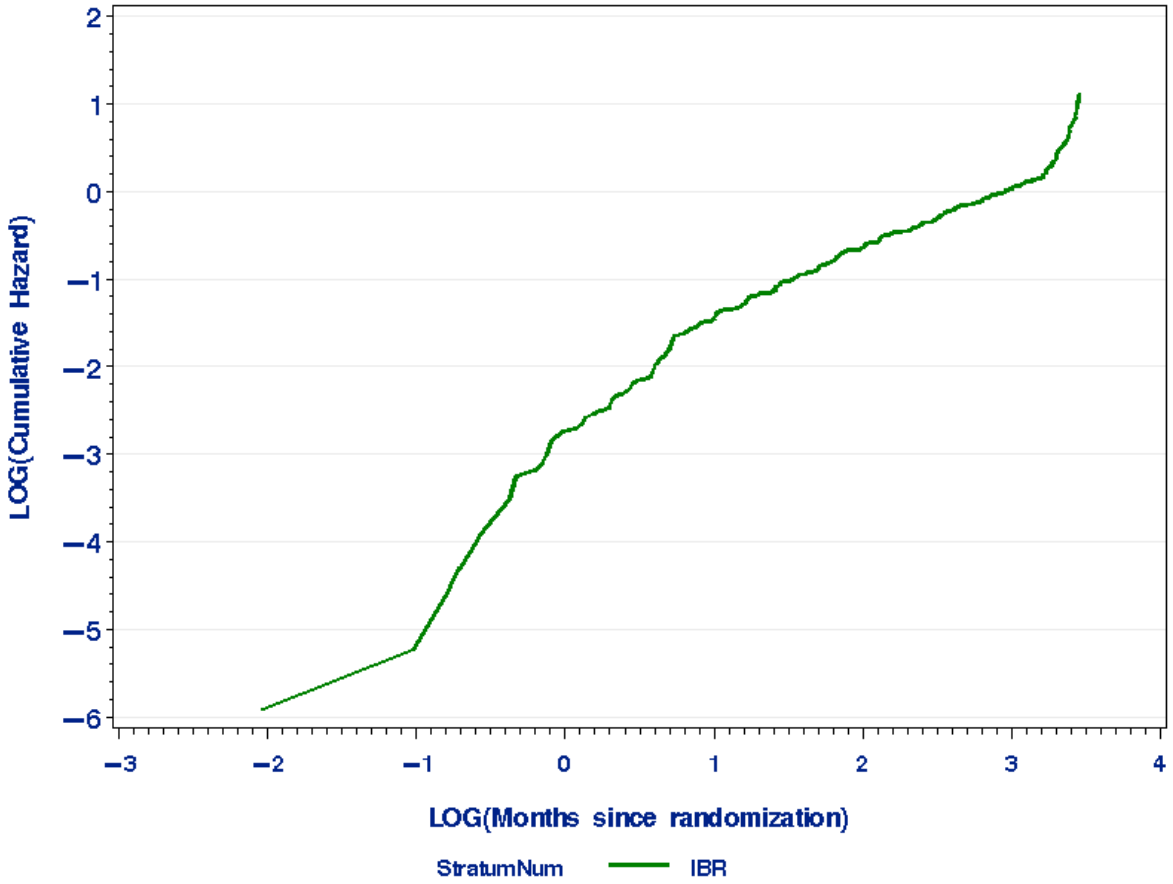
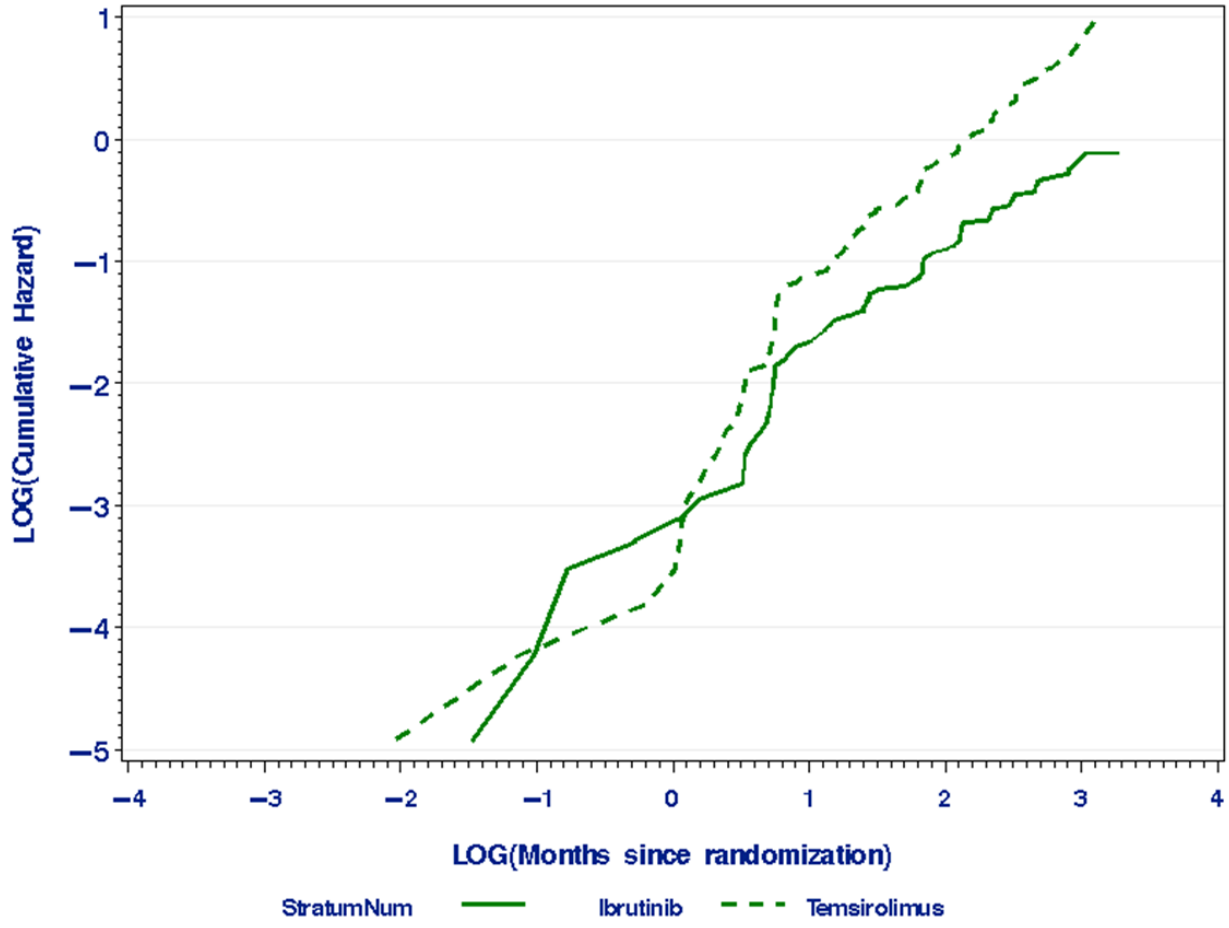


Table 138: TOT AIC / BIC statistics

Statistic	Weibull	Log-normal	Exponential	Log-logistic
AIC	1165.331	1156.509	1166.49	1167.094
BIC	1173.158	1164.336	1170.404	1174.921

PFS: RAY (MCL3001): ibrutinib and temsirolimus

Figure 53: Log-cumulative hazard plot for PFS in RAY (MCL3001)



Appendix 16: Temsirolimus: PFS curve used in scenario analysis to inform comparative efficacy

Figure 54: Modelled PFS: Ibrutinib vs R-chemo (using the TEM PFS HR as a proxy for R-chemo)

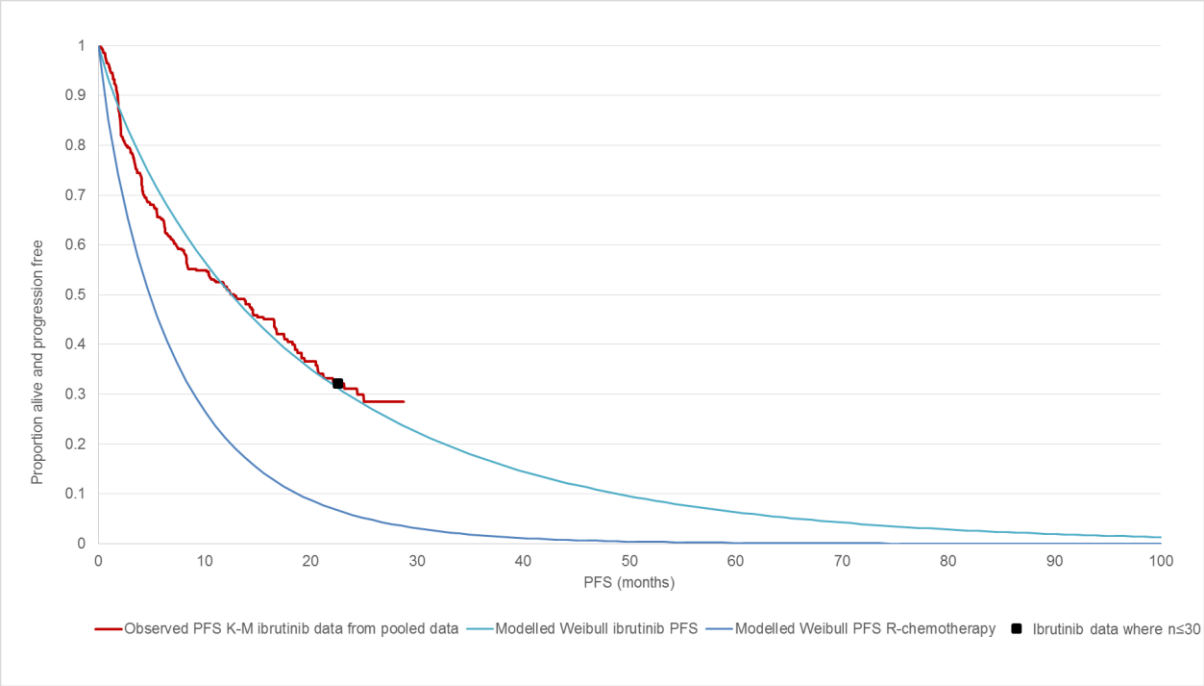
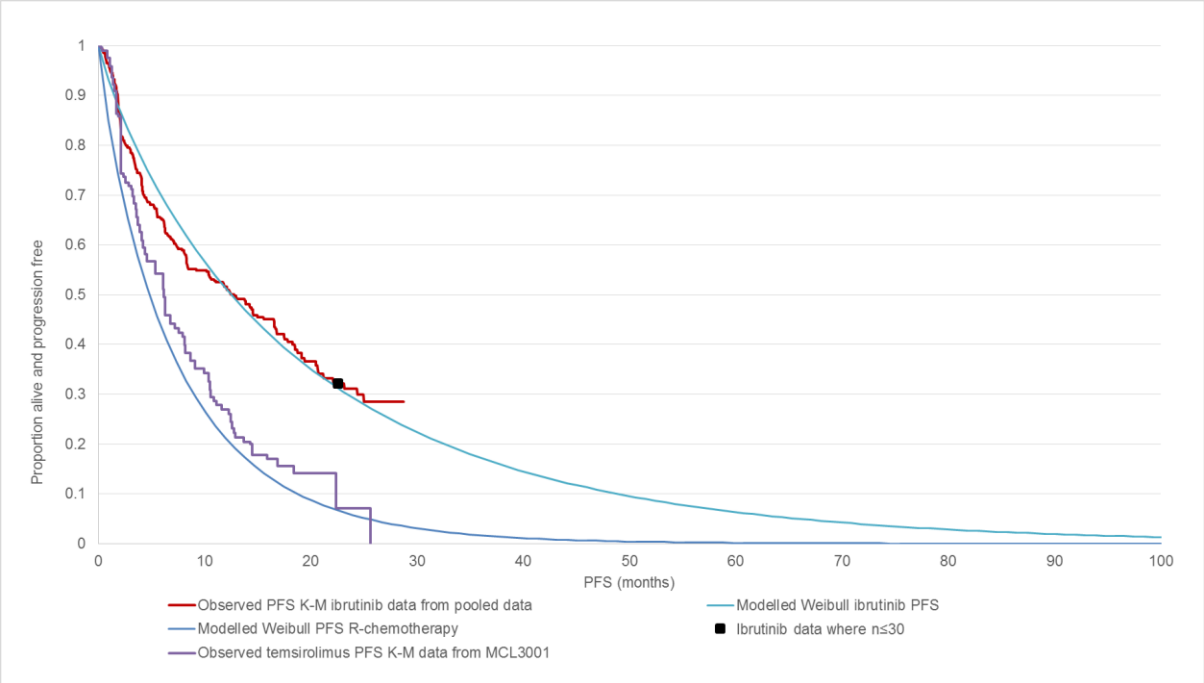


Figure 55: Modelled PFS: Ibrutinib (pooled dataset) vs R-chemo (TEM in RAY (MCL3001)), (unadjusted)



Appendix 17: EQ-5D completion rates

Table 139: EQ-5D-5L Completion rates RAY (MCL3001)

Analysis set: intent-to-treat (n=139)	Ibrutinib		
Timing of assessment	**Expected**	**Received**	**Missing**
Baseline	139	130 (93.5%)	9 (6.5%)
Cycle 2	130	117 (90.0%)	13 (10.0%)
Cycle 3	126	120 (95.2%)	6 (4.8%)
Cycle 4	118	109 (92.4%)	9 (7.6%)
Cycle 5	115	108 (93.9%)	7 (6.1%)
Cycle 6	111	105 (94.6%)	6 (5.4%)
Cycle 7	110	103 (93.6%)	7 (6.4%)
Cycle 8	104	97 (93.3%)	7 (6.7%)
Cycle 11	97	92 (94.8%)	5 (5.2%)
Cycle 14	88	75 (85.2%)	13 (14.8%)
Cycle 17	81	73 (90.1%)	8 (9.9%)
Cycle 20	72	69 (95.8%)	3 (4.2%)
Cycle 28	48	23 (47.9%)	25 (52.1%)
Cycle 36	10	6 (60.0%)	4 (40.0%)
End of treatment	74	26 (35.1%)	48 (64.9%)

Table 140: EQ-5D-5L Completion rates RAY (MCL3001) by progression state

Timing of assessment RAY (MCL3001)	Expected	Received	Missing
Pre-progressive disease follow-up	8	4	4
Post- progressive disease follow-up	31	31	0

Table 141: EQ-5D-5L Completion rates SPARK (MCL2001)

Population: all treated (n=120)	Ibrutinib	
Assessment visit	**Expected**	**Missing**
Baseline	120	8 (6.7%)
Cycle 2	117	6 (5.1%)
Cycle 3	105	5 (4.8%)
Cycle 4	94	3 (3.2%)
Cycle 5	89	7 (7.9%)
Cycle 6	85	5 (5.9%)
Cycle 7	80	12 (15.0%)
Cycle 8	73	5 (6.8%)
Cycle 9	73	10 (13.7%)
Week 34	63	6 (9.5%)
Week 43	59	5 (8.5%)
Week 52	53	8 (15.1%)
Week 61	34	2 (5.9%)
Week 85	4	3 (75.0%)

Appendix 18: Search strategy for HRQoL studies

Embase (2015)

Table 142: Search terms for Embase (2015)

#	Embase R/R MCL QoL Search String	Hits
Population		
#1	'mantle cell lymphoma'/exp	7,205
#2	'mantle cell lymphoma':ab,ti OR 'mantle-cell lymphoma':ab,ti	5,160
#3	'mantle cell':ab,ti OR 'mantle-cell':ab,ti AND (lymphoma:ab,ti OR lymphomas:ab,ti)	5,830
#4	#1 OR #2 OR #3	8,045
Intervention/comparators		
#5	'salvage chemotherapy':ab,ti OR 'salvage treatment':ab,ti OR 'salvage therapy'/exp OR 'resistant chemotherapy':ab,ti OR 'chemotherapy resistant':ab,ti OR 'treatment resistant':ab,ti	33,431
#6	'second line' OR '2nd line' OR (second:ab,ti AND line:ab,ti)	50,263
#7	'third line' OR 'third-line' OR '3rd line' OR (third:ab,ti AND line:ab,ti)	17,102
#8	refractory:ab,ti OR refractor*:ab,ti OR resistant:ab,ti OR relaps*:ab,ti OR recurrent:ab,ti OR 'previously treated' OR 'drug resistance':ab,ti	976,423
#9	failed:ab,ti OR failure:ab,ti AND (treatment:ab,ti OR therapy:ab,ti OR prior:ab,ti OR previous:ab,ti)	419,563
#10	chemotherapy:ab,ti OR treatmen*:ab,ti OR regime*:ab,ti OR medication*:ab,ti OR therap*:ab,ti AND (refractory:ab,ti OR recurrent:ab,ti OR resistant:ab,ti OR rescue:ab,ti OR salvage:ab,ti OR failed:ab,ti OR failure:ab,ti)	800,236
#11	#5 OR #6 OR #7 OR #8 OR #9 OR #10	1,452,327
Outcomes		
#12	'eq-5d':ab,ti OR eq5d:ab,ti OR euroqol:ab,ti OR 'euro qol':ab,ti	8,641
#13	sf16:ab,ti OR 'sf 16':ab,ti OR 'short form 16':ab,ti OR 'shortform 16':ab,ti OR 'sf sixteen':ab,ti OR sfsixteen:ab,ti OR 'shortform sixteen':ab,ti OR 'short form sixteen':ab,ti OR sf12:ab,ti OR 'sf 12':ab,ti OR 'short form 12':ab,ti OR 'shortform 12':ab,ti OR 'sf twelve':ab,ti OR sftwelve:ab,ti OR 'shortform twelve':ab,ti OR 'short form twelve':ab,ti OR sf36:ab,ti OR 'sf 36':ab,ti OR 'short form 36':ab,ti OR 'shortform 36':ab,ti OR 'sf thirtysix':ab,ti OR 'sf thirty six':ab,ti OR 'shortform thirtysix':ab,ti OR 'shortform thirty six':ab,ti OR 'short form thirtysix':ab,ti OR 'short form thirty six':ab,ti OR fact:ab,ti OR 'functional assessment of cancer therapy':ab,ti OR eortc:ab,ti OR qlq:ab,ti OR utility:ab,ti OR utilities:ab,ti	441,460
#14	'patient reported':ab,ti OR 'patient-reported':ab,ti OR 'patients reported':ab,ti	49,828
#15	'self reported':ab,ti OR 'self report':ab,ti OR 'functional status':ab,ti OR 'health status':ab,ti OR 'physical function':ab,ti OR 'time trade off':ab,ti	184,171
#16	disab*:ab,ti OR satisfa*:ab,ti	438,552
#17	questionnaire:ab,ti OR satisfaction:ab,ti OR sexual:ab,ti OR sleep:ab,ti OR 'sickness impact profile':ab,ti	746,284
#18	burden:ab,ti AND (patient:ab,ti OR carer:ab,ti OR caregiver:ab,ti)	35,217
#19	'quality of life' OR 'health related quality of life':ab,ti OR hrqol:ab,ti OR hqol:ab,ti OR 'hr qol':ab,ti OR 'quality of life':ab,ti OR qol:ab,ti	340,817
#20	'medical leave':ab,ti OR (work:ab,ti AND disability:ab,ti) OR 'work disability':ab,ti OR absenteeism:ab,ti OR 'sick leave':ab,ti OR 'sick day':ab,ti	22,312
#21	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	1,815,465
Study design/limits		
#22	[editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim	2,636,955

PICOS combined		
#23	#4 AND #11 AND #21 NOT #22	206

Embase In Process (2015)

Table 143: Search terms for Embase In Process (2015)

#	Embase R/R MCL QoL Search String	Hits
Population		
#1	'mantle cell lymphoma' OR 'mantle-cell lymphoma'	7,771
#2	'mantle cell' OR 'mantle-cell' AND (lymphoma OR lymphomas)	8,090
#3	#1 OR #2	8,090
Intervention/comparators		
#4	'salvage chemotherapy' OR 'salvage treatment' OR 'salvage therapy' OR 'resistant chemotherapy' OR 'chemotherapy resistant' OR 'treatment resistant'	29,112
#5	'second line' OR '2nd line' OR (second AND line)	68,949
#6	'third line' OR 'third-line' OR '3rd line' OR (third AND line)	24,821
#7	refractory OR refractor* OR resistant OR relaps* OR recurrent OR 'previously treated' OR 'drug resistance'	1,153,974
#8	failed OR failure AND (treatment OR therapy OR prior OR previous)	778,954
#9	chemotherapy OR treatmen* OR regime* OR medication* OR therap* AND (refractory OR recurrent OR resistant OR rescue OR salvage OR failed OR failure)	1,299,941
#10	#4 OR #5 OR #6 OR #7 OR #8 OR #9	1,956,173
Outcomes		
#11	'eq-5d' OR eq5d OR euroqol OR 'euro qol'	8,801
#12	sf16 OR 'sf 16' OR 'short form 16' OR 'shortform 16' OR 'sf sixteen' OR sfsixteen OR 'shortform sixteen' OR 'short form sixteen' OR sf12 OR 'sf 12' OR 'short form 12' OR 'shortform 12' OR 'sf twelve' OR sftwelve OR 'shortform twelve' OR 'short form twelve' OR sf36 OR 'sf 36' OR 'short form 36' OR 'shortform 36' OR 'sf thirtysix' OR 'sf thirty six' OR 'shortform thirtysix' OR 'shortform thirty six' OR 'short form thirtysix' OR 'short form thirty six' OR fact OR 'functional assessment of cancer therapy' OR eortc OR qlq OR utility OR utilities	455,604
#13	'patient reported' OR 'patient-reported' OR 'patients reported'	50,577
#14	'self reported' OR 'self report' OR 'functional status' OR 'health status' OR 'physical function' OR 'time trade off'	278,855
#15	disab* OR satisfa*	583,062
#16	questionnaire OR satisfaction OR sexual OR sleep OR 'sickness impact profile'	1,118,773
#17	burden AND (patient OR carer OR caregiver)	63,969
#18	'health related quality of life' OR hrqol OR hqol OR 'hr qol' OR 'quality of life' OR qol	340,944
#19	'medical leave' OR (work AND disability) OR 'work disability' OR absenteeism OR 'sick leave' OR 'sick day'	42,117
#20	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	2,279,776
Study design/limits		
#21	[editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim	2,637,512
PICOS combined		
#22	#3 AND #10 AND #20 NOT #21	259
#23	#22 AND [in process]/lim	0

PubMed (2015)

Table 144: Search terms for PubMed (2015)

#	PubMed R/R MCL QoL Search String	Hits
Population		
#1	("mantle cell"[tiab] OR "mantle-cell"[tiab]) AND (lymphoma[tiab])	3,454
#2	“mantle cell lymphoma” OR “mantle-cell lymphoma”	3,480
#3	"Lymphoma, Mantle-Cell"[Mesh]	2,054
#4	#1 OR #2 OR #3	3,736
Intervention/comparators		
#5	"salvage chemotherapy" OR "salvage treatment" OR "salvage therapy" OR “salvage therapy”[Mesh]	14,562
#6	"resistant chemotherapy" OR "chemotherapy resistant" OR "treatment resistant"	6,203
#7	“second line" OR second-line OR "2nd line" OR "2'nd line" OR (second[tiab] AND line[tiab])	34,479
#8	“third line” OR “third-line” OR “3rd line” OR "3'rd line" OR (third[tiab] AND line[TIAB])	11,690
#9	refractory[tiab] OR refractor*[tiab] OR resistant[tiab] OR relaps*[tiab] OR recurrent[tiab] OR “drug resistance, neoplasm”[MeSH] OR "previously treated"[tiab]	742,660
#10	(failed[tiab] OR failure[tiab]) AND (treatment[tiab] OR therapy[tiab] OR prior[tiab] OR previous[tiab])	295,112
#11	(chemotherapy[tiab] OR treatmen*[tiab] OR regime*[tiab] OR medication*[tiab] OR therap*[tiab]) AND (refractory[tiab] OR recurrent[tiab] OR resistant[tiab] OR rescue[tiab] OR salvage[tiab] OR failed[tiab] OR failure[tiab])	568,608
#12	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	1,081,636
Outcomes		
#13	“eq-5d”[TIAB] OR eq5d[TIAB] OR euroqol[TIAB] OR “euro qol”[TIAB]	4,993
#14	sf16[TIAB] OR “sf 16”[TIAB] OR “short form 16”[TIAB] OR “shortform 16”[TIAB] OR “sf sixteen”[TIAB] OR sfsixteen[TIAB] OR “shortform sixteen”[TIAB] OR “short form sixteen”[TIAB] OR sf12[TIAB] OR “sf 12”[TIAB] OR “short form 12”[TIAB] OR “shortform 12”[TIAB] OR “sf twelve”[TIAB] OR sftwelve[TIAB] OR “shortform twelve”[TIAB] OR “short form twelve”[TIAB] OR sf36[TIAB] OR “sf 36”[TIAB] OR “short form 36”[TIAB] OR “shortform 36”[TIAB] OR “sf thirtysix”[TIAB] OR “sf thirty six”[TIAB] OR “shortform thirtysix”[TIAB] OR “shortform thirty six”[TIAB] OR “short form thirtysix”[TIAB] OR “short form thirty six”[TIAB] OR FACT[TIAB] OR “functional assessment of cancer therapy”[TIAB] OR EORTC[TIAB] OR QLQ[TIAB] OR utility[TIAB] OR utilities[TIAB]	340,053
#15	“patient reported”[TIAB] OR “patient-reported”[TIAB] OR “patients reported”[TIAB]	31,293
#16	“self reported”[TIAB] OR “self report”[TIAB] OR “functional status”[TIAB] OR “health status”[TIAB] OR “physical function”[TIAB] OR “time trade off”[TIAB]	147,719
#17	disab*[TIAB] OR satisfa*[TIAB]	336,581
#18	questionnaire[TIAB] OR satisfaction[TIAB] OR sexual[TIAB] OR sleep[TIAB] OR “sickness impact profile”[TIAB]	566,135
#19	burden[TIAB] AND (patient[TIAB] OR carer[TIAB] OR caregiver[TIAB])	19,260
#20	“quality of life” OR “health related quality of life”[TIAB] OR hrqol[TIAB] OR hqol[TIAB] OR “hr qol”[TIAB] OR qol[TIAB]	210,644
#21	“medical leave”[TIAB] OR (work[TIAB] AND disability[TIAB]) OR “work disability”[TIAB] OR absenteeism[TIAB] OR “sick leave”[TIAB] OR “sick day”[TIAB]	16,830
#22	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	1,356,109
Study design/limits		
#23	Editorial[ptyp] OR "Published Erratum"[ptyp] OR Letter[ptyp] OR Comment[ptyp]	1,406,214

PICOS combined		
#24	(#4 AND #12 AND #22) NOT #23	43

PubMed In-Process (2015)

Table 145: Search terms for PubMed In-Process (2015)

#	PubMed R/R MCL QoL Search String	Hits
Population		
#1	("mantle cell" OR "mantle-cell") AND (lymphoma)	3,785
#2	“mantle cell lymphoma” OR “mantle-cell lymphoma”	3,480
#3	"Lymphoma Mantle-Cell"	2,060
#4	#1 OR #2 OR #3	3,785
Intervention/comparators		
#5	"salvage chemotherapy" OR "salvage treatment" OR "salvage therapy"	14,562
#6	"resistant chemotherapy" OR "chemotherapy resistant" OR "treatment resistant"	6,203
#7	“second line" OR “second-line” OR "2nd line" OR "2'nd line" OR (second AND line)	53,313
#8	“third line” OR “third-line” OR “3rd line” OR "3'rd line" OR (third AND line)	19,218
#9	refractory OR refractor* OR resistant OR relaps* OR recurrent OR “drug resistance neoplasm” OR "previously treated"	751,001
#10	(failed OR failure) AND (treatment OR therapy OR prior OR previous)	565,532
#11	(chemotherapy OR treatmen* OR regime* OR medication* OR therap*) AND (refractory OR recurrent OR resistant OR rescue OR salvage OR failed OR failure)	714,418
#12	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	1,355,108
Outcomes		
#13	“eq-5d” OR eq5d OR euroqol OR ”euro qol”	5,009
#14	sf16 OR “sf 16” OR “short form 16” OR “shortform 16” OR “sf sixteen” OR sfsixteen OR “shortform sixteen” OR “short form sixteen” OR sf12 OR “sf 12” OR “short form 12” OR “shortform 12” OR “sf twelve” OR sftwelve OR “shortform twelve” OR “short form twelve” OR sf36 OR “sf 36” OR “short form 36” OR “shortform 36” OR “sf thirtysix” OR “sf thirty six” OR “shortform thirtysix” OR “shortform thirty six” OR “short form thirtysix” OR “short form thirty six” OR FACT OR “functional assessment of cancer therapy” OR EORTC OR QLQ OR utility OR utilities	344,814
#15	“patient reported” OR “patient-reported” OR “patients reported”	31,546
#16	“self reported” OR “self report” OR “functional status” OR “health status” OR “physical function” OR “time trade off”	216,475
#17	disab* OR satisfa*	494,168
#18	questionnaire OR satisfaction OR sexual OR sleep OR “sickness impact profile”	915,276
#19	burden AND (patient OR carer OR caregiver)	56,848
#20	“quality of life” OR ”health related quality of life” OR hrqol OR hqol OR ”hr qol” OR qol	210,676
#21	“medical leave” OR (work AND disability) OR ”work disability” OR absenteeism OR ”sick leave” OR ”sick day”	29,042
#22	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	1,809,283
Study design/limits		
#23	Editorial[ptyp] OR "Published Erratum"[ptyp] OR Letter[ptyp] OR Comment[ptyp]	1,406,214
#24	“2014/12/01”[PDat] : “2015/12/31”[PDat]	652,549
PICOS combined		

#25	(#4 AND #12 AND #22 AND #24) NOT #23	1

CENTRAL/Cochrane Search (2015)

Table 146: Search terms for CENTRAL/Cochrane (2015)

#	CENTRAL/Cochrane R/R MCL QoL Search String	Hits
Population		
#1	("mantle cell":ti,ab,kw or "mantle-cell":ti,ab,kw) and lymphoma:ti,ab,kw	172
#2	“mantle cell lymphoma” or "mantle-cell lymphoma"	163
#3	MeSH descriptor: [Lymphoma, Mantle-Cell] explode all trees	48
#4	#1 or #2 or #3	182
Intervention/comparators		
#5	“salvage chemotherapy” or "salvage treatment" or "salvage therapy"	1,021
#6	“resistant chemotherapy” or "chemotherapy resistant" or "treatment resistant"	1,315
#7	“second line” or “second-line” or "2nd line" or "2'nd line" or (second:ti,ab,kw and line:ti,ab,kw)	3,576
#8	“third line” or "third-line" or "3rd line" or "3'rd line" or (third:ti,ab,kw and line:ti,ab,kw)	860
#9	(refractory:ti,ab,kw or refractor*:ti,ab,kw or resistant:ti,ab,kw or relaps*:ti,ab,kw or recurrent:ti,ab,kw or "previously treated":ti,ab,kw)	44,963
#10	MeSH descriptor: [Drug Resistance, Neoplasm] explode all trees	346
#11	(failed:ti,ab,kw or failure:ti,ab,kw) and (treatment:ti,ab,kw or therapy:ti,ab,kw or prior:ti,ab,kw or previous:ti,ab,kw)	39,023
#12	(chemotherapy:ti,ab,kw or treatmen*:ti,ab,kw or regime*:ti,ab,kw or medication*:ti,ab,kw or therap*:ti,ab,kw) and (refractory:ti,ab,kw or recurrent:ti,ab,kw or resistant:ti,ab,kw or rescue:ti,ab,kw or salvage:ti,ab,kw or failed:ti,ab,kw or failure:ti,ab,kw)	64,218
Combined		
#13	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12	88,104
#14	#4 and #13	88
#15	#4 and #13 - *results for “Trials”*	78
#16	#4 and #13 - *results for “Cochrane Reviews”*	7
#17	#4 and #13 - *results for “Other Reviews”*	1
#18	#4 and #13 - *results for “Economic Evaluations”*	0
#19	#4 and #13 - *results for “Technology Assessments”*	2

DARE/NHS EED/HTA (2015)

Table 147: Search terms for DARE/NHS EED/HTA (2015)

#	DARE/NHS EED / HTA RR-MCL QoL Search String	Hits
Population		
#1	MeSH DESCRIPTOR Lymphoma, Mantle-Cell EXPLODE ALL TREES	8
#2	((mantle cell lymphoma) OR (mantle-cell lymphoma))	10
#3	(((mantle cell):ti OR (mantle-cell):ti) AND (lymphoma:ti OR lymphomas:ti))	7
#4	(#1 OR #2 OR #3)	12
Outcomes		
#5	((eq-5d) OR eq5d OR euroqol OR (euro qol))	783

#6	(sf16 OR (sf 16) OR (short form 16) OR (shortform 16) OR (sf sixteen) OR sfsixteen OR (shortform sixteen) OR (short form sixteen) OR sf12 OR (sf 12) OR (short form 12) OR (shortform 12) OR (sf twelve) OR sftwelve OR (shortform twelve) OR (short form twelve) OR sf36 OR (sf 36) OR (short form 36) OR (shortform 36) OR (sf thirtysix) OR (sf thirty six) OR (shortform thirtysix) OR (shortform thirty six) OR (short form thirtysix) OR (short form thirty six) OR FACT OR (functional assessment of cancer therapy) OR EORTC OR QLQ OR utility OR utilities)	7,204
#7	((patient reported) OR (patient-reported) OR (patients reported))	559
#8	((self reported) OR (self report) OR (functional status) OR (health status) OR (physical function) OR (time trade off))	2,770
#9	(disab* OR satisfa*)	5,493
#10	(questionnaire OR satisfaction OR sexual OR sleep OR (sickness impact profile))	5,277
#11	(burden AND (patient OR carer OR caregiver))	508
#12	((quality of life) OR (health related quality of life) OR hrqol OR hqol OR (hr qol) OR (quality of life) OR qol)	8,109
#13	((medical leave) OR (work AND disability) OR (work disability) OR absenteeism OR (sick leave) OR (sick day))	660
Combined		
#14	(#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)	18,287
#15	(#4 AND #14)	2

Embase (2014)

Table 148: Search terms for Embase (2014)

Search Number	Embase R/R MCL QoL Search String	Yield
Patient population		
1.	‘mantle cell lymphoma’/exp	6,592
2.	(‘mantle cell lymphoma’:ab,ti) OR (‘mantle-cell lymphoma’:ab,ti)	4,277
3.	(‘mantle cell’:ab,ti OR ‘mantle-cell’:ab,ti) AND (lymphoma:ab,ti OR lymphomas:ab,ti)	4,867
4.	#1 OR #2 OR #3	6,852
Intervention or comparator		
5.	'salvage chemotherapy':ab,ti OR 'salvage treatment':ab,ti OR 'salvage therapy'/exp OR 'resistant chemotherapy':ab,ti OR 'chemotherapy resistant':ab,ti OR 'treatment resistant':ab,ti	30,847
6.	'second line' OR '2nd line' OR ('second':ab,ti AND 'line':ab,ti)	43,756
7.	'third line' OR 'third-line' OR '3rd line' OR ('third':ab,ti AND 'line':ab,ti)	14,888
8.	refractory:ab,ti OR refractor*:ab,ti OR resistant:ab,ti OR relaps*:ab,ti OR recurrent:ab,ti OR 'previously treated' OR 'drug resistance':ab,ti OR 'previously treated':ab,ti	880,324
9.	failed:ab,ti OR failure:ab,ti AND (treatment:ab,ti OR therapy:ab,ti OR prior:ab,ti OR previous:ab,ti)	376,529
10.	chemotherapy:ab,ti OR treatmen*:ab,ti OR regime*:ab,ti OR medication*:ab,ti OR therap*:ab,ti AND (refractory:ab,ti OR recurrent:ab,ti OR resistant:ab,ti OR rescue:ab,ti OR salvage:ab,ti OR failed:ab,ti OR failure:ab,ti)	713,541
11.	#5 OR #6 OR #7 OR #8 OR #9 OR #10	1,307,615
Outcomes		
12.	'eq-5d':ab,ti OR eq5d:ab,ti OR euroqol:ab,ti OR 'euro qol':ab,ti	6,765

13.	sf16:ab,ti OR 'sf 16':ab,ti OR 'short form 16':ab,ti OR 'shortform 16':ab,ti OR 'sf sixteen':ab,ti OR sfsixteen:ab,ti OR 'shortform sixteen':ab,ti OR 'short form sixteen':ab,ti ORsf12:ab,ti OR 'sf 12':ab,ti OR 'short form 12':ab,ti OR 'shortform 12':ab,ti OR 'sf twelve':ab,ti OR sftwelve:ab,ti OR 'shortform twelve':ab,ti OR 'short form twelve':ab,ti ORsf36:ab,ti OR 'sf 36':ab,ti OR 'short form 36':ab,ti OR 'shortform 36':ab,ti OR 'sf thirtysix':ab,ti OR 'sf thirty six':ab,ti OR 'shortform thirtysix':ab,ti OR 'shortform thirty six':ab,ti OR 'short form thirtysix':ab,ti OR 'short form thirty six':ab,ti OR FACT:ab,ti OR 'functional assessment of cancer therapy':ab,ti	242,095
14.	'patient reported':ab,ti OR 'patient-reported':ab,ti OR 'patients reported':ab,ti	41,617
15.	'self reported':ab,ti OR 'self report':ab,ti OR 'functional status':ab,ti OR 'health status':ab,ti OR 'physical function':ab,ti OR 'time trade off':ab,ti	160,440
16.	disab*:ab,ti OR satisfa*:ab,ti	395,018
17.	'questionnaire':ab,ti OR 'satisfation':ab,ti OR 'sexual':ab,ti OR 'sleep':ab,ti OR 'sickness impact profile':ab,ti	588,609
18.	burden:ab,ti AND patient:ab,ti OR carer:ab,ti OR caregiver:ab,ti	45,935
19.	'quality of life' OR 'health related quality of life':ab,ti OR hrqol:ab,ti OR 'hqol':ab,ti OR 'hr qol':ab,ti OR 'quality of life':ab,ti OR qol:ab,ti	310,217
20.	'medical leave':ab,ti OR (work:ab,ti AND disability:ab,ti) OR 'work disability':ab,ti OR 'absenteeism':ab,ti OR 'sick leave':ab,ti OR 'sick day':ab,ti	19,963
21.	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	1,502,792
Study design		
22.	[Editorial]/lim OR [Erratum]/lim OR [Letter]/lim OR [Note]/lim OR [Short Survey]/lim	2,497,280
PICO Combined		
23.	#4 AND #11 AND #21 NOT #22	121

Embase In Process (2014)

Table 149: Search terms for Embase In Process (2014)

Search Number	Embase R/R MCL QoL Search String	Yield
Patient population		
1.	'mantle cell lymphoma'/exp	6,600
2.	('mantle cell lymphoma') OR ('mantle-cell lymphoma')	6,600
3.	('mantle cell' OR 'mantle-cell') AND (lymphoma OR lymphomas)	6,868
4.	#1 OR #2 OR #3	6,868
Intervention or comparator		
5.	'salvage chemotherapy' OR 'salvage treatment' OR 'salvage therapy'/exp OR 'resistant chemotherapy' OR 'chemotherapy resistant' OR 'treatment resistant'	31,338
6.	'second line' OR '2nd line' OR ('second' AND 'line')	59,834
7.	'third line' OR 'third-line' OR '3rd line' OR ('third' AND 'line')	21,593
8.	refractory OR refractor* OR resistant OR relaps* OR recurrent OR 'previously treated' OR 'drug resistance' OR 'previously treated'	1,111,007
9.	failed OR failure AND (treatment OR therapy OR prior OR previous)	801,350
10.	chemotherapy OR treatmen* OR regime* OR medication* OR therap* AND (refractory OR recurrent OR resistant OR rescue OR salvage OR failed OR failure)	1,179,413

11.	#5 OR #6 OR #7 OR #8 OR #9 OR #10	1,917,356
Outcomes		
12.	'eq-5d' OR eq5d OR euroqol OR 'euro qol'	6,904
13.	sf16 OR 'sf 16' OR 'short form 16' OR 'shortform 16' OR 'sf sixteen' OR sfsixteen OR 'shortform sixteen' OR 'short form sixteen' ORsf12 OR 'sf 12' OR 'short form 12' OR 'shortform 12' OR 'sf twelve' OR sftwelve OR 'shortform twelve' OR 'short form twelve' ORsf36 OR 'sf 36' OR 'short form 36' OR 'shortform 36' OR 'sf thirtysix' OR 'sf thirty six' OR 'shortform thirtysix' OR 'shortform thirty six' OR 'short form thirtysix' OR 'short form thirty six' OR FACT OR 'functional assessment of cancer therapy'	246,887
14.	'patient reported' OR 'patient-reported' OR 'patients reported'	42,256
15.	'self reported' OR 'self report' OR 'functional status' OR 'health status' OR 'physical function' OR 'time trade off'	276,923
16.	disab* OR satisfa*	529,585
17.	'questionnaire' OR 'satisfation' OR 'sexual' OR 'sleep' OR 'sickness impact profile'	924,889
18.	burden AND patient OR carer OR caregiver	92,827
19.	'quality of life' OR 'health related quality of life' OR hrqol OR 'hqol' OR 'hr qol' OR 'quality of life' OR qol	310,790
20.	'medical leave' OR (work AND disability) OR 'work disability' OR 'absenteeism' OR 'sick leave' OR 'sick day'	41,139
21.	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	1,997,827
Study design		
22.	[Editorial]/lim OR [Erratum]/lim OR [Letter]/lim OR [Note]/lim OR [Short Survey]/lim	2,499,269
23.	[2013 -2014]/py	800,617
PICO Combined		
24.	(#4 AND #11 AND #21 AND #23) NOT #22	21

PubMed (2014)

Table 150: Search terms for PubMed (2014)

Search Number	PubMed R/R MCL QoL Search String	Yield
Population		
1.	("mantle cell"[tiab] OR "mantle-cell"[tiab]) AND (lymphoma[tiab])	3,168
2.	"mantle cell lymphoma" OR "mantle-cell lymphoma"	3,190
3.	"Lymphoma, Mantle-Cell"[Mesh]	1,949
4.	(#1 OR #2 OR #3)	3,434
Interventions or Comparators		
5.	("salvage chemotherapy" OR "salvage treatment" OR "salvage therapy" OR "salvage therapy"[Mesh])	13,478
6.	"resistant chemotherapy" OR "chemotherapy resistant" OR "treatment resistant"	5,447
7.	("second line" OR second-line OR "2nd line" OR "2'nd line" OR (second[tiab] AND line[tiab]))	31,702

8.	(“third line” OR “third-line” OR “3rd line” OR "3'rd line" OR ("third"[tiab] AND "line"[TIAB])	10,828
9.	(refractory[tiab] OR refractor*[tiab] OR resistant[tiab] OR relaps*[tiab] OR recurrent[tiab] OR “drug resistance, neoplasm”[MeSH] OR "previously treated"[tiab])	692,887
10.	((failed[tiab] OR failure[tiab]) AND (treatment[tiab] OR therapy[tiab] OR prior[tiab] OR previous[tiab]))	276,058
11.	(chemotherapy[tiab] OR treatmen*[tiab] OR regime*[tiab] OR medication*[tiab] OR therap*[tiab]) AND (refractory[tiab] OR recurrent[tiab] OR resistant[tiab] OR rescue[tiab] OR salvage[tiab] OR failed[tiab] OR failure[tiab])	527,559
12.	(#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)	1,008,985
Outcomes		
13.	(“eq-5d”[TIAB] OR eq5d[TIAB] OR euroqol[TIAB] OR ”euro qol”[TIAB])	4,160
14.	sf16[TIAB] OR ”sf 16”[TIAB] OR ”short form 16”[TIAB] OR ”shortform 16”[TIAB] OR ”sf sixteen”[TIAB] OR sfsixteen[TIAB] OR ”shortform sixteen”[TIAB] OR ”short form sixteen”[TIAB] ORsf12[TIAB] OR ”sf 12”[TIAB] OR ”short form 12”[TIAB] OR ”shortform 12”[TIAB] OR ”sf twelve”[TIAB] OR sftwelve[TIAB] OR ”shortform twelve”[TIAB] OR ”short form twelve”[TIAB] ORsf36[TIAB] OR ”sf 36”[TIAB] OR ”short form 36”[TIAB] OR ”shortform 36”[TIAB] OR ”sf thirtysix”[TIAB] OR ”sf thirty six”[TIAB] OR ”shortform thirtysix”[TIAB] OR ”shortform thirty six”[TIAB] OR ”short form thirtysix”[TIAB] OR ”short form thirty six”[TIAB] OR FACT[TIAB] OR “functional assessment of cancer therapy”[TIAB]	189,048
15.	“patient reported”[TIAB] OR “patient-reported”[TIAB] OR “patients reported”[TIAB]	27,689
16.	“self reported”[TIAB] OR “self report”[TIAB] OR “functional status”[TIAB] OR “health status”[TIAB] OR “physical function”[TIAB] OR “time trade off”[TIAB]	132,783
17.	disab*[TIAB] OR satisfa*[TIAB]	310,176
18.	“questionnaire”[TIAB] OR “satisfation”[TIAB] OR “sexual”[TIAB] OR “sleep”[TIAB] OR “sickness impact profile”[TIAB]	460,324
19.	burden[TIAB] AND patient[TIAB] OR carer[TIAB] OR caregiver[TIAB]	29,568
20.	“quality of life” OR ”health related quality of life”[TIAB] OR hrqol[TIAB] OR ”hqol”[TIAB] OR ”hr qol”[TIAB] OR ”quality of life”[TIAB] OR qol[TIAB]	189,574
21.	“medical leave”[TIAB] OR (work[TIAB] AND disability[TIAB]) OR ”work disability”[TIAB] OR ”absenteeism”[TIAB] OR ”sick leave”[TIAB] OR ”sick day”[TIAB]	15,569
22.	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	1,144,367
Study of Interest		
23.	(Editorial[ptyp] OR "Published Erratum"[ptyp] OR Letter[ptyp] OR Comment[ptyp])	1,317,442
PICO Combined		
24.	(#4 AND #12 AND #22) NOT #23	26

PubMed In-Process (2014)

Table 151: Search terms for PubMed In-Process (2014)

Search Number	PubMed R/R MCL QoL Search String	Yield
Population		
1.	("mantle cell" OR "mantle-cell") AND (lymphoma)	3,439

2.	“mantle cell lymphoma” OR “mantle-cell lymphoma”	3,152
3.	"Lymphoma, Mantle-Cell"	1,860
4.	(#1 OR #2 OR #3)	3,439
Interventions or Comparators		
5.	("salvage chemotherapy" OR "salvage treatment" OR "salvage therapy" OR “salvage therapy”[Mesh])	13,490
6.	"resistant chemotherapy" OR "chemotherapy resistant" OR "treatment resistant"	5,458
7.	(“second line" OR second-line OR "2nd line" OR "2'nd line" OR (second AND line))	48,966
8.	(“third line” OR “third-line” OR “3rd line” OR "3'rd line" OR ("third" AND "line")	17,689
9.	(refractory OR refractor* OR resistant OR relaps* OR recurrent OR “drug resistance, neoplasm”[MeSH] OR "previously treated")	700,789
10.	((failed OR failure) AND (treatment OR therapy OR prior OR previous))	533,103
11.	(chemotherapy OR treatmen* OR regime* OR medication* OR therap*) AND (refractory OR recurrent OR resistant OR rescue OR salvage OR failed OR failure)	665,552
12.	(#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)	1,268,609
Outcomes		
13.	(“eq-5d” OR eq5d OR euroqol OR ”euro qol”)	4,182
14.	sf16 OR ”sf 16” OR ”short form 16” OR ”shortform 16” OR ”sf sixteen” OR sfsixteen OR ”shortform sixteen” OR ”short form sixteen” ORsf12 OR ”sf 12” OR ”short form 12” OR ”shortform 12” OR ”sf twelve” OR sftwelve OR ”shortform twelve” OR ”short form twelve” ORsf36 OR ”sf 36” OR ”short form 36” OR ”shortform 36” OR ”sf thirtysix” OR ”sf thirty six” OR ”shortform thirtysix” OR ”shortform thirty six” OR ”short form thirtysix” OR ”short form thirty six” OR FACT OR “functional assessment of cancer therapy”	190,218
15.	“patient reported” OR “patient-reported” OR “patients reported”	27,844
16.	“self reported” OR “self report” OR “functional status” OR “health status” OR “physical function” OR “time trade off”	196,407
17.	disab* OR satisfa*	474,381
18.	“questionnaire” OR “satisfation” OR “sexual” OR “sleep” OR “sickness impact profile”	538,590
19.	burden AND patient OR carer OR caregiver	86,321
20.	“quality of life” OR ”health related quality of life” OR hrqol OR ”hqol” OR ”hr qol” OR ”quality of life” OR qol	189,781
21.	“medical leave” OR (work AND disability) OR ”work disability” OR ”absenteeism” OR ”sick leave” OR ”sick day”	27,140
22.	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	1,442,856
Limitations		
23.	(Editorial[ptyp] OR "Published Erratum"[ptyp] OR Letter[ptyp] OR Comment[ptyp])	1,317,442
24.	"2013/01 /01"[PDat] : "2014/12/31"[PDat]	1,563,858
PICO Combined		
25.	(#4 AND #12 AND #22 AND #24) NOT #23	0

CENTRAL/Cochrane Search (2014)

Table 152: Search terms for CENTRAL/Cochrane (2014)

ID	CENTRAL/Cochrane Search	Yield
Patient population		
#1	("mantle cell":ti,ab,kw or "mantle-cell":ti,ab,kw) and lymphoma:ti,ab,kw	0
#2	mantle cell lymphoma or "mantle-cell lymphoma"	133
#3	Lymphoma, Mantle-Cell	0
#4	#1 or #2 or #3	133
Intervention or comparator		
#5	salvage chemotherapy or "salvage treatment" or "salvage therapy"	917
#6	resistant chemotherapy or "chemotherapy resistant" or "treatment resistant"	1,106
#7	second line or second-line or "2nd line" or "2'nd line" or (second:ti,ab,kw and line:ti,ab,kw)	3,217
#8	third line or "third-line" or "3rd line" or "3'rd line" or ("third":ti,ab,kw and "line":ti,ab,kw)	682
#9	(refractory:ti,ab,kw or refractor*:ti,ab,kw or resistant:ti,ab,kw or relaps*:ti,ab,kw or recurrent:ti,ab,kw or "Drug Resistance, Neoplasm" or "previously treated":ti,ab,kw)	39,259
#10	((failed:ti,ab,kw or failure:ti,ab,kw) and (treatment:ti,ab,kw or therapy:ti,ab,kw or prior:ti,ab,kw or previous:ti,ab,kw))	37,221
#11	(chemotherapy:ti,ab,kw or treatmen*:ti,ab,kw or regime*:ti,ab,kw or medication*:ti,ab,kw or therap*:ti,ab,kw) and (refractory:ti,ab,kw or recurrent:ti,ab,kw or resistant:ti,ab,kw or rescue:ti,ab,kw or salvage:ti,ab,kw or failed:ti,ab,kw or failure:ti,ab,kw)	58,572
#12	#5 or #6 OR #7 or #8 or #9 or #10 or #11	79,704
PICO Combined		
#13	#4 and #12	58

Appendix 19: Summary of HRQoL studies found within the SLR

Table 153: HRQoL evidence from studies identified within the HRQoL search

Study	Sample Size	Point when measurements were made	Method of elicitation	Method of valuation	Consistency with reference case	Results	Appropriateness of study for CEA
Ruan *et al.*, 2009[185]	22	QoL assessed at baseline, every 2 months until month 6, and every 6 months until progression	Patient self-administered	FACT-G questionnaire was used; includes five subscales: physical well-being, social/family well-being, relationship with doctor, emotional well-being, and functional well-being). The sum of physical well-being and functional wellbeing scores was defined as the modified Trial Outcome Index (TOI). ANOVA was used to compare the difference in the means of QoL total score and modified TOI among the different time	The FACT-G is a cancer-specific HRQoL measure, not a generic utility elicitation tool as recommended by the NICE reference case.	Baseline FACT-G Score: 83.3, (SD 18.8) Trial Outcome Index: 38.7 (SD 13.6) Means of baseline FACT-G scores did not correlate with IPI or clinical response on RT-PEPC. FACT-G scores on average remained unchanged during treatment. In four long-term responders (PFS > 31 months and ongoing), the mean FACT-G scores remained stable or slightly improved. Importantly, the FACT-G scores on average remained unchanged (total score: 89.4±5.5, p=0.16; TOI:	The FACT-G does not produce utility scores that can be directly implemented in CEA. Furthermore, the study did not map or otherwise transform FACT-G scores into utility values, which makes the results not appropriate for CEA.

Study	Sample Size	Point when measurements were made	Method of elicitation	Method of valuation	Consistency with reference case	Results	Appropriateness of study for CEA
				points.		43.5±3.5, p=0.27) during treatment	
Cuyun *et al.*, 2009 (abstract only)[186]	58	EQ-5D data were available for 58 of 60 enrolled patients at baseline and for 38 patients at discontinuation	Not reported	EQ-5D and visual analogue scale (VAS)	The EQ-5D and VAS are generic, validated methods of HRQoL elicitation, which fits the recommendation of the NICE reference case.	There was a statistically significant (p <0.05) difference in baseline EQ-5D index (0.81, 0.63, 0.58) and visual analogue scale (VAS) (66.9, 56.4, 44.7) by ECOG performance scale (PS) group (0, 1, 2, respectively) and at discontinuation by PS group for the index (0.77, 0.61, 0.28). There were no significant differences for the index or VAS scores by International Prognosis Index (IPI) group. Those patients with worsened PS (n = 12) had significantly worse index and VAS scores than those patients with improved/stable PS (n = 18).	The EQ-5D and VAS produce utility scores that can be directly implemented in

Study	Sample Size	Point when measurements were made	Method of elicitation	Method of valuation	Consistency with reference case	Results	Appropriateness of study for CEA
Rule S *et al.*, 2015 (abstract only)[187]	254	At baseline, after cycles 2, 4, 6, and 8, and at treatment discontinuation	NR	EORTC QLQ-C30	EORTC QLQ-C30 is not a generic QoL measuring instrument like EQ-5D and hence not consistent with NICE reference case	Patients treated with lenalidomide reported similar QoL vs IC single agents across all domain/scale scores and at each follow-up visit. A trend towards higher rates of clinically meaningful improvement in QoL was observed in lenalidomide treated patients across most function and symptom domains/scales at one or more follow-up visits. Statistically significant QoL differences (≥10%) comparing lenalidomide vs IC treatment arms were identified for physical function (24% vs 8%, P=0.003) and pain (29% vs 18%; P=0.047). CIs not reported	The EORTC QLQ-C30 does not produce utility scores that can be directly implemented in CEA. Furthermore, the study did not map or otherwise transform EORTC QLQ-C30 scores into utility values, which make the results not appropriate for CEA.

Study	Sample Size	Point when measurements were made	Method of elicitation	Method of valuation	Consistency with reference case	Results	Appropriateness of study for CEA
Schenkel *et al.*, 2014 (abstract only)[97]	23	NA	Patient self-reported	EQ-5D score	EQ-5D is used which is as per NICE standard	The mean EQ-5D self-reported score for health state (0 = worst imaginable to 100 = best imaginable) was 61 Mean satisfaction with treatment (1 = extremely dissatisfied to 7 = extremely satisfied) was 5.3.	EQ-5D scores can be used directly as utility values for CEA.
Hess et al 2015[3]	280	The FACT-Lym was administered before any tests, procedures, or other consultations, and was used until disease progression, death, or the clinical cut off, whichever came first.	Patient self-reported	FACT-Lym questionnaire	The FACT-LYM is a lymphoma r-specific HRQoL measure, not a generic utility elicitation tool as recommended by the NICE reference case.	The proportion of patients with worsening from baseline on the FACT-Lym lymphoma subscale was lower for ibrutinib compared with temsirolimus (26.6% vs 51.8%, respectively). The proportion of patients with a clinically meaningful improvement from baseline on the FACT-Lym lymphoma subscale was higher for ibrutinib compared	The FACT-LYM does not produce utility scores that can be directly implemented in CEA. Furthermore, the study did not map or otherwise transform FACT-LYM scores into utility values, which makes the results not appropriate for CEA.

Study	Sample Size	Point when measurements were made	Method of elicitation	Method of valuation	Consistency with reference case	Results	Appropriateness of study for CEA
						with temsirolimus (61.9% vs 35.5%, respectively).	

QoL: quality of life, EQ-5D: EuroQoL 5 dimensions, NA: not applicable, TOI: trial outcome index, ANOVA: analysis of variance, VAS: visual analogue scale, NICE: National Institute for Health and Care Excellence, IC: investigator's choice, HRQoL: health-related quality of life, IPI: International Prognosis Index, RT-PEPC: rituximab, thalidomide, and prednisone, etoposide, procarbazine, cyclophosphamide

Appendix 20 : Cost-effectiveness results using agreed discount price

Base-case results: using applied discount

This section outlines the results of the CEA when using an agreed discount of ibrutinib of [redacted].

Base-case incremental cost effectiveness analysis results

Base case results of the economic comparison between ibrutinib and R-CHOP discounted at 3.5% for costs and QALYs over the 15 year time horizon are presented in Table 154.

Ibrutinib was estimated to generate an additional 1.23 life years and 0.94 QALYs. This represents a substantial improvement to both length and QoL for patients with an extremely poor prognosis. The mean life years estimated for patients treated with ibrutinib are over double compared to what estimated for R-chemo. The resulting ICER with the agreed discount is £74,256.

Table 154: Base case discounted results, ibrutinib versus R-CHOP using agreed discount price for ibrutinib

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Ibrutinib	[redacted]	[redacted]	[redacted]	£69,528	1.23	0.94	£74,256
R-CHOP	[redacted]	[redacted]	[redacted]				
ICER: incremental cost-effectiveness ratio, QALYs:, quality-adjusted life years, R-CHOP: rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone,							

Disaggregated results of the base case incremental cost effectiveness analysis

Table 155 summarises the total QALYs for both arms of the base case model, disaggregated by the model health states. Table 156 summarises the total life years accrued over the time horizon for both arms of the model. As expected the majority of the difference between the two model arms is observed in the pre-progression health state. Table 157 shows the predicted total incremental costs for ibrutinib versus R-CHOP. The majority of the costs are incurred within the pre-progression health state, and represent the drug costs associated with treating patients with R/R MCL. Table 158 shows these data further split by the category of cost incurred within the model.

Table 155: Base case: total discounted QALYs gained by health state

	QALY ibrutinib	QALY R-CHOP	Increment
PFS	[redacted]	[redacted]	0.99
PPS	[redacted]	[redacted]	-0.05
Total	[redacted]	[redacted]	0.94
QALY: quality-adjusted life year, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone, PFS: progression-free survival, PPS: post-progression survival			

Table 156: Base case: total undiscounted LYs gained by health state

	LY ibrutinib	LY R-CHOP	Increment
PFS	[redacted]	[redacted]	1.29
PPS	[redacted]	[redacted]	-0.06
Total	[redacted]	[redacted]	1.23

LY: life year, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone, PFS: progression-free survival, PPS: post-progression survival

Table 157: Base case: total discounted costs accrued in each health state

	Costs ibrutinib	Costs R-CHOP	Increment
PFS	[redacted]	[redacted]	£70,507
PPS	[redacted]	[redacted]	-£979
Total	[redacted]	[redacted]	£69,528

LY: life year, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone, PFS: progression-free survival, PPS: post-progression survival

Table 158: Base case: category of discounted costs accrued within the model

Item	Cost ibrutinib	Cost R-CHOP	Increment
PFS drug cost	[redacted]	[redacted]	£67,862
PFS administration cost	[redacted]	[redacted]	-£1,427
PFS routine follow up	[redacted]	[redacted]	£4,158
AE cost	[redacted]	[redacted]	-£86
Subsequent treatment	[redacted]	[redacted]	£0
PPS routine follow up cost	[redacted]	[redacted]	-£693
Terminal care cost	[redacted]	[redacted]	-£286
Total costs	[redacted]	[redacted]	£69,528

AE: adverse event, PFS: progression-free survival, PPS: post-progression survival, R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

Sensitivity analyses

Probabilistic sensitivity analysis

PSA was performed within the CEA for 1,000 iterations of ibrutinib versus R-CHOP, randomly sampling parameters within their chosen distributions. This analysis demonstrates the impact of parameter uncertainty within the economic model. The results of this analysis are presented in Figure 56, which shows the incremental costs and QALYs for each iteration. Incremental QALYs range from approximately 0.6-1.4, while incremental costs range from £55,000 to £90,000. The largest spread of uncertainty was across the x axis reporting the incremental QALYs. Overall the average incremental QALYs gained from ibrutinib was 0.94 with a mean incremental cost of £70,790, resulting in a mean probabilistic ICER of £75,328. The overall average results were very close to the deterministic base case results (0.94 and £69,528 incremental QALYs and costs respectively), indicating that there is no bias in the deterministic ICER caused by skewed uncertainty within the model parameters.

Based on the 1,000 iterations performed within the PSA, a CEAC was constructed and is presented in Figure 57. This graph shows the likelihood that each treatment is the most cost-effective option at different WTP thresholds.

Figure 56: Cost-effectiveness plane from 1,000 PSA iterations

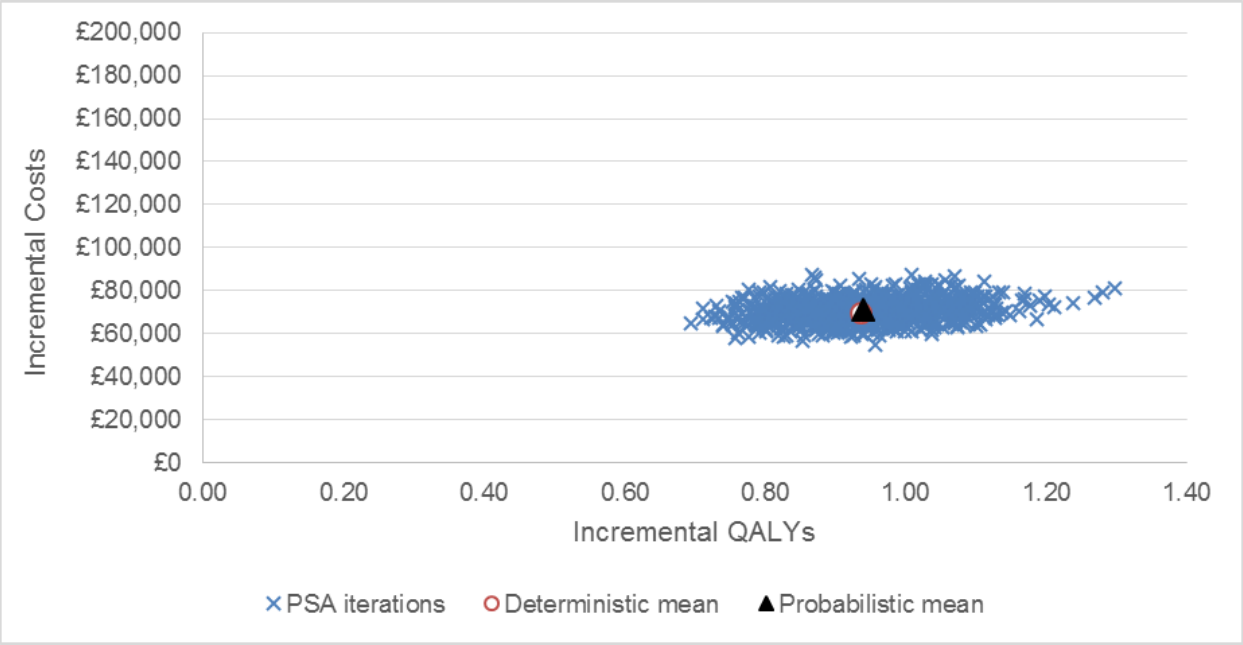
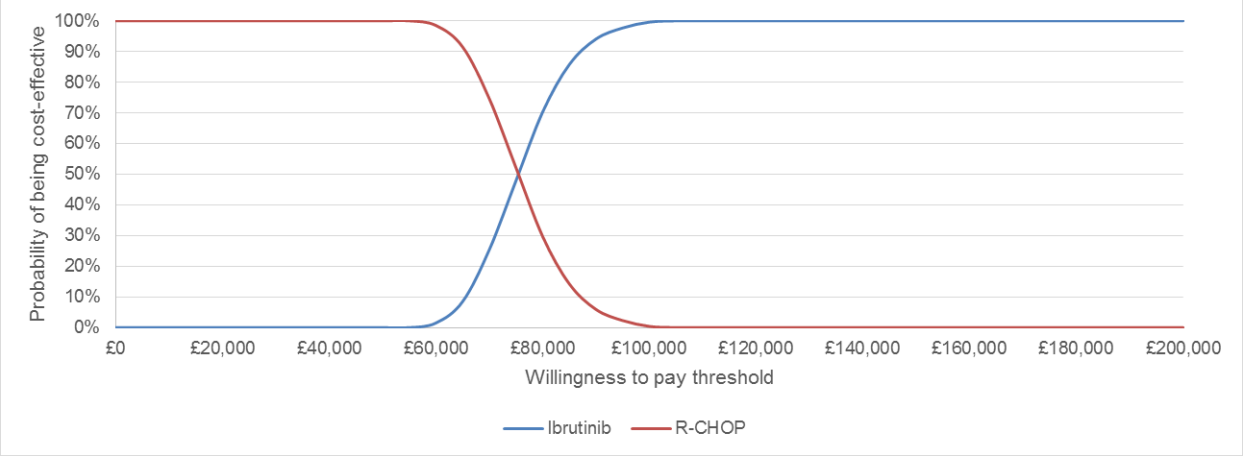


Figure 57: Incremental cost-effectiveness acceptability curve



Deterministic sensitivity analysis

Figure 58 presents a tornado diagram showing the parameters with the greatest impact on the net NMB of ibrutinib, with descending sensitivity.

The NMB was calculated as:

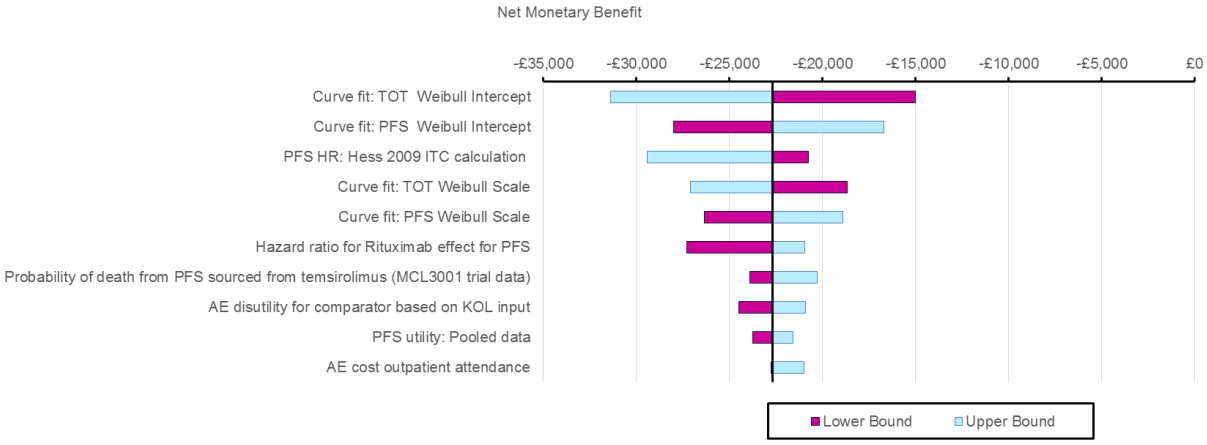
$$NMB = (WTP \times Incremental\ QALYs) - Incremental\ Costs$$

The WTP was set at £50,000/QALY, on the assumption that ibrutinib meets the *end-of-life* criteria in this indication (see Section 4.14.3).

As for the results with no discount, NMB was used in order to account for any issues which may arise as a result of dominant or dominated results where negative ICERs are created. Where the NMB is positive, ibrutinib represents a cost-effective treatment based on a WTP

threshold of £50,000 per QALY. Figure 58 shows the ten most influential parameters. The NMB was most sensitive to the uncertainty within the curve fit parameters for TOT and PFS. Parameters informing the HR for comparative efficacy were also influential within the CEA as would be expected. The utility data informing the model were also influential, with both the PFS utility and the disutility associated with R-chemo appearing within the top 10 parameters.

Figure 58: Tornado diagram



Scenario analysis

Table 159 shows the results of the extensive scenario analyses performed which tested the structural uncertainty within the model and are described in Section 5.6. Overall the model was most sensitive to the PPS assumed for the R-chemo arm. Within scenario testing PPS a HR was applied to the PPS for R-chemo that reduced the time spent in PPS. The HR selected minimised the difference between the median OS within the model and the median survival reported within the HMRN data (which was estimated to be 8.4 months for patients on second line treatment regimens)[7].

The model was also sensitive to the dataset used to inform PFS of R-chemo. Testing the PFS of TEM from RAY (MCL3001) as proxy for R-chemo increased the ICER as the estimate used to inform R-chemo here was higher than the one in the base case. It should be noted that no evidence is available regarding the comparative effectiveness of TEM and R-chemo.

In general, results from scenario analyses were consistent with the base case results, meaning that there is not a great deal of uncertainty in key assumptions.

Table 159: Scenario analyses conducted within the economic model

Scenario	Ibrutinib			R-CHOP			Incremental outcomes			
	Total Costs	Total QALYs	Total LYs	Total Costs	Total QALYs	Total LYs	Inc. Costs	Inc. QALYs	Inc. LYs	ICER
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£69,528	0.94	1.23	£74,256
Comparator efficacy HR for PFS using TEM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£67,440	0.82	1.01	£82,685
Time horizon: 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£69,266	0.93	1.22	£74,617
Time horizon: 20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£69,547	0.94	1.24	£74,217
Comparator: R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£70,853	0.94	1.23	£75,671
Comparator FCR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£67,360	0.94	1.23	£71,941
Comparator RC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£68,587	0.94	1.23	£73,251
Treatment mix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£69,552	0.94	1.23	£74,282
No wastage included	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£69,954	0.94	1.23	£74,711
Utility decrement for R-chemo based on Schenkel *et al.* 2014	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£69,528	0.93	1.23	£75,120
No age-adjusted utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£69,528	0.95	1.23	£73,289
Sequential approach (OS ibrutinib = PFS ibrutinib + PFS R-chemo + PPS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£81,620	1.08	1.43	£75,623
Including FCR as subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£67,946	0.94	1.23	£72,567
PFS curve: exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£66,045	0.83	1.06	£79,254
PFS curve: log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£91,633	1.30	1.88	£70,530
PFS curve: log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£96,462	1.32	1.93	£73,085
Risk of death during PFS for R-chemo assumed equal to ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£69,281	0.92	1.21	£75,521
Response rates of R-chemo equal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£69,269	0.94	1.23	£73,980

Scenario	Ibrutinib			R-CHOP			Incremental outcomes			
	Total Costs	Total QALYs	Total LYs	Total Costs	Total QALYs	Total LYs	Inc. Costs	Inc. QALYs	Inc. LYs	ICER
to TEM response										
Response rates of R-chemo equal to response in Hess, 2009	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£68,352	0.94	1.23	£73,001
Response rates of R-chemo equal to ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£69,663	0.94	1.23	£74,400
No benefit from rituximab in PFS HR (rituximab HR = 1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£71,220	1.00	1.35	£71,223
Rituximab PFS HR applied to Hess, 2009 ITC = 0.75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£69,914	0.95	1.26	£73,360
Rituximab PFS HR applied to Hess, 2009 ITC = 0.89	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£70,698	0.98	1.32	£71,937
Rituximab PFS HR applied to Hess 2009 ITC = 1.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£73,158	1.05	1.44	£69,671
Applying a HR to PPS of R-chemo to adjust survival to be as close as possible to HMRN anticipated survival (8.4 months for patients on 2nd line treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£109,851	1.87	2.64	£58,757

HR: hazard ratio, PFS: progression-free survival, TEM: temsirolimus, R-CVP: rituximab + cyclophosphamide + vincristine + prednisone, FCR: fludarabine + cyclophosphamide + rituximab, RC: rituximab + cytarabine, R-chemo: rituximab-based chemotherapy, OS: overall survival, ITC: indirect treatment comparison, PPS: post-progression survival, HMRN: haematological malignancy research network, QALY: quality-adjusted life year, LY: life year, Inc: incremental

Summary of sensitivity analyses results

PSA indicates that the results obtained within the base case where fairly robust to parameter uncertainty, with average PSA results very similar to the deterministic results. The model results showed that the majority of uncertainty lies within the estimated QALYs, however, in all cases a substantial QALY improvement was expected for ibrutinib compared to R-chemo (QALY gains expected to lie between 0.6 and 1.4).

Key uncertainties within the model parameterisation surrounded the parametric curve fits to TOT and PFS and the HR assumed for comparative efficacy within the model. Within scenario analysis the model was also sensitive to the PPS assumed for R-chemo, with the ICER reducing when HMRN data were used to inform PPS. The model was also sensitive to the dataset used to inform the PFS of R-chemo, with the use of the TEM arm of RAY (MCL3001) as proxy for R-chemo producing an increased estimate of the ICER.

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

Subgroup analysis

Results of the economic comparison between ibrutinib and R-CHOP for subgroups of 1 prior LOT versus 2+ prior LOTs are presented in Table 160 and Table 161. Substantially higher estimates of LYs and QALYs were produced for ibrutinib in the subgroup of patients only receiving one prior LOT. These results are consistent with the findings of the *post-hoc* analysis of RAY (MCL3001) presented in Section 4.8.2, clearly demonstrating that an increased benefit is observed when ibrutinib is used early in the treatment pathway for R/R MCL, which were also confirmed in the pooled dataset (Section 4.12.2). In those patients with 1 prior LOT, ibrutinib produces 3.65 LYs, compared to 1.91 LYs in patients with 2+ prior LOTs. This strongly suggests that whilst all R/R MCL patients can benefit from ibrutinib, the benefit is more pronounced the earlier they receive it.

Table 160: Base case discounted results, ibrutinib versus R-CHOP: 1 prior LOT

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Ibrutinib	[redacted]	[redacted]	[redacted]	£107,299	2.34	1.67	£64,099
R-CHOP	[redacted]	[redacted]	[redacted]				
ICER: incremental cost-effectiveness ratio, QALYs:, quality-adjusted life years, R-CHOP: rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone							

Table 161: Base case discounted results, ibrutinib versus R-CHOP: 2 + prior LOTs

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Ibrutinib	[redacted]	[redacted]	[redacted]	£58,760	0.92	0.72	£81,966
R-CHOP	[redacted]	[redacted]	[redacted]				
ICER: incremental cost-effectiveness ratio, QALYs:, quality-adjusted life years, R-CHOP: rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone,							

Threshold analysis on comparative efficacy

A similar analysis as the one reported in Section 5 was performed using the discounted price of ibrutinib.

Table 162 shows how the ICER changes with an increase in HR of R-chemo (i.e., decreasing the comparative effectiveness of ibrutinib over R-chemo). The analysis shows that the ICER is relatively insensitive to any increase in R-chemo HR. Even when the HR is increased by as much as 90% (HR=0.53) the ICER only increases by 21.90%. This HR of 0.53 could be considered clinically implausible as this would represent a mean PFS for R-chemo of 10.09 months, which is considerably greater than that observed in clinical practice (1.9 months in Hess, 2009 and 2.8 months in Skåne).

A similar message is given by the 'threshold' analysis on the effect of adding rituximab to the HR derived from Hess, 2009 (Table 163). Decreasing the HR of adding rituximab (which increases the overall PFS HR of R-chemo, thus reducing the estimate of comparative efficacy of ibrutinib over R-chemo) does not impact the ICER substantially (for example a decrease of 45% only raises the ICER by 18.29%). The ICER raises substantially only when unrealistic HRs for the rituximab effect are tested, such as a HR of 0.17, which would mean that rituximab would add an additional benefit of 83% to the one observed in Hess, 2009.

Thus these 'threshold' analyses show how, despite there being uncertainty in the estimates of the comparative efficacy of comparators from the NICE scope in this submission, the ICER remains relatively stable.

Table 162: Threshold analysis on the PFS HR of R-chemo

Increase in HR of R-chemo	R-chemo HR	ICER	Increase in ICER
Base case	**0.28**	£74,256	
15%	0.32	£76,401	2.89%
30%	0.36	£78,621	5.88%
45%	0.41	£81,123	9.25%
60%	0.45	£83,923	13.02%
75%	0.49	£87,044	17.22%
90%	0.53	£90,518	21.90%
105%	0.57	£94,388	27.11%
120%	0.62	£98,703	32.92%
135%	0.66	£103,529	39.42%
150%	0.70	£108,948	46.72%

R-chemo: rituximab in combination with chemotherapy, HR: hazard ratio, ICER: incremental cost-effectiveness ratio

Table 163: Threshold analysis on the PFS HR for the effect of adding rituximab

Increase in HR of the effect of rituximab	Effect of rituximab HR	ICER	Increase in ICER
Base case	**0.69**	£74,256	
-15%	0.59	£76,484	3.00%
-30%	0.48	£80,341	8.19%
-45%	0.38	£87,838	18.29%
-60%	0.28	£107,387	44.62%
-75%	0.17	£229,144	208.59%
R-chemo: rituximab in combination with chemotherapy, HR: hazard ratio, ICER: incremental cost-effectiveness ratio			

Appendix 21 Parameters used to inform base case results

Table 164: Parameters used to inform base case analysis

Variable	Value	Distribution (CI)	Section
Starting age	68	Not tested in sensitivity analysis	5.1
BSA	1.95	Not tested in sensitivity analysis	5.4
Ibrutinib survival Progression free survival (PFS)			
PFS IRC Ibrutinib Exponential: Intercept	6.323	Multivariate normal distribution: var/covar 0.004587 0 0 0	5.3
PFS IRC Ibrutinib Exponential: Scale	1.000		
PFS IRC Ibrutinib Weibull: Intercept	6.359	Multivariate normal distribution: var/covar 0.006282 0.001296 0.001296 0.004437	5.3
PFS IRC Ibrutinib Weibull: Scale	1.134		
PFS IRC Ibrutinib Log-normal: Intercept	5.866	Multivariate normal distribution: var/covar 0.007999 0.002282 0.002282 0.006182	5.3
PFS IRC Ibrutinib Log-normal: Scale	1.511		
PFS IRC Ibrutinib Log-logistic: Intercept	5.857	Multivariate normal distribution: var/covar 0.007694 0.000926 0.000926 0.002626	5.3
PFS IRC Ibrutinib Log-logistic: Scale	0.902		
Ibrutinib survival Time on treatment (ToT)			
TOT Ibrutinib Exponential: Intercept	6.255	Multivariate normal distribution: var/covar 0.003623 0.00000 0.000000 0.00000	5.3
TOT Ibrutinib Exponential: Scale	1.000		
TOT Ibrutinib Weibull: Intercept	6.254	Multivariate normal distribution: var/covar 0.004338 0.000044 0.000044 0.003181	5.3
TOT Ibrutinib Weibull: Scale	1.094		
TOT Ibrutinib Log-normal: Intercept	5.723	Multivariate normal distribution: var/covar 0.0061 0.000863 0.000863 0.00412	5.3
TOT Ibrutinib Log-normal: Scale	1.43		
TOT Ibrutinib Log-logistic: Intercept	5.748	Multivariate normal distribution: var/covar 0.006197 0.000211 0.000211 0.001805	5.3
TOT Ibrutinib Log-logistic: Scale	0.853		
Ibrutinib survival Post progression survival (PPS)			
PPS IRC Ibrutinib Exponential: Intercept	5.498	Multivariate normal distribution: var/covar	5.3

Variable	Value	Distribution (CI)	Section
PPS IRC Ibrutinib Exponential: Scale	1.000	0.0200 0.0000 0.0000 0.0000	
Hazard ratios (HR) for comparative efficacy			
HR for Rituximab effect from HMRN data	0.69	Lognormal(0.42-1.13)	5.3
HR for PFS from Hess 2009 ITC	0.19	Lognormal(0.10-0.36)	5.3
HR for comparative PFS: calculated using the Hess 2009 ITC and HR for rituximab effect. Comparator vs ibrutinib	3.63	Not tested in sensitivity analysis (Calculation and parameters used to inform this are varied)	5.3
HR for comparative PFS: calculated temsirolimus data from MCL3001 as a proxy for R-chemotherapy	0.43	Lognormal(0.32-0.58)	5.3
Response Rates			
Ibrutinib complete response rate IRC response	20.81%	Beta(16.83%%-25.09%)	5.3
Ibrutinib partial response rate IRC response	45.41%	Beta(40.37%-50.49%)	5.3
HMRN overall response rate	57.93%	Beta(35.5% - 81.6%)	5.3
Odds Ratio from Hess ITC for overall response	60.26	Lognormal(7.07-513.40)	5.3
Utilities			
PFS utility	0.78	Beta(0.76-0.80)	5.4
PPS utility	0.68	Beta(0.63-0.73)	5.4
Disutility associated with R-chemotherapy regimens	0.20	Uniform (0.10-0.30)	5.4
Costs			
Inpatient non-surgical / medical cost	£2,922	Normal(£1,777-£2,931)	5.5
Biopsy cost	£4,213	Normal(£2,561-£5,358)	5.5
AE cost outpatient attendance	£162	Normal(£99-£1,813)	5.5
AE cost Infection / CMV reactivation	£563	Normal(£342-£627)	5.5
AE cost Febrile Neutropenia	£633	Normal(£385-£854)	5.5
AE cost Renal failure	£3,055	Normal(£1,857-£3,303)	5.5
AE cost Pneumonia	£2,720	Normal(£1,654-£3,917)	5.5
AE cost Major bleed	£738	Normal(£449-£1,804)	5.5
UK MRU Cost Full blood count	£3	Normal(£2-£4)	5.5
UK MRU Cost X-ray	£30	Normal(£18-£42)	5.5
UK MRU Cost Blood glucose	£1	Normal(£1-£2)	5.5
UK MRU Cost LDH	£1	Normal(£1-£2)	5.5
UK MRU Cost Lymphocyte Counts	£3	Normal(£2-£4)	5.5
UK MRU Cost Bone marrow exam	£288	Normal(£176-£402)	5.5
UK MRU Haematologist	£150	Normal(£91-£209)	5.5
UK MRU Blood transfusion	£288	Normal(£175-£401)	5.5
UK MRU Platelet infusion	£288	Normal(£175-£401)	5.5

Variable	Value	Distribution (CI)	Section
AE rates			
AE rate ibrutinib Neutropenia	16.80%	Beta(13.17%-20.77%)	5.4
AE rate ibrutinib Anaemia	8.90%	Beta(6.22%-12.00%)	5.4
AE rate ibrutinib Pneumonia	8.10%	Beta(5.55%-11.08%)	5.4
AE rate ibrutinib Leukopenia	0.00%		5.4
AE rate ibrutinib Febrile neutropenia	0.00%		5.4
AE rate ibrutinib Infection	0.00%		5.4
AE rate ibrutinib Major bleeding	4.30%	Beta(2.48%-6.59%)	5.4
AE rate ibrutinib Atrial fibrillation	5.10%	Beta(3.10%-7.56%)	5.4
AE rate ibrutinib Tumour lysis syndrome	0.50%	Beta(0.05%-1.43%)	5.4
AE rate ibrutinib Leukostasis	0.00%	Beta(0.01%-1.06%)	5.4
AE rate ibrutinib Lymphocytosis	0.80%	Beta(0.16%-1.93%)	5.4
AE rate ibrutinib Renal failure	1.10%	Beta(0.31%-2.39%)	5.4
AE rate ibrutinib Cytomegalovirus (CMV) reactivation	0.00%		5.4
AE rate ibrutinib Abnormal liver function test	0.50%	Beta(0.05%-1.43%)	5.4
AE rate comparator Neutropenia	60.00%	Beta(53.73%-66.11%)	5.4
AE rate comparator Anaemia	12.00%	Beta(8.20%-16.40%)	5.4
AE rate comparator Pneumonia	0.00%	Beta(2.30%-7.50%)	5.4
AE rate comparator Leukopenia	59.00%	Beta(52.71%-65.15%)	5.4
AE rate comparator Febrile neutropenia	17.00%	Beta(12.52%-22.00%)	5.4
AE rate comparator Infection	14.00%	Beta(9.91%-18.66%)	5.4
AE rate comparator Major bleeding	0.55%	Beta(0.10%-1.36%)	5.4
AE rate comparator Atrial fibrillation	5.50%	Beta(1.06%-13.22%)	5.4
AE rate comparator Tumour lysis syndrome	0.06%	Beta(0.01%-0.14%)	5.4
AE rate comparator Leukostasis	0.00%		5.4
AE rate comparator Lymphocytosis	0.00%		5.4
AE rate comparator Renal failure	0.01%	Beta(0.00%-0.04%)	5.4
AE rate comparator Cytomegalovirus (CMV) reactivation	1.95%	Beta(1.26%-2.78%)	5.4
AE rate comparator Abnormal liver function test	1.00%	Beta(0.16%-2.59%)	5.4

AE: adverse event, BSA: body surface area, PFS: progression-free survival, IRC: independent review committee, TOT: time on treatment, HMRN: haematological malignancy research network, HR: hazard ratio, ITC: indirect treatment comparison, PPS: post-progression survival, CMV: cytomegalovirus, MRU: medical resource use, LDH: lactate dehydrogenase

Appendix 22: BIA results using agreed discount price

Results of the base case analysis (with discount)

The base case budget impact of introducing ibrutinib with the [redacted] discount is presented in Table 165 and Table 166. The net total budget impact was £7,208,318 in 2017, increasing to £11,149,377 in 2021.

Table 165: Budget impact of introducing ibrutinib to NHSE (with discount)

	World without ibrutinib	World with ibrutinib	Budget impact
2017	£4,700,662	[redacted]	[redacted]
2018	£4,736,855	[redacted]	[redacted]
2019	£4,773,328	[redacted]	[redacted]
2020	£4,810,085	[redacted]	[redacted]
2021	£4,847,128	[redacted]	[redacted]
Total	**£23,868,058**	[redacted]	[redacted]

Table 166: Drug acquisition + administration costs in the world with ibrutinib

	2017	2018	2019	2020	2021
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FCR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone, R-CVP: rituximab + cyclophosphamide + vincristine + prednisone, FCR: fludarabine + cyclophosphamide + rituximab, RC: rituximab + cytarabine

Results of the Scenario analyses (with discount)

The estimate of MCL prevalence together with the proportion of patients receiving 2nd LOT for MCL were varied by ±20%, the same way as for the results of the BIA at list price (Scenario 1, see Table 93). Results of Scenario 1 with the discount are shown in Table 167.

Table 167: Description and results of Scenario analysis 1 of the BIA (with discount)

	Base case	High Scenario (+20%)	Low Scenario (-20%)
Prevalence of MCL	0.0016%	0.0019%	0.0013%
Prevalence of R/R MCL (among MCL)	36.69%	44.03%	29.35%
Results			
2017	[redacted]	[redacted]	[redacted]
2018	[redacted]	[redacted]	[redacted]
2019	[redacted]	[redacted]	[redacted]
2020	[redacted]	[redacted]	[redacted]
2021	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

R/R MCL: relapsed or refractory mantle cell lymphoma

Scenario analysis 2 was also replicated using the discount, with the market penetration of ibrutinib being tested (±20%), see Table 94. Results are shown in Table 168.

Table 168: Results of Scenario analysis 2 of the BIA (with discount)

	Base case	High Scenario (+20%)	Low Scenario (-20%)
2017	[redacted]	[redacted]	[redacted]
2018	[redacted]	[redacted]	[redacted]
2019	[redacted]	[redacted]	[redacted]
2020	[redacted]	[redacted]	[redacted]
2021	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Similar to the results of the scenario analyses for the BIA without the discount, The BIA estimates considering the discount were most sensitive to variations in the estimate of R/R MCL prevalence. A variation of +20% once again increased the budget impact by 42% each year (from [redacted] in 2017 to [redacted] in 2021) and a variation of -20% decreased the budget impact by 35% equally each year (from [redacted] in 2017 to [redacted] in 2021. The budget impact varied from [redacted] in 2017 to [redacted] in 2021 when the ibrutinib uptake was increased by 20%. When ibrutinib uptake was decreased by 20% it varied from [redacted] in 2017 to [redacted] in 2021.

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Single Technology Appraisal (STA)

Lymphoma (mantle cell, relapsed, refractory) - ibrutinib [ID753]

Dear [redacted]

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 13th of April 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 24th May 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] in the first instance.

Yours sincerely

Zoe Charles
Technical Advisor – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: General matters of clarification

A1. Page 26. Please clarify when the final price for ibrutinib is expected to be agreed.

A2. Page 34, Figure 2. Do the data represented in the graph relate only to incident cases i.e. new patients starting ibrutinib?

A3. Page 102, Table 38. There appears to be a number missing in the table for *"> prior lines of therapy."* Please clarify.

Section B: Clarification on effectiveness data

Searches

B1. Please clarify whether any forward citation tracking (i.e. searching for later articles which cite those already found) was conducted using included studies.

B2. Some of the Boolean logic used to combine PICO(S) concepts appears to omit parentheses which would affect the outcome of the search string. For example, in Table 101 (Embase/updated SLR), line 18 reads:

"#4 and #11 and #14 not #16"

Should this read:
"(#4 and #11 and #14) not #16" ?
Or
"#4 and #11 and (#14 not #16)" ?

The results will be different in each case.

See also line 19 of table 101: "#4 and #11 and #15 and #17 not #16" and line 13 of table 102: "#4 and #11 not #12".
Please clarify.

Clinical effectiveness review

B3**. PRIORITY.** Page 31. The text at the bottom of the page mentions the use of concomitant medications alongside ibrutinib. Please provide information on concomitant medications used alongside ibrutinib/TEMS in RAY (MCL3001), SPARK (MCL2001) and PCYC1104 (drugs used and number of patients receiving these in each group).

B4. The database searches are almost a year old. Please clarify why the searches were not updated.

B5. Page 48. The exclusion criteria state that studies without at least 85% patients with R/R MCL were excluded. As this is such a rare condition it may have been more appropriate to include any studies with R/R MCL patients provided the results are reported separately for

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this subgroup. Please provide a list of studies including subgroups of patients with R/R MCL treated with ibrutinib.

B6. Page 50. The PRISMA diagram is unclear. The 29 studies included in the write up refer to studies listed in the appendix, some of which were excluded. Please revise the diagram to reflect the correct studies that were included in the review of ibrutinib for MCL.

B7. **PRIORITY.** Page 57. Please confirm whether the FACT-Lym measure has been validated in MCL patients. Please provide a supporting reference.

B8. **PRIORITY.** Page 59, Table 14. Please clarify which outcomes were pre-specified secondary endpoints and which were exploratory analyses defined *post hoc.*

B9. **PRIORITY.** Page 59. Please clarify the *"strict criteria" based on the revised International Working Group criteria for NHL* applied in the RAY (MCL3001) study for measuring PFS.

B10. **PRIORITY.** Page 60. The company submission refers to a censor at switch analysis of overall survival within the RAY (MCL3001) study. However, the results of this analysis are not presented in the company submission. Please provide these results.

B11. Page 66, Table 17. Please provide more information on prior lines of therapy (LOT), i.e. the percentage of patients with LOT=1, 2, 3 etc.

B12. Page 70, Figure 11. The curve suggests a high OS rate at 12 months for TEMS (~60%). Please clarify why this is so different from the estimate derived from the HMRN audit (approximately 30%, HMRN Audit, Figure 9).

B13. Page 78, Figure 14. Please provide *p*-values for a difference between subgroups (test for interaction).

B14. Page 79. Please confirm that the 1 prior LOT subgroup is a *post hoc* analysis. Also, please clarify whether a treatment by subgroup interaction test was undertaken?

B15. **PRIORITY.** Multiple locations (for example, page 71, Table 22 and throughout). Please explain why some patients were "not evaluable." Were these patients excluded from the analyses or were they imputed as non-responders?

B16. **PRIORITY.** Page 95. The meaning of the highlighted text presented in the paragraph at the bottom of the page is unclear. Please state the reasons for study discontinuation for all 55 patients. Death is cited as reason for discontinuation for 44 patients but discontinuation is unclear for the remaining 11 subjects. Were the 10 patients for whom response was not evaluable included amongst those who discontinued treatment?

B17. Page 101. How is the criterion of *"no longer achieving clinical benefit"* defined in the compassionate use programme (CUP)?

B18. Page 102. How were patients identified and recruited into the CUP? What inclusion criteria were applied?

B19. **PRIORITY.** Page 105. Within the pooled dataset, please clarify which therapies patients received after they discontinued ibrutinib or TEMS (in RAY only). Please provide a list of subsequent therapies by treatment group together with numbers of patients receiving each.

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B20. Page 108, Tables 41 and 42. What is the date of the updated datacut?

B21. Page 110. Please provide *p*-values for differences in AEs for the following categories: "all grade 3/4 adverse events", "serious adverse events" and "severe adverse events."

B22. Page 123. Please clarify when the long term follow-up data from SPARK will be available. If these data are available now, please provide them in the response.

Section C: Clarification on cost-effectiveness data

Health-related quality of life

C1. PRIORITY. Page 150. Please clarify why the company considers that the EQ-5D is unable to fully capture impacts of fatigue through the dimensions of usual activities, mobility and self-care. Is the argument that the EQ-5D cannot measure these elements in this population, or that the societal valuations of the tariff are incorrect? Also, please suggest a better preference-based alternative. Please clarify how the company's proposed longitudinal study including the EQ-5D and a disease-specific instrument will reduce this apparent uncertainty.

C2. PRIORITY. Page 151. Please provide justification for the assumed value of 0.015 QALYs lost due to R-CHEMO per cycle. If possible, provide evidence supporting the magnitude of this utility decrement. Please also comment on the resulting assumption that whilst patients are progression-free on R-CHEMO, their HRQoL is lower than when they have failed R-CHEMO and have progressive disease. Please also comment on why the toxicity decrement is applied universally to all patients rather than based on the incidence and duration of chemotherapy-related adverse events.

C3. Page 149. Please comment on whether the "euphoric effect" of ibrutinib has been observed and measured using the EQ-5D within a blinded study design.

C4. Page 145. Please clarify the frequency of EQ-5D measurement in the SPARK (MCL2001) study.

C5. Page 146. Given the dearth of HRQoL values identified in the company's review of utility studies, why were studies undertaken in similar disease areas not considered (as was done in Technology Appraisal 370)?

Evidence synthesis and indirect treatment comparisons

C6. Page 105. Please clarify which formal tests (if any) were used to determine whether it was appropriate to combine data from the ibrutinib studies.

C7. Page 80. Please clarify why study MCL002 (SPRINT) was not included in the indirect comparison.

C8. PRIORITY. Page 23. Please explain why the ITC with adjustment for the "rituximab effect" was not undertaken for the outcome of overall survival.

C9. PRIORITY. Page 82. Indirect comparisons were made using the Bucher method, which is essentially the same as a fixed effect network meta-analysis (NMA). Please justify the use

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of this approach. Also, please provide results from a random effects NMA, with predictive intervals, to illustrate the uncertainty in a future study (as recommended by the NICE Technical Support Document 3 "Heterogeneity: subgroups, meta-regression, bias and bias adjustment"). In the absence of further information on which to base the choice of prior, use of a weakly informative prior may be appropriate (see NICE TSD3 pg 73 and Turner *et al.* 2012, "Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews").

C10. PRIORITY. Page 120. Please clarify which data from the HMRN audit have been used to estimate the "rituximab effect" (give page numbers and refer to specific figures/tables used). Please also explain the precise method used to derive the hazard ratio.

C11. PRIORITY. Page 139. A point estimate of 0.28 is provided for the adjusted comparison of ibrutinib versus R-CHEMO. Please clarify the uncertainty associated with this treatment comparison. Also, please provide estimates for this treatment comparison from a random effects NMA (including RAY, Hess and HMRN). Though there may be concerns over combining these studies in a NMA, the ERG considers that a random effects NMA would give a better representation of the uncertainty than the presented adjustment.

Model structure and surrogate relationships

C12. PRIORITY. Page 25. Please clarify why overall survival was modelled as PFS+PPS rather than by fitting curves to the observed Kaplan-Meier data on overall survival from the point of randomisation. Please comment on the potential limitations of this approach with reference to the statement on page 71 which states that: "rapid progressors" may have a different mortality hazard to slower progressors.

C13. Page 25. With reference to the statistical analyses presented in Lee *et al* (*Ann Oncol*, 2011), please justify the statement *"Available literature within MCL indicates that PFS is a good surrogate for OS."*

C14. Page 130. Why were PFS follow-up costs modelled according to best overall response? Would this response be maintained over the entire progression-free period?

C15. Page 132. Both "Method 1 – fixed PPS" and "Method 2 – sequential approach" are referred to as the base case. However, in the results section of the company submission (page 166), only Method 1 is presented as the base case. Please confirm that Method 1 (fixed PPS) is the base case and that Method 2 (sequential approach) should be considered as a scenario analysis.

C16. Page 136. The CS refers to a *"fixed PPS period",* however from scrutiny of the model it appears that it is the risk of death conditional on prior progression that is fixed, rather than the sojourn time in the post-progression state. Did you intend to assume a fixed post-progression sojourn time for all treatment groups?

C17. PRIORITY. Page 142. The company submission states *"A constant rate of mortality of 10.83% per cycle was assumed to avoid the requirement to use tunnel states to track patient movements into PPS."* Please clarify whether the hazard rate for post-progression mortality appears to be time-dependent and if so, please justify why time-dependent hazards have not been included in the model.

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C18. PRIORITY. Please justify exclusion of subsequent-line therapy costs from the health economic model.

C19. PRIORITY. Please provide evidence of individual-level surrogacy (i.e. individual-level correlation) of PFS for overall survival using the data from RAY (MCL3001), SPARK (MCL2001) and PCYC1104.

Survival modelling

C20. PRIORITY. Why was a treatment switching analysis not presented for the RAY data to adjust for confounding due to TEMS patients crossing over to ibrutinib? Is such an analysis planned?

C21. Page 137. The company submission states *"Based upon the log-cumulative hazard plot which indicated that the use of a standard parametric curve was appropriate…"* The plot presented in Appendix 15 appears to show log(-log($S(t)$)) vs log(t) for PFS. This is not appropriate for assessing accelerated failure time models. Please present the appropriate plots for the log logistic and log normal survivor functions.

C22. PRIORITY. Page 141. The model assumes a fixed rate of death for patients whilst in the progression-free state (pre-progression mortality). This appears to assume that the hazard of pre-progression death is proportional to the hazard of progression. Please provide evidence from the ibrutinib studies which supports this assumption.

C23. PRIORITY. Pages 155-156, Figure 36. Given that the Kaplan-Meier curve presented in Figure 36 appears to be complete (with no right censoring), please explain why a parametric curve was fitted to the time on treatment data. Please comment on the apparently poor fit of the parametric curve. Please also comment on why the observed hazard of discontinuing ibrutinib increases sharply at around 27 months.

C24. Pages 137 and 155. Please clarify why the generalised gamma, generalised F and Gompertz curves were not fitted to the available time-to-event data for the outcomes of PFS and time to treatment discontinuation.

C25. Pages 141-143. Please clarify why only the exponential model was fitted to the available time-to-event data for pre-progression mortality.

C26. Pages 141-143. Please clarify why only the exponential model was fitted to the available time-to-event data for post-progression mortality.

C27. Given that the comparative effectiveness of ibrutinib versus chemotherapy is modelled on the basis of a relative hazard ratio, please comment on the validity of applying hazard ratios to accelerated failure time survivor functions.

C28. Please clarify why a scenario using only the RAY (MCL3001) trial, rather than the pooled dataset, was not presented in the health economic analysis.

Questions relating to the model

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C29. Worksheet “Cost derivation”, cell B2. Please clarify why the model refers to “Scottish tariffs”.

C30. Worksheet “PFS Curve fits to KM data.” Please comment on the poor fit of the log logistic survivor function in the graph.

C31. PRIORITY. Given that the sequential method attempts to model ibrutinib->R-CHEMO versus R-CHEMO, please explain why when the sequential method is selected, the mean survival gain for ibrutinib remain unchanged, yet the R-CHEMO survival decreases.

C32. Worksheet “Parameters”, cell Q28. Why is no uncertainty around the compliance rate assumed?

C33. Worksheet “AE”. With reference to the ibrutinib studies, please comment on the validity of the assumption that adverse events occur only once during the first cycle.

C34. Worksheet “Parameters”, cells D28:D29. Please justify the assumption of equal relative dose intensity in both the ibrutinib and R-CHEMO groups. Why were other external data not used to inform this parameter for the R-CHEMO group?

C35. PRIORITY. Worksheet “Clinical Inputs” overall survival graph. Please comment on the discrepancy between the model predicted overall survival and the observed Kaplan-Meier curve for ibrutinib.

Section D: Data request

D1. Please provide estimates of EQ-5D utilities for the progression-free and post-progression states for the TEMS group in the RAY (MCL3001) trial.

D2. Please provide individual patient-level survival data for overall survival for ibrutinib from RAY (MCL3001), SPARK (MCL2001) and PCYC1104. Please present the equivalent data for TEMS from RAY (MCL3001). If possible, apply crossover adjustment methods to the data from RAY (MCL3001).

Janssen Clarification Questions Response
Lymphoma (mantle cell, relapsed, refractory) - ibrutinib [ID753]

Section A: General matters of clarification

A1. Page 26. Please clarify when the final price for ibrutinib is expected to be agreed.

Janssen do not yet know. This will be confirmed.

A2. Page 34, Figure 2. Do the data represented in the graph relate only to incident cases i.e. new patients starting ibrutinib?

Yes the data represent only incident cases / new patients starting ibrutinib.

A3. Page 102, Table 38. There appears to be a number missing in the table for *"> prior lines of therapy."* Please clarify.

The number missing is 3. The line in Table 38: Baseline characteristics of the 715 patients in the CUP should read:

[redacted]	[redacted]

Section B: Clarification on effectiveness data

Searches

B1. Please clarify whether any forward citation tracking (i.e. searching for later articles which cite those already found) was conducted using included studies.

No forward citation tracking was conducted using included studies. The clinical systematic literature review (SLR) has however been updated since the submission by Janssen– please see question B4 for details of the updated clinical SLR.

B2. Some of the Boolean logic used to combine PICO(S) concepts appears to omit parentheses which would affect the outcome of the search string. For example, in Table 101 (Embase/updated SLR), line 18 reads:

"#4 and #11 and #14 not #16"

Should this read:

"(#4 and #11 and #14) not #16" ?

Or

"#4 and #11 and (#14 not #16)" ?

The results will be different in each case.

See also line 19 of table 101: “#4 and #11 and #15 and #17 not #16” and line 13 of table 102: “#4 and #11 not #12”.

Please clarify.

In lines #18 and #19, the Boolean operators (“AND”) are removed in the search history output on the Embase.com platform. The database reads the search syntax correctly, combining all of the “AND” strings before applying the “NOT” exclusion. Parentheses were not included for Embase.com in an effort to streamline the look of the search history.

Clinical effectiveness review

B3**. PRIORITY.** Page 31. The text at the bottom of the page mentions the use of concomitant medications alongside ibrutinib. Please provide information on concomitant medications used alongside ibrutinib/TEMS in RAY (MCL3001), SPARK (MCL2001) and PCYC1104 (drugs used and number of patients receiving these in each group).

RAY (MCL3001)

Details of concomitant medications of special interest used in RAY (MCL3001) are presented in Table 1 below.

Table 1: Concomitant medications of special interest in RAY (MCL3001); Safety analysis set

	Ibrutinib	Temsirolimus	Total
Analysis set: safety	139	139	278
Received medications of special interest	[redacted]	[redacted]	[redacted]
Anti-coagulation	[redacted]	[redacted]	[redacted]
Enoxaparin sodium	[redacted]	[redacted]	[redacted]
Heparin	[redacted]	[redacted]	[redacted]
Nadroparin calcium	[redacted]	[redacted]	[redacted]
Dalteparin	[redacted]	[redacted]	[redacted]
Enoxaparin	[redacted]	[redacted]	[redacted]
Nadroparin	[redacted]	[redacted]	[redacted]
Dalteparin sodium	[redacted]	[redacted]	[redacted]
Tinzaparin sodium	[redacted]	[redacted]	[redacted]
Acenocoumarol	[redacted]	[redacted]	[redacted]
Antithrombin iii	[redacted]	[redacted]	[redacted]
Certoparin sodium	[redacted]	[redacted]	[redacted]
Fondaparinux sodium	[redacted]	[redacted]	[redacted]
Mesoglycane sodium	[redacted]	[redacted]	[redacted]
Phenprocoumon	[redacted]	[redacted]	[redacted]
Rivaroxaban	[redacted]	[redacted]	[redacted]
Sulodexide	[redacted]	[redacted]	[redacted]
Tinzaparin	[redacted]	[redacted]	[redacted]
Bemiparin	[redacted]	[redacted]	[redacted]
Bemiparin sodium	[redacted]	[redacted]	[redacted]
Dabigatran etexilate	[redacted]	[redacted]	[redacted]
Dabigatran etexilate mesilate	[redacted]	[redacted]	[redacted]
Heparin sodium	[redacted]	[redacted]	[redacted]
Heparinoid	[redacted]	[redacted]	[redacted]

	Ibrutinib	Temsirolimus	Total
Protease	[redacted]	[redacted]	[redacted]
Warfarin	[redacted]	[redacted]	[redacted]
Anti-platelets	[redacted]	[redacted]	[redacted]
Acetylsalicylic acid	[redacted]	[redacted]	[redacted]
Ibuprofen	[redacted]	[redacted]	[redacted]
Acetylsalicylate lysine	[redacted]	[redacted]	[redacted]
Clopidogrel	[redacted]	[redacted]	[redacted]
Clopidogrel bisulfate	[redacted]	[redacted]	[redacted]
Meloxicam	[redacted]	[redacted]	[redacted]
Naproxen	[redacted]	[redacted]	[redacted]
Clopidogrel besylate	[redacted]	[redacted]	[redacted]
Indometacin	[redacted]	[redacted]	[redacted]
Ketoprofen	[redacted]	[redacted]	[redacted]
Ketorolac tromethamine	[redacted]	[redacted]	[redacted]
Loxoprofen sodium	[redacted]	[redacted]	[redacted]
Paynocil	[redacted]	[redacted]	[redacted]
Triflusal	[redacted]	[redacted]	[redacted]
Zaltoprofen	[redacted]	[redacted]	[redacted]
Carol-f	[redacted]	[redacted]	[redacted]
Dexketoprofen	[redacted]	[redacted]	[redacted]
Dexketoprofen trometamol	[redacted]	[redacted]	[redacted]
Diclofenac potassium	[redacted]	[redacted]	[redacted]
Ketorolac	[redacted]	[redacted]	[redacted]
Ticlopidine hydrochloride	[redacted]	[redacted]	[redacted]
CYP3A/4 inhibitors	[redacted]	[redacted]	[redacted]
Ciprofloxacin	[redacted]	[redacted]	[redacted]
Clarithromycin	[redacted]	[redacted]	[redacted]
Azithromycin	[redacted]	[redacted]	[redacted]
Fluconazole	[redacted]	[redacted]	[redacted]
Chloramphenicol	[redacted]	[redacted]	[redacted]
Erythromycin	[redacted]	[redacted]	[redacted]
Itraconazole	[redacted]	[redacted]	[redacted]
Voriconazole	[redacted]	[redacted]	[redacted]
Amiodarone	[redacted]	[redacted]	[redacted]
Cimetidine	[redacted]	[redacted]	[redacted]
Diltiazem	[redacted]	[redacted]	[redacted]
Fluvoxamine	[redacted]	[redacted]	[redacted]
Verapamil	[redacted]	[redacted]	[redacted]
Norfloxacin	[redacted]	[redacted]	[redacted]
CYP3A/4 inducers	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]
Carbamazepine	[redacted]	[redacted]	[redacted]
Growth factors/cytokines	[redacted]	[redacted]	[redacted]
Filgrastim	[redacted]	[redacted]	[redacted]
Lenograstim	[redacted]	[redacted]	[redacted]
Granulocyte colony stimulating factor	[redacted]	[redacted]	[redacted]
Darbepoetin alfa	[redacted]	[redacted]	[redacted]
Livalavin	[redacted]	[redacted]	[redacted]

	Ibrutinib	Temsirolimus	Total
Pegfilgrastim	[redacted]	[redacted]	[redacted]
Epoetin alfa	[redacted]	[redacted]	[redacted]
Erythropoietin	[redacted]	[redacted]	[redacted]
Transfusions	[redacted]	[redacted]	[redacted]
Packed Red Blood Cells (Units)	[redacted]	[redacted]	[redacted]
Platelets (cc)	[redacted]	[redacted]	[redacted]
Whole Blood (Units)	[redacted]	[redacted]	[redacted]
Fresh Frozen Plasma (Units)	[redacted]	[redacted]	[redacted]
Cryoprecipitate	[redacted]	[redacted]	[redacted]
Filtered Plateletaphresis	[redacted]	[redacted]	[redacted]
Leukocyte(Packed)	[redacted]	[redacted]	[redacted]
Source: RAY (MCL3001) Clinical Study Report[1]			

SPARK (MCL2001)

Details of selected concomitant medicines of interest use in SPARK (MCL2001) are presented in Table 2 below.

Table 2: Selected concomitant medications of interest in SPARK (MCL2001); All-treated population

	Ibrutinib
Population: all treated	120
Subjects received any anticoagulants	[redacted]
Enoxaparin sodium	[redacted]
Dabigatran etexilate mesilate	[redacted]
Heparin	[redacted]
Enoxaparin	[redacted]
Rivaroxaban	[redacted]
Warfarin sodium	[redacted]
Fondaparinux sodium	[redacted]
Heparin calcium	[redacted]
Heparin sodium	[redacted]
Alteplase	[redacted]
Dalteparin	[redacted]
Dalteparin sodium	[redacted]
Fluindione	[redacted]
Nadroparin calcium	[redacted]
Subjects received any antiplatelets	[redacted]
Ibuprofen	[redacted]
Clopidogrel bisulfate	[redacted]
Naproxen	[redacted]
Naproxen sodium	[redacted]
Cilostazol	[redacted]
Ketoprofen	[redacted]
Ketorolac	[redacted]
Ketorolac tromethamine	[redacted]
Lornoxicam	[redacted]
Meloxicam	[redacted]
Prasugrel hydrochloride	[redacted]

	Ibrutinib
Subjects received growth factors/cytokines	[redacted]
Filgrastim	[redacted]
Pegfilgrastim	[redacted]
Erythropoietin human	[redacted]
Granulocyte colony stimulating factor	[redacted]
Subjects received transfusions	[redacted]
Packed red blood cells (units)	[redacted]
Platelets (cc)	[redacted]
Whole blood (units)	[redacted]
Fresh frozen plasma (units)	[redacted]
Prefiltered leukopoor pc	[redacted]
Unknown	[redacted]
Source: SPARK (MCL2001) Clinical Study Report[2]	

PCYC1104

Details of selected concomitant medicines of interest use in PCYC1104 are presented in Table 3 below.

Table 3: Concomitant medications of special interest in PCYC1104; All-treated population

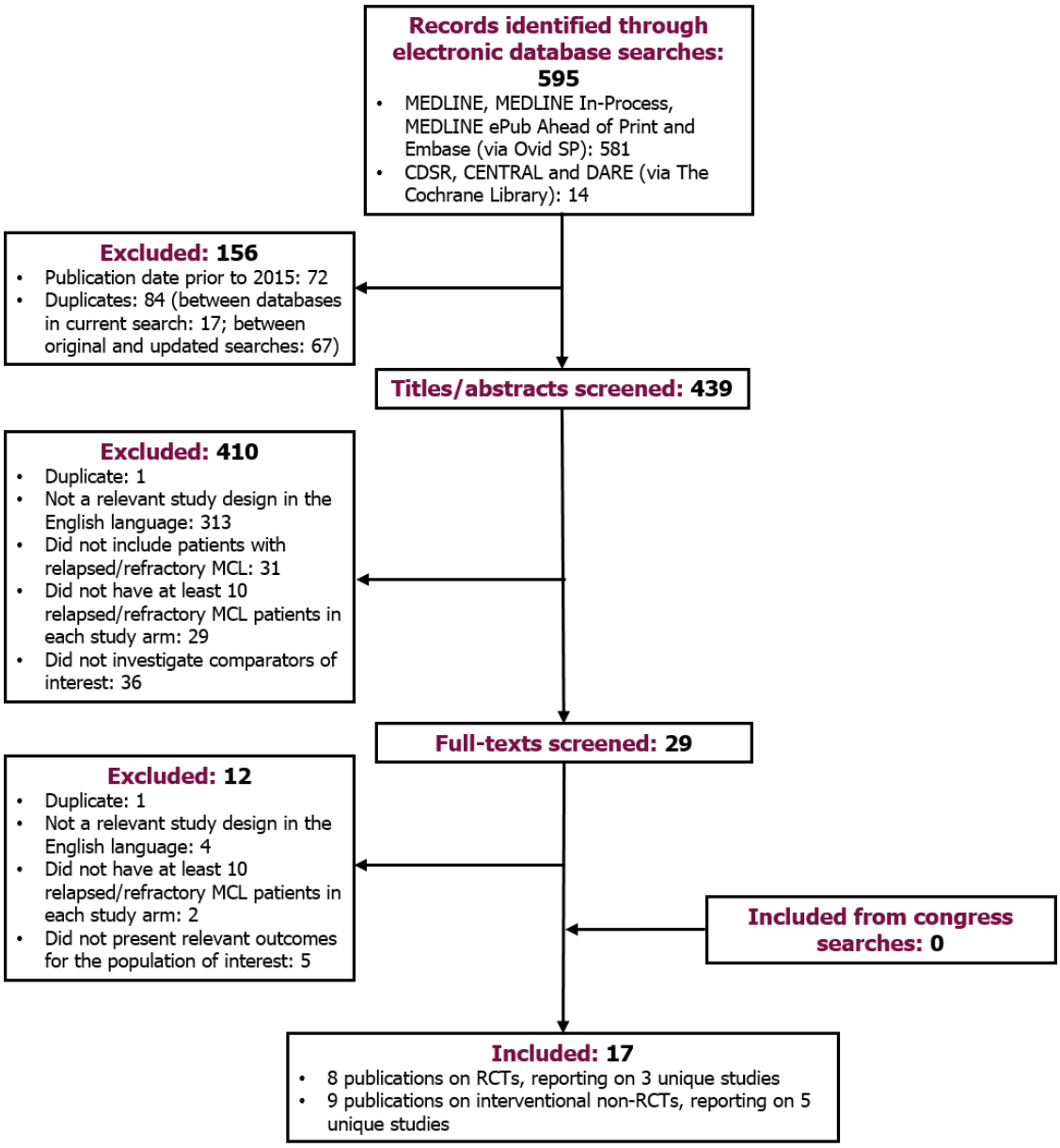
	Ibrutinib		
	Bortezomib-Naive	Bortezomib-Exposed	Combined
Population: all treated	63	48	111
Received medications of special interest	[redacted]	[redacted]	[redacted]
Coagulation	[redacted]	[redacted]	[redacted]
Acetylsalicylic acid	[redacted]	[redacted]	[redacted]
Enoxaparin	[redacted]	[redacted]	[redacted]
Warfarin	[redacted]	[redacted]	[redacted]
Clopidogrel	[redacted]	[redacted]	[redacted]
Heparin	[redacted]	[redacted]	[redacted]
Tinzaparin	[redacted]	[redacted]	[redacted]
Alteplase	[redacted]	[redacted]	[redacted]
Dalteparin	[redacted]	[redacted]	[redacted]
Nadroparin	[redacted]	[redacted]	[redacted]
Transfusions	[redacted]	[redacted]	[redacted]
Red blood cells, concentrated	[redacted]	[redacted]	[redacted]
Platelets	[redacted]	[redacted]	[redacted]
Red blood cells	[redacted]	[redacted]	[redacted]
Blood, whole	[redacted]	[redacted]	[redacted]
Platelets, concentrated	[redacted]	[redacted]	[redacted]
Growth factors/ cytokines	[redacted]	[redacted]	[redacted]
Filgrastim	[redacted]	[redacted]	[redacted]
Strong CYP3A inhibitor	[redacted]	[redacted]	[redacted]
Clarithromycin	[redacted]	[redacted]	[redacted]
Itraconazole	[redacted]	[redacted]	[redacted]
Source: PCYC1104 Clinical Study Report[3]			

B4. The database searches are almost a year old. Please clarify why the searches were not updated.

All three SLRs (clinical SLR, cost-effectiveness, cost and resource use SLR, and health-related quality of life SLR) are currently being updated. These June 2016 updates to the SLRs apply a consistent methodology to the original SLRs (which had also been updated in June 2015) and the same eligibility criteria for inclusion and exclusion of studies. The final results of these three June 2016 update SLRs will be available by mid-June 2016 and provided to NICE and the ERG upon completion.

At this point in time, for the June 2016 clinical SLR update the database searches have been run and all abstracts and full texts have been reviewed. In total, 17 publications corresponding to 8 studies (3 RCTs, 5 non-RCTs) were deemed to meet the eligibility criteria for inclusion in the clinical SLR update, as shown in the PRISMA flow diagram (Figure 1).

Figure 1: PRISMA flow diagram for the update to the clinical SLR (June 2016)



An overview of the 8 included studies and their associated publications is provided in Table 4. Importantly, none of the identified studies provided any additional evidence to inform relative effectiveness estimates for ibrutinib and the appropriate comparators beyond the evidence that had already been considered and presented in our submission.

Table 4: Summary of studies included in the update SLR and discussion of their relevance to the decision problem of the submission

	Trial identifier	Primary publication identified by SLR	Linked secondary publications identified by the SLR	MCL population or MCL sub-population?	Intervention	Relevance to submission
RCTs						
1	RAY (MCL3001)	Dreyling et al. 2016a[4]	Dreyling et al. 2016b[5] Rule et al. 2015a[6]	MCL population	Ibrutinib monotherapy vs. temsirolimus	Study relevant to the decision problem and was presented in full in the submission.
2	MCL-002 (SPRINT)	Primary journal article for MCL-002 (SPRINT) identified by original clinical SLR	Trneny et al. 2015a[7] Trneny et al. 2015b[8] Trneny et al. 2016[9]	MCL population	Lenalidomide monotherapy vs. investigator's choice	Study already discussed in Appendix 4 (Table 106) and Appendix 9 of our submission. Not relevant. Although this study contained an investigator's choice arm, similarly to Hess, 2009 these interventions were single-agent chemotherapy options that are not used in current UK clinical practice. However, unlike Hess, 2009, the lenalidomide comparator in this study does not permit an ITC with the RAY (MCL3001) study. Therefore, this study could not be used to inform the submission.
3	Stil NHL 2–2003 (NCT01456351)	Rummel et al. 2016[10]	Anonymous 2016[11]	MCL sub-population	Bendamustine plus rituximab vs. fludarabine plus rituxiumab	Study already discussed in Appendix 9 (Table 113) of our submission.
Non-RCTs						
1	PCYC1104	Primary journal article for PCYC1104 identified by original clinical	Wang et al. 2015a[12] Dreyling et al. 2015[13]	MCL population	Ibrutinib monotherapy	Study relevant to the decision problem and was presented in full in the submission.

		SLR				
2	SPARK (MCL2001)	Rule et al. 2015b[14]		MCL population	Ibrutinib monotherapy	Study relevant to the decision problem and was presented in full in the submission. The Rule *et al.* congress abstract identified in this June 2016 clinical SLR update presents results for the same data cut-off as presented in Section 4.11.2 of our submission (ie. 29th April 2014). This abstract presents a small number of results not reported in our submission: Proportion of patients with stable disease or better but progressive disease within 12 months ('moderate response' [MR] group) Proportion of patients with stable disease or better maintained for >12 months ('durable response' [DR} group) Median PFS in the MR and DR groups Proportion of 'responders' achieving clinically meaningful improvement in quality of life
3	Not reported	Czuczman et al. 2015[15]	Lamonica et al. 2015[16]	MCL population	Bendamustine plus rituximab	Study already discussed in Appendix 4 (Table 107) of our submission. Interventions considered are not relevant to the decision problem.
4	Not reported	Kolibaba et al. 2015[17]		MCL population	Ibrutinib in combination with ublituximab	New study not considered in original submission. However, this study is not relevant to the decision problem (i.e. adds no more relevant evidence) as it considers an intervention of ibrutinib in combination with another therapy as opposed to ibrutinib monotherapy.
5	NCT01880567	Wang et al. 2016[18]	Wang et al. 2015b[19] Wang et al. 2015c[20]	MCL population	Ibrutinib in combination with rituximab	New study not considered in original submission. However, this study is not relevant to the decision problem (i.e. adds no more relevant evidence) as it considers an intervention of ibrutinib in combination with another therapy as opposed to ibrutinib monotherapy.

B5. Page 48. The exclusion criteria state that studies without at least 85% patients with R/R MCL were excluded. As this is such a rare condition it may have been more appropriate to include any studies with R/R MCL patients provided the results are reported separately for this subgroup. Please provide a list of studies including subgroups of patients with R/R MCL treated with ibrutinib.

No studies were excluded where results for R/R MCL subgroups were reported separately (provided there were at least 10 patients with MCL in each treatment arm). The 85% criterion was only applied to studies of mixed populations for which results were not reported separately.

B6. Page 50. The PRISMA diagram is unclear. The 29 studies included in the write up refer to studies listed in the appendix, some of which were excluded. Please revise the diagram to reflect the correct studies that were included in the review of ibrutinib for MCL.

To clarify, the clinical SLR reported in the submission identified a total of 29 studies (4 RCTs, 25 non-RCTs) that met all eligibility criteria and were therefore ultimately included in the SLR (i.e. deemed to meet the eligibility criteria at full text review). As such, Table 106 in Appendix 4 listed all 29 studies for transparency of reporting.

However, although all 29 of these studies were included in the SLR on the basis of meeting the eligibility criteria, some of these studies were not considered relevant to the decision problem of the submission. For example, the list of interventions and comparators considered eligible by the criteria of the SLR included a number of comparators that were not relevant to the specifics of the decision problem as they are therapies that are not used in current UK clinical practice. Table 106 in Appendix 4 therefore also documented which of the 29 studies were not considered relevant to the decision problem, in order to transparently justify why these studies did not inform the evidence base within the submission. Of the 25 non-RCTs meeting the eligibility criteria of the SLR and presented in Table 106 in Appendix 4, 22 studies were noted as not relevant to the submission on the basis of not considering a relevant intervention or comparator for the decision problem. Of the 4 RCTs meeting the eligibility criteria of the SLR and presented in Table 106 in Appendix 4, 2 studies were noted as not relevant to the submission: one (Trneny 2014) on the basis of not permitting an ITC with the RAY (MCL3001) study and one (Forstpointner 2004) on the basis of not considering a relevant intervention or comparator for the decision problem.

Please note that some small errors in the text of the submission have been identified upon revisiting these sections. The text at the beginning of Appendix 4 refers to a total of 28 studies and a total of 75 publications having been identified by the clinical SLR. As per the PRISMA flow diagram in Section 4.1 and the number of studies and references provided in Table 106 of Appendix 4, this text should instead refer to 29 studies and 74 publications.

B7. **PRIORITY.** Page 57. Please confirm whether the FACT-Lym measure has been validated in MCL patients. Please provide a supporting reference.

The FACT-Lym was originally developed to assess functional status and well-being of patients with non-Hodgkin lymphoma[21] and has been validated for use in a relapsed/refractory MCL population, showing ability to differentiate MCL patients based on

ECOG performance status and responsiveness to change associated with worsening health status[21]. The FACT-Lym questionnaire has been used in other MCL clinical trials and to assess the HRQoL of patients with other haematological diseases, such as myelofibrosis[22, 23].

B8. **PRIORITY.** Page 59, Table 14. Please clarify which outcomes were pre-specified secondary endpoints and which were exploratory analyses defined *post hoc.*

Of the outcomes listed in Table 14, overall response rate (complete response + partial response), overall survival, one-year survival rate, duration of response, time to next treatment, FACT-Lym, EQ-5D-5L and safety were all pre-specified secondary endpoints. PFS2 was a pre-specified exploratory endpoint.

As detailed in B14, the analysis of 1 prior line of therapy (LOT) was a *post hoc analysis.*

B9. **PRIORITY.** Page 59. Please clarify the *"strict criteria" based on the revised International Working Group criteria for NHL* applied in the RAY (MCL3001) study for measuring PFS.

The criteria used to measure PFS in RAY (MCL3001) were those defined in the paper by Cheson 2007, see Table 4. The use of the term 'strict criteria' had intended to refer to the fact that the Cheson criteria represent a well-defined classification system with strictly defined clinical criteria for assigning different levels of response.

Table 5: Explanation of the various levels of response: revised Cheson criteria[24]

Response	Definition	Nodal masses	Spleen, Liver	Bone marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		

Relapsed disease or PD	Any new lesion or increase by 50% of previously involved sites from nadir	Appearance of a new lesion(s)1.5 cm in any axis, 50% increase in SPD of more than one node, or 50% increase in longest diameter of a previously identified node1 cm in short axis	50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy
CR: complete remission, FDG: [18F] fluorodeoxyglucose, PET: positron emission tomography, CT: computed tomography, PR: partial remission, SPD: sum of the product of the diameters, SD: stable disease, PD: progressive disease				

B10. **PRIORITY.** Page 60. The company submission refers to a censor at switch analysis of overall survival within the RAY (MCL3001) study. However, the results of this analysis are not presented in the company submission. Please provide these results.

See Table 6. The hazard ratio (HR) is consistent to what observed in the intent-to-treat (ITT) analysis (0.76). The HR may become significant in favour of ibrutinib by the time of the final datacut of RAY (MCL3001) (final patient expected to be visited in November 2016). It may be that patients who progressed on TEM and crossed over to ibrutinib or other effective (possibly unlicensed) subsequent treatment, are still alive thanks to the effect of salvage therapy.

The table below shows that 58.2% of TEM patients were censored in this analysis, of which 22.3% crossed over to ibrutinib as part of the amended protocol or as subsequent treatment.

Table 6: Overall survival censored at initiation of subsequent ibrutinib therapy; intent-to-treat analysis set in RAY (MCL3001)

	Ibrutinib	Temsirolimus
Analysis set: intent-to-treat	139	141
Subject status		
Died (event)	[redacted]	[redacted]
Censored	[redacted]	[redacted]
Overall Survival (months)[a]		
25% quantile (95% CI)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
75% quantile (95% CI)	[redacted]	[redacted]
6-months OS rate (95% CI)	[redacted]	[redacted]
12-months OS rate (95% CI)	[redacted]	[redacted]
18-months OS rate (95% CI)	[redacted]	[redacted]
24-months OS rate (95% CI)	[redacted]	[redacted]
P-value[b]	[redacted]	
Hazard ratio (95% CI)[c]	[redacted]	
NE=not estimable; [a] Based on Kaplan-Meier product limit estimates. [b] Based on stratified Log rank test with MIPI and prior lines of therapy from IWRS as stratification factors. [c] Based on stratified Cox´s model with MIPI and prior lines of therapy from IWRS as stratification factors. A hazard ratio < 1 indicates an advantage for Ibrutinib.		

B11. Page 66, Table 17. Please provide more information on prior lines of therapy (LOT), i.e. the percentage of patients with LOT=1, 2, 3 etc.

Table 7: Details on number of previous treatments received by patients in RAY (MCL3001)

Prior Line	Ibrutinib (n=139)	Temsirolimus (n=141)
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
9	[redacted]	[redacted]

B12. Page 70, Figure 11. The curve suggests a high OS rate at 12 months for TEMS (~60%). Please clarify why this is so different from the estimate derived from the HMRN audit (approximately 30%, HMRN Audit, Figure 9).

The OS estimates between TEM in the RAY (MCL3001) study and HMRN audit are indeed different. This can be explained due to a number of reasons:

1. Different comparators: as can be observed in Table 7 of the HMRN audit, most patients after relapse received R-chemo and none of them received TEM
2. Results from a clinical trial are likely to be different to real life results. A proportion of patients observed in the HMRN audit would have likely not met the criteria to be enrolled in RAY (MCL3001)
3. Results from the HMRN audit are uncontrolled and include a smaller sample size (n=57), which increases uncertainty.

Results from Table 9 of the HMRN audit were tested within the submission document (last scenario analysis of Table 159). When OS of R-chemo in the model is adjusted to be close to the one of R-chemo in HMRN, the ICER decreases considerably as would be expected.

B13. Page 78, Figure 14. Please provide *p*-values for a difference between subgroups (test for interaction).

Table 8: Subgroup analysis of PFS in RAY (MCL3001): p-values for test for interaction

Variable	Interaction p-value for PFS (IRC)
Age	[redacted]
Gender	[redacted]
Race	[redacted]
Region	[redacted]
# prior therapies	[redacted]
Prior Lenalidomide	[redacted]
Prior Bortezomib	[redacted]
RAI-Stage	[redacted]
Extranodal	[redacted]
MIPI	[redacted]

Variable	Interaction p-value for PFS (IRC)
ECOG at Baseline	[redacted]
Bulky Disease(>=5cm)	[redacted]
Bulky Disease(>=10cm)	[redacted]
Blastoid History	[redacted]
Refractory disease	[redacted]
Use of CYP3A4 Inhibitor	[redacted]
Use of CYP3A4 Inducer	[redacted]
* MIPI(IWRS)	[redacted]
* # prior therapies(IWRS)	[redacted]
(*) Based on IWRS (interactive web response system) assignment PFS: progression-free survival, IRC: Independent Review Committee	

B14. Page 79. Please confirm that the 1 prior LOT subgroup is a *post hoc* analysis. Also, please clarify whether a treatment by subgroup interaction test was undertaken?

With regards to the subgroup analysis in RAY (MCL3001), the analysis of 1 prior LOT was a *post hoc analysis.* No treatment by subgroup test for interaction was undertaken.

B15. **PRIORITY.** Multiple locations (for example, page 71, Table 22 and throughout). Please explain why some patients were “not evaluable.” Were these patients excluded from the analyses or were they imputed as non-responders?

[redacted]

Response analysis in RAY (MCL3001) used the intention-to-treat population and those patients deemed “not evaluable” were included in this and imputed as non-responders.

[redacted] Response analyses in SPARK (MCL2001) were conducted in the ‘response evaluable’ population’ hence these [redacted] were excluded from the response analyses.

In PCYC1104, patients were deemed “not evaluable” if they did not receive at least 1 dose of study drug, have measurable disease at baseline and have at least 1 adequate post-treatment disease assessment by investigator before the start of subsequent anti-cancer therapy. [redacted] Response analyses in PCYC1104 were conducted in the all-treated population and therefore this patient was imputed as a non-responder.

B16. **PRIORITY.** Page 95. The meaning of the highlighted text presented in the paragraph at the bottom of the page is unclear. Please state the reasons for study discontinuation for all 55 patients. Death is cited as reason for discontinuation for 44 patients but discontinuation is unclear for the remaining 11 subjects. Were the 10 patients for whom response was not evaluable included amongst those who discontinued treatment?

At the time of the clinical data cut-off in the SPARK (MCL2001) study (29th of April 2014), 55 out of the 120 patients initially enrolled in the study had discontinued the study. The reason for study discontinuation for these 55 patients was [redacted].

The primary analysis of overall response rate was performed using the response evaluable population (n=110), which included all enrolled subjects who received at least 1 dose of study drug, had measurable disease at baseline, and underwent at least 1 post-baseline tumour/response assessment. [redacted]

B17. Page 101. How is the criterion of *“no longer achieving clinical benefit”* defined in the compassionate use programme (CUP)?

This would be defined as a patient developing progressive disease. Matters such as intolerable toxicity would also be taken into account. Treatment withdrawal criteria as per protocol are as follows:

The patient can at any time decide to stop treatment with ibrutinib (withdrawal of consent, if applicable) within the context of the CUP, and in this case must be withdrawn from the program. The overall risk benefit of stopping treatment should be carefully considered. Once daily dosing of ibrutinib is important to maintain the inhibition of BTK. Without once daily dosing the patient may not benefit from treatment.

It is strongly recommended that the inclusion and exclusion criteria are re-evaluated, and if appropriate, the patient be withdrawn from the CUP if:

- The physician considers it to be in the best interest of the patient, for safety reasons, that he/she be withdrawn
- Persistent or recurrent toxicities occur following two dose reductions
- The patient starts treatment with one of the medications reported on the list of disallowed (e.g., warfarin) medications and cannot avoid their use
- A (serious) adverse event occurs
- The patient starts treatment with one of the medications reported on the list of disallowed medications (see Section 5.4)
- The patient becomes pregnant
- Ibrutinib is withdrawn or clinical development is discontinued
- The patient develops progressive disease and is no longer receiving clinical benefit from ibrutinib
- Ibrutinib is available locally by doctor's prescription and is reimbursed in his/her country.

B18. Page 102. How were patients identified and recruited into the CUP? What inclusion criteria were applied?

Patients were enrolled into the CUP following clinician enquiry regarding compassionate access. Janssen did not solicit investigator/patient enrolment. The programme was open to all for a limited period of time for those meeting the inclusion/exclusion criteria.

Inclusion criteria:

1. Patient is ≥ 18 years of age
2. Access to the patients complete medical history file
3. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2
4. Patient confirmed to have a diagnosis of MCL, such as pathologically confirmed overexpression of cyclin D1 or presence of t(11;14)
5. Patient confirmed to have R/R MCL defined as failure to achieve a partial response with, or documented progression after, the most recent treatment regimen
6. Patient has biochemical values within the following limits:
    a. Serum creatinine ≤ 2 times upper limit of normal (ULN) or estimated Glomerular Filtration Rate (GFR [Cockroft-Gault]) ≥ 30 mL/minute
    b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 times ULN
    c. Total bilirubin ≤ 1.5 times ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin) for whom the upper limit of serum bilirubin is 3 mg/dl

7. Patient is able to swallow capsules whole
8. Patient meets one of the following criteria:
    a. Patient is female: not of childbearing potential OR of childbearing potential and has a confirmed negative pregnancy test and will practice a highly effective method of birth control during and after participation in the CUP. These restrictions apply for 1 month after the last dose of ibrutinib
    b. Patient is male: either sexually inactive or agrees to practice a highly effective birth control during and after participation in the CUP, and agrees not to donate sperm during and after ibrutinib treatment. These restrictions apply for 3 months after the last dose of ibrutinib.

Exclusion criteria:

1. Patient previously participated in an ibrutinib clinical trial (ibrutinib or comparator arm)
2. Patient is eligible to participate in a currently recruiting ibrutinib clinical trial in your country
3. Patient previously received a Bruton's tyrosine kinase (BTK) inhibitor other than ibrutinib
4. Patient is currently enrolled in an interventional clinical trial
5. Patient is currently receiving chemotherapy, anticancer immunotherapy, or experimental therapy
6. Patient is currently recovering from acute toxicities of prior treatment for MCL
7. Patient has received stem cell transplantation within the past 6 months
8. Patient has evidence of graft versus host disease (GVHD) and/or requires immunosuppressant therapy
9. Patient has had major surgery within the past 4 weeks or a major wound that has not fully healed
10. Patient has a history of human immunodeficiency virus (HIV) or active infection with Hepatitis C or B
11. Patient has an on-going uncontrolled active systemic infection
12. Patient has central nervous system leukaemia/lymphoma
13. Patient has severe hepatic impairment (Child-Pugh class C)
14. Patient has been diagnosed or is currently being treated for a malignancy other than MCL, except for:
    a. Malignancy treated with curative intent and with no known active disease prior to entering this named patient program and considered to be at low risk for recurrence
    b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    c. Adequately treated cervical carcinoma in situ without evidence of disease
15. Patient has had a stroke within the past 6 months
16. Patient has had an intracranial haemorrhage within the past 6 months
17. Patient requires anticoagulation with warfarin or equivalent vitamin K antagonist (e.g. phenprocoumon)
18. Patient requires treatment with a strong CYP3A inhibitor
19. Patient has clinically significant cardiovascular disease such as:
    a. Uncontrolled or symptomatic arrhythmias
    b. Congestive heart failure

c. Myocardial infarction within the past 6 months
d. Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification

20. Patient has any life-threatening illness, medical condition, clinically significant issue or concern, or organ system dysfunction that could compromise his/her safety.

B19. **PRIORITY.** Page 105. Within the pooled dataset, please clarify which therapies patients received after they discontinued ibrutinib or TEMS (in RAY only). Please provide a list of subsequent therapies by treatment group together with numbers of patients receiving each.

A summary of the subsequent anti-neoplastic therapies used in >2% of patients from the PCYC1104 and RAY (MCL3001) studies is presented in Table 9 below.

Table 9: Summary of antineoplastic therapy used in at least 2% of patients subsequent to ibrutinib or temsirolimus in PCYC1104 and RAY (MCL3001)

	PCYC1104	SPARK (MCL2001)	RAY (MCL3001)	
Analysis set: intent-to-treat	**Ibrutinib (n=111)**	**Ibrutinib (n=120)**	**Ibrutinib (n=139)**	**Temsirolimus (n=141)**
Antineoplastic systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]
Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Bendamustine	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]	[redacted]	[redacted]
Cytarabine	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]
Prednisolone	[redacted]	[redacted]	[redacted]	[redacted]
Etoposide	[redacted]	[redacted]	[redacted]	[redacted]
Vincristine	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]
Temsirolimus	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Fludarabine	[redacted]	[redacted]	[redacted]	[redacted]
Mitoxantrone	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]
Investigational drug	[redacted]	[redacted]	[redacted]	[redacted]
Melphalan	[redacted]	[redacted]	[redacted]	[redacted]
Methylprednisolone	[redacted]	[redacted]	[redacted]	[redacted]
Chlorambucil	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Ifosfamide	[redacted]	[redacted]	[redacted]	[redacted]
Stem cell transplant	[redacted]	[redacted]	[redacted]	[redacted]
Procarbazine	[redacted]	[redacted]	[redacted]	[redacted]
Source: RAY (MCL3001) Clinical Study Report[1]; PCYC1104 Clinical Study Report[3]				

B20. Page 108, Tables 41 and 42. What is the date of the updated datacut?

Table 10: Datacuts of ibrutinib phase II trials

	PCYC1104	SPARK (MCL2001)
First datacut	26th of December 2012	29th of April 2014
Final datacut	17th of January 2014	31st of May 2015

B21. Page 110. Please provide *p*-values for differences in AEs for the following categories: "all grade 3/4 adverse events", "serious adverse events" and "severe adverse events."

	Ibrutinib (n=139)	TEM (n=139)	p-value
Any AE	138 (99.3%)	138 (99.3%)	[redacted]
Grade ≥3	94 (67.6%)	121 (87.1%)	[redacted]
Any serious AE	[redacted]	[redacted]	[redacted]
Grade ≥3	[redacted]	[redacted]	[redacted]

AE: adverse event, TEM: temsirolimus

B22. Page 123. Please clarify when the long term follow-up data from SPARK will be available. If these data are available now, please provide them in the response.

The final data cut of SPARK (MCL2001) was on the 31st of May 2015. The statement in the submission referring to SPARK (MCL2001) being ongoing was incorrect. Data from the final data cut were used within the pooled dataset. Both CSRs were shared with NICE (interim and final data cut).

Section C: Clarification on cost-effectiveness data

Health-related quality of life

C1. PRIORITY. Page 150. Please clarify why the company considers that the EQ-5D is unable to fully capture impacts of fatigue through the dimensions of usual activities, mobility and self-care. Is the argument that the EQ-5D cannot measure these elements in this population, or that the societal valuations of the tariff are incorrect? Also, please suggest a better preference-based alternative. Please clarify how the company's proposed longitudinal study including the EQ-5D and a disease-specific instrument will reduce this apparent uncertainty.

We believe that while the EQ-5D dimensions of usual activities, mobility and self-care may capture some impacts of fatigue, it does not fully capture the quality of life impact of varying severity of fatigue or important quality of life improvement through reduction in fatigue and increased energy. While clinical experts and the FACT-Lym quality of life and lymphoma-specific sub-scales of the RAY (MCL3001) study describe dramatic and clinically significant improvement in symptoms, physical, functional and emotional well-being in MCL patients on ibrutinib in RAY (MCL3001), modelled EQ-5D values indicate a utility gain of only 0.05 from baseline. The EQ-5D domain-level scores in RAY (MCL3001) do show some level of change

in quality of life impact on mobility, self-care and usual activities but this is small and not of the clinically meaningful magnitude indicated by FACT-Lym and EQ-VAS scores from the same patients. [redacted]

[redacted]

[redacted]

As a result, we believe the underestimation of utility benefit is driven by lack of sensitivity of the EQ-5D instrument to fatigue-related quality of life impact rather than the societal valuations of the tariff. Re-scoring with the new EQ-5D-5L value set for England[25] resulted in implausibly high utility values for the level of QoL impact associated with MCL and was no more effective at capturing the QoL treatment benefit indicated by FACT-Lym and EQ-VAS scores. Similar concerns were noted by the review committee in the draft Appraisal Consultation Document (ACD) from the recent NICE review of ibrutinib for the treatment of CLL.

We are currently in the process of finalising the protocol for our longitudinal study. The following preference-weighted instruments are being considered for data collection alongside the EQ-5D-5L in the study (Table 11):

Table 11: Preference-weighted measures under consideration for longitudinal study

Instrument	Description	Rationale
FACT-Lym with utility scored from FACT-G items[26]	Utilities derived from application of preference weights to 10 FACT-G items, covering physical, social/family, emotional and functional wellbeing domains. Visual Analogue Scale (VAS)-based preference weights elicited from a general population sample in England and Wales (n=433). Originally developed for FACT-L but may be applied more broadly to all cancer patients[27].	Utility scoring includes items directly relevant to fatigue (forced to spend time in bed, lack energy, able to work, able to enjoy life) as well as other QoL domains. Allows comparison with values from RAY (MCL3001). Could not previously be used in the economic analysis due to lack of comparative FACT data from MCL patients on R-chemo.
EORTC-8D scored from the EORTC QLQ-C30[28]	Utilities derived from 8 dimensions of the EORTC QLQ-C30 (physical functioning, role functioning, social functioning, emotional functioning, pain, fatigue and sleep disturbance, nausea, constipation and diarrhoea). Time-trade-off (TTO)-based preference weights elicited from UK general population sample (n=350).	EORTC-8D includes a fatigue and sleep disturbance domain based on tiredness in the past week, as well as impact on role and social functioning. Other domains of relevance to QoL impact of R-chemo. Potential to use with the QLQ-CLL16 module to capture additional leukaemia-specific QoL impact for sample description.
SF-6D scored from the SF-36 v2[29]	Preference-weighted scoring of 11 the generic SF-36 v2 instrument. Utilities derived from 11 items across 6 domains (physical functioning, bodily pain, mental health, vitality, social functioning, role limitation). Standard Gamble (SG)-based preference-weights elicited from UK general population sample (n=611).	Generic preference-weighted instrument which includes a specific vitality domain based on feeling worn out in the past 4 weeks, as well as impact on role limitation and social functioning. Potentially better sensitivity to fatigue-related QoL impacts than the EQ-5D[30].

The study will collect sample descriptive and quality of life data from UK patents (and possibly their carers) with MCL, with EQ-5D and disease-specific/alternative generic utilities calculated and compared for MCL patients on ibrutinib, R-chemo, other treatment and no current treatment. Data collection will include stage of disease/treatment (remission/progressing/watch and wait/line of treatment/before start of treatment/after recent treatment) and will be repeated after the end of treatment for participants on treatment and at relevant time-points for participants not receiving treatment at baseline (e.g. start of expected treatment). Study feasibility has been informed by pilot online data collection with MCL patients and their carers completed January 2016.

C2. PRIORITY. Page 151. Please provide justification for the assumed value of 0.015 QALYs lost due to R-CHEMO per cycle. If possible, provide evidence supporting the magnitude of this utility decrement. Please also comment on the resulting assumption that whilst patients are progression-free on R-CHEMO, their HRQoL is lower than when they have failed R-CHEMO and have progressive disease. Please also comment on why the toxicity decrement is applied universally to all patients rather than based on the incidence and duration of chemotherapy-related adverse events.

Feedback on the HRQoL of R/R MCL was provided by clinical experts at a recent advisory board[31]. Clinical experts acknowledged that there was a noticeable difference in the HRQoL

between patients receiving ibrutinib and those receiving R-chemo regimens. It was noted that patients receiving ibrutinib have relatively good quality of life (QoL), similar to the general population and are able to lead very normal lifestyles, able to go to work, exercise and go on holidays etc. In contrast the clinical experts noted that treatment with R-chemo is unpleasant for patients, with patients feeling ill for around 10 days post receipt of the dose, often experiencing fatigue and diarrhoea, and as a result often having to take concomitant medications. The lifestyle of patients receiving R-chemo regimens is limited not only by its side effects, but also by scheduled treatment visits from district nurses, limiting an individual's ability to return to work and a usual routine.

The clinical experts felt that a utility decrement of 0.2 between patients on ibrutinib compared to those receiving R-chemo was appropriate to reflect the differences in HRQoL. When adjusted to account for a 28-day cycle length, this led to a 0.015 QALY decrement per cycle.

There is limited evidence available that reports the utility decrement of R-chemo regimens for patients with R/R MCL. The values estimated by the clinical experts seemed therefore the most appropriate to use given their experience of treating patients with both ibrutinib and R-chemo; however, scenario analysis was performed that tested a decrement of R-chemo which was estimated using the difference between the pre-progression utility from the pooled ibrutinib data (0.78) and the utility of patients (measured by a VAS) for 75 patients with CLL and MCL (0.61) from a study identified within the HRQoL SLR. This analysis resulted in a difference in utility between the two arms of 0.17 the equivalent to a cyclical utility decrement of 0.013 per cycle, very similar to the decrement suggested by the clinicians.

The model assumes that all patients QoL will return to normal immediately upon ending R-chemo treatment (either on or prior to progression), resulting in an increase in utility for R-chemo patients who will no longer be suffering the associated side effects of chemotherapy.

For patients who are not suffering the side effects of treatment this is a reasonable assumption as, clinically, the side effects of treatment can have a much greater impact upon patient QoL compared to the impacts of disease progression observed via scan. Clinical experts consulted indicated that "patients do not feel much worse on recorded progression because they feel terrible anyway – usually progression is picked up due to symptoms starting prior to progression."

It should be noted that the utility assumed for patients in progressive disease has limited impact upon modelled outcomes as the same mortality rate post progression is assumed for both treatment arms. Table 12 to Table 14 demonstrate this by testing three available alternative inputs for PPS (literature values sourced from TA370 and clinician feedback from the advisory board to use the average of the two available values at the time the advisory board was conducted; prior to the availability of analysis of results from the ibrutinib pooled dataset.

The application of R-chemo side effects only whilst patients are on treatment was considered a conservative assumption within the model as, during the advisory board, it was acknowledged that the QoL of patients receiving R-chemo may take up to 6 months to return to the way it was before starting R-chemo, however, the model assumes that the reduction in HRQoL stops as soon as treatment has ended.

The incidence and duration of chemotherapy-related AEs was not used to estimate the QoL impact within the model of interest within R/R MCL for two reasons. Firstly, due to the paucity of available of AE data for the R-chemo regimens using this information to estimate the impact on QoL would seriously underestimate the impact of treatment with R-chemo on patients (in the same way that the impact on cost is likely underestimated). Secondly, the impact on QoL is not limited to side effects as discussed earlier – the impact of the frequent hospital visits required for R-chemo treatment on a patient's ability to conduct a normal life can itself have a large impact on HRQoL.

Please note that in formulating answers to these clarification questions an error was spotted within the cost-effectiveness model. This was in relation to the cost of follow-up care based upon the level of response; stable disease, partial response or complete response, whereby the resource use reported as complete response was mislabelled as partial response and vice versa. The error can be easily fixed by applying the following changes within the model:

- Sheet "UK MRU" Cell G31 should read "Partial Response"
- Sheet "UK MRU" Cell G32 should read "Complete Response (CR)"
- Sheet "UK MRU" Cell N38 should read =H38*$S$32+$S$31*I38+K38*$S$30 (in the version submitted this read =H38*$S$31+$S$32*I38+K38*$S$30)
- Sheet "UK MRU" Cell N39 should read =H39*$S$32+$S$31*I39+K39*$S$30 (in the version submitted this read =H39*$S$31+$S$32*I39+K39*$S$30)

All scenarios presented within this document have been tested with the relevant correction applied, and all results of the cost-effectiveness model have been re-run and are provided as an appendix to this document.

Table 12: Cost effectiveness analysis results using utility value of 0.55 for PPS (advisory board input). No discount

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Ibrutinib	[redacted]	[redacted]	[redacted]	£95,233	1.23	0.95	£100,591
R-CHOP	[redacted]	[redacted]	[redacted]				
LYG: life years gained; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio							

Table 13: Cost effectiveness analysis results using utility value of 0.45 for PPS (Doorduijn 2005[32]). No discount

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Ibrutinib	[redacted]	[redacted]	[redacted]	£95,233	1.23	0.95	£99,748
R-CHOP	[redacted]	[redacted]	[redacted]				
LYG: life years gained; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio							

Table 14: Cost effectiveness analysis results using utility value of 0.636 for PPS (Beusterien 2010[33]). No discount

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Ibrutinib	[redacted]	[redacted]	[redacted]	£95,233	1.23	0.94	£101,328
R-CHOP	[redacted]	[redacted]	[redacted]				

LYG: life years gained; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio

C3. Page 149. Please comment on whether the "euphoric effect" of ibrutinib has been observed and measured using the EQ-5D within a blinded study design.

The description of "euphoric effect" has been personally defined by an expert in MCL following the expert's experience of treating patients with ibrutinib in the R/R MCL setting. There has been no formal evaluation using EQ-5D or another quality of life instrument.

C4. Page 145. Please clarify the frequency of EQ-5D measurement in the SPARK (MCL2001) study.

In SPARK (MCL2001), the EQ-5D questionnaire was administered on day 1 of every 21-day cycle during the first 6 months, then every 9 weeks up to 15 months after the first dose of study drug; thereafter, the EQ-5D was assessed every 24 weeks until disease progression, death, or study end, whichever occurred first. The questionnaire was completed before any other assessments and before subjects were clinically evaluated by the study nurse or physician.

C5. Page 146. Given the dearth of HRQoL values identified in the company's review of utility studies, why were studies undertaken in similar disease areas not considered (as was done in Technology Appraisal 370)?

Within the TA370 appraisal, no studies were identified within the SLR that were specifically relating to MCL, therefore a secondary wider search was conducted that looked at studies from other disease areas to help inform the decision question. Within the SLR conducted for the NICE submission of ibrutinib, 5 studies were identified directly relevant to the disease area which were more applicable to the decision question than those found within TA370, and 2 of the 5 studies reported utility values. Therefore it was not considered necessary to explore similar disease areas as was done in the prior appraisal, with more relevant studies and evidence sourced within this review than compared to the ones identified in the wider search within TA370. Of the studies identified within the current SLR, one was used in sensitivity analysis to test the uncertainty around the utility decrement applied to the R-chemo arm for pre-progression patients within the model[34]. It is also noted that only low quality evidence was identified within the wider review conducted for TA370.

Evidence synthesis and indirect treatment comparisons

C6. Page 105. Please clarify which formal tests (if any) were used to determine whether it was appropriate to combine data from the ibrutinib studies.

No formal test was undertaken before pooling data from the three ibrutinib trials. Testing heterogeneity would be relevant in case of pooling data from comparative trials (like in a traditional pairwise meta-analysis). In this case, as only the ibrutinib arms were pooled, no formal test was required.

C7. Page 80. Please clarify why study MCL002 (SPRINT) was not included in the indirect comparison.

The MCL002 (SPRINT) trial was not included in the ITC as no common arm was available to be used as link for the comparison (no ibrutinib study in R/R MCL is available comparing to lenalidomide). Hess, 2009 could be used as TEM (175/75 mg) was common to the Hess, 2009 and the RAY (MCL3001) study.

C8. PRIORITY. Page 23. Please explain why the ITC with adjustment for the "rituximab effect" was not undertaken for the outcome of overall survival.

The direct use of ibrutinib OS trial data and therefore application of a HR to estimate OS for R-chemo was considered inappropriate therefore the model did not require the estimation of adjusted OS (see question C12).

It should be noted that there are considerable limitations with the ITC presented for OS given that no information is available on the subsequent therapies received by patients within the Hess, 2009 study. Adding further adjustment would only serve to compound these issues.

C9. PRIORITY. Page 82. Indirect comparisons were made using the Bucher method, which is essentially the same as a fixed effect network meta-analysis (NMA). Please justify the use of this approach. Also, please provide results from a random effects NMA, with predictive intervals, to illustrate the uncertainty in a future study (as recommended by the NICE Technical Support Document 3 "Heterogeneity: subgroups, meta-regression, bias and bias adjustment"). In the absence of further information on which to base the choice of prior, use of a weakly informative prior may be appropriate (see NICE TSD3 pg 73 and Turner *et al.* 2012, "Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews").

We would strongly argue against the use of a random effects model for this network as there is not enough information to properly estimate between study variability given that only 2 studies are available to inform comparison (Hess, 2009 and RAY (MCL3001)[4, 35]. Producing a random effects Network Meta-Analysis (NMA) for the studies available is similar to calculating the variance of 2 data points: whilst it is technically possible the results are not interpretable.

Results of this analysis are provided below and, given the limited network, as would be expected the medians from the random effects models (constructed using 2 different uninformative priors) are consistent with the fixed effects model.

Additionally we would argue that the use of predictive intervals is not relevant. In the NICE DSU,[36] the following is stated: “This issue has been discussed before, and it has been proposed that, **in the presence of heterogeneity**, the predictive distribution, rather than the distribution of the mean treatment effect, better represents our uncertainty about the comparative effectiveness of treatments in a future “roll out” of a particular intervention.”

The presence (or absence) of heterogeneity cannot be assessed statistically when only 2 studies are available. This issue is reflected within the exceedingly wide intervals shown below.

Table 15: Results of the Bayesian analysis

Endpoint	Model	median	CrI95%	Mean	SD	prob	median (predictive)	CrI 95% (predictive)
ORR	FE	60.52	[7.09; 514]	60.28	2.98	1		
	RE U[0,2]	60.34	[1.06; 3422]	60.28	7.12	0.98	59.92	[0.00; 14E9]
	RE U[0,5]	59.62	[0.01; 49E4]	59.26	67.97	0.87	63.24	[0.00; 1E27]
PFS IRC	FE	0.19	[0.10; 0.36]	0.19	1.39	1		
	RE U[0,2]	0.19	[0.01; 7.04]	0.19	5.25	0.87	0.19	[0.00; 13E8]
	RE U[0,5]	0.19	[0.00; 1411]	0.19	60.7	0.73	0.18	[0.00; 3E26]
OS	FE	0.59	[0.31; 1.09]	0.59	1.38	0.95		
	RE U[0,2]	0.58	[0.02; 21.4]	0.58	5.26	0.69	0.61	[0.00; 3E9]
	RE U[0,5]	0.59	[0.00; 4541]	0.6	59.26	0.6	0.47	[0.00; 4E26]

ORR: objective response rate; PFS: progression-free survival; IRC: independent review committee; OS: overall survival

C10. PRIORITY. Page 120. Please clarify which data from the HMRN audit have been used to estimate the "rituximab effect" (give page numbers and refer to specific figures/tables used). Please also explain the precise method used to derive the hazard ratio.

The HMRN audit titled "Clinical management and outcome in mantle cell lymphoma" was used to estimate the effect of rituximab to inform the comparative evidence for R-chemo regimens. The audit presents a value of 0.69 in Table 11 (page 31), which is the adjusted PFS HR for rituximab chemotherapy excluding autologous stem cell transplant (ASCT). The HR for the rituximab effect, represents the difference in PFS for patients who received rituximab therapy and those who did not.

The PFS HR used to estimate the efficacy of ibrutinib vs R-chemo was calculated by using the HR derived from the ITC (between Hess, 2009 and RAY (MCL3001)). The PFS HR derived from the ITC was 0.19 for ibrutinib vs Physician's choice. To account for the effect of rituximab, the value of 0.69 described above was applied to the ITC using the following formula:

$$R - chemo\ PFS\ HR = ITC\ HR * (\frac{1}{HMRN\ rituximab\ HR})$$

$$R - chemo\ PFS\ HR = 0.19 * \left(\frac{1}{0.69}\right) = 0.28$$

A PFS HR of 0.28 was used in the economic model to compare ibrutinib to R-chemo.

C11. PRIORITY. Page 139. A point estimate of 0.28 is provided for the adjusted comparison of ibrutinib versus R-CHEMO. Please clarify the uncertainty associated with this treatment comparison. Also, please provide estimates for this treatment comparison from a random effects NMA (including RAY, Hess and HMRN). Though there may be concerns over combining these studies in a NMA, the ERG considers that a random effects NMA would give a better representation of the uncertainty than the presented adjustment.

As noted within the answer to C9 we do not consider the presentation of a random effects NMA to be valid for the network of studies available. As explained within the answer to question to C8, there are considerable limitations with the ITC presented for OS given that no information is available on the subsequent therapies received by patients within the Hess, 2009 study. Adding the HMRN audit on top of this would only serve to compound these issues; particularly as the HMRN audit is not a randomised study, i.e. any treatment effect for rituximab is subject to potential issues of confounding. This analysis is therefore not presented. It should be noted that there is no evidence to prove that the use of rituximab has an effect on survival beyond extension of PFS.

Model structure and surrogate relationships

C12. PRIORITY. Page 25. Please clarify why overall survival was modelled as PFS+PPS rather than by fitting curves to the observed Kaplan-Meier data on overall survival from the point of randomisation. Please comment on the potential limitations of this approach with reference to the statement on page 71 which states that: "rapid progressors" may have a different mortality hazard to slower progressors.

The model estimates OS using a PFS + fixed PPS approach, which assumes a constant risk of death during PPS that is equivalent in both arms of the model. This approach uses the evidence available to show that PFS is a good surrogate for OS to model OS outcomes without making considerable leaps of faith regarding the evidence available for OS.

Overall survival data was modelled as PFS + PPS as opposed to the extrapolation of observed Kaplan-Meier (K-M) OS data for multiple reasons:

- Substantial pollution of the evidence available for OS from the ibrutinib pooled dataset from use of subsequent therapies which do not reflect UK clinical practice
- Crossover from TEM to ibrutinib within the Phase III clinical trial adding to the pollution of OS data
- Immaturity of the available OS data leading to clinically implausible direct projection OS estimates for ibrutinib – median OS has only just been met within the pooled trial dataset and has not yet been met within the Phase III MCL3001 trial
- Lack of evidence on subsequent therapy use in the other potential comparator dataset (Hess 2009) and use of treatments which do not form current UK standard practice polluting data which might have been used to calculate a rituximab treatment effect for OS in the HMRN dataset
- The availability of evidence indicating that PFS acts as a good surrogate for OS in MCL

It has been noted by ERGs in prior appraisals that the extrapolation of immature data where the median OS has not yet been met, may bias the overall results[37].

The approach taken uses PFS as a surrogate for OS in MCL which has been utilised in a prior NICE appraisal in MCL (TA370), and has been indicated as a good surrogate for OS with strong correlation between the PFS and OS[38]. It should be noted that IRC-assessed PFS is the primary endpoint within the RAY (MCL3001) trial indicating that the regulatory bodies consider that PFS is important for prognosis.

A substantial amount of PFS data are available from all ibrutinib trials to be able to quantify the PFS benefit and these data are mature. Because of this, the approach taken within the health economic model using PFS data and then adding on a fixed PPS to both arms is more appropriate as it avoids making any potentially unjustified assumptions around PPS, which would be implicit in modelling PFS and OS separately.

As well as the avoidance of making any unjustified assumptions relating to the PPS benefit of ibrutinib, using the current methodology of PFS + fixed PPS also reduces bias associated with fitting parametric curves to OS data which may arise as a result of differential subsequent therapies received by patients within the clinical trials.

In some instances the subsequent therapies encountered by patients in the ibrutinib clinical trials are not in line with current UK clinical practice. For example 31.7% of ibrutinib patients and 58.2% of TEM patients in RAY (MCL3001) receiving subsequent treatment, had a treatment involving bendamustine, which is no longer available for R/R MCL in the UK. Subsequent therapy pollution becomes even more relevant when considering the comparison to R-chemo. There is no information available on subsequent therapy use within the Hess, 2009 trial, therefore any bias implicit is unknown in size when comparing using the ITC. Data from HMRN for OS / the impact of rituximab on OS are also difficult to interpret as UK clinical practice has changed substantially over-time. Pollution of the TEM arm by crossover is also an issue if directly observed data from the RAY (MCL3001) trial were to be used as a proxy for survival with R-chemo (22.3% of patients cross over to ibrutinib).

The immaturity of the ibrutinib trial data and potential issues with subsequent therapy pollution were particularly evident within this submission as initial attempts to directly extrapolate OS lead to highly clinically unrealistic estimates of long-term survival. This is shown in Table 16 below which reports the projected 1, 2, 5 and 10 year survival of ibrutinib in the current model approach vs the estimated survival of ibrutinib extrapolating OS K-M data from the pooled trial evidence. As shown within the table curve fits to the OS data are similar to the PFS + fixed PPS approach within the first year, however beyond a 1 - 2 year period the extrapolation of the OS curves begins to show higher levels of survival not considered clinically plausible during the advisory board. By ten years the best fitting curve (lognormal) based on the AIC / BIC statistic predicts 16.16% of patients surviving for ten years, which was deemed unrealistic for patients with R/R MCL.

Table 16: Projected survival of ibrutinib PFS+Fixed PPS vs Extrapolation of OS data

	Proportion of patients alive				
Time	**Current model approach (PFS + Fixed PPS)**	**Extrapolation of K-M OS data**			
		Lognormal Curve	**Weibull Curve**	**Exponential Curve**	**Log-logistic Curve**
1 year	70.32%	67.24%	69.42%	71.24%	67.79%
2 years	42.37%	50.80%	50.44%	51.39%	50.05%
5 years	8.98%	29.05%	20.37%	19.29%	27.02%
10 years	0.84%	16.16%	4.86%	3.77%	14.78%

With regard to the mortality HR of rapid and slow progressors, this is unlikely to have been captured within the OS data available for ibrutinib, due to the immaturity of the datasets meaning that a high proportion of slow-progressors are unlikely to have yet experienced a death event. It is therefore likely that under the current approach the PPS curve generated within the model is an underestimation of true PPS for both treatment arms. Nonetheless the data available are applied to both arms equally in the base case analysis and this is therefore the most conservative approach which limits the bias which may form as a lack of follow-up data.

While UK experts in the treatment of MCL were confident that ibrutinib would provide a PFS benefit compared to current clinical practice, there was less consensus on what degree of PPS benefit could be expected. Whilst it may be possible that the use of ibrutinib would extend PPS in UK clinical practice (as it reserves the ability to use R-chemo as the next LOT upon progression) there is no evidence available from the clinical trials to support this assumption. Equally there is no evidence to prove that the use of rituximab has an effect on survival beyond extension of PFS.

Overall the current approach taken within the economic analysis (PFS+fixed PPS) seems a more appropriate and conservative method of estimating OS without having to make unjustified assumptions given the limited data available with regard to both the immature data of ibrutinib and the OS of R-chemo regimens in a R/R MCL setting. This approach assumes that ibrutinib has no PPS benefit and any benefit encountered is from the PFS health-state only. This methodology was discussed at a recent advisory board with expert clinicians who supported the approach undertaken within the analysis given the evidence limitations[31].

In order to explore the uncertainty around assumptions in the PPS period the following scenarios are provided within the main submission document:

- Impact of a sequential treatment pathway where introducing an extra line of R-chemo improves PPS on the ibrutinib arm
- Using OS data from the HMRN dataset to estimate the effectiveness of R-chemo in UK clinical practice.

C13. Page 25. With reference to the statistical analyses presented in Lee *et al* (*Ann Oncol*, 2011), please justify the statement *"Available literature within MCL indicates that PFS is a good surrogate for OS."*

The analyses conducted within Lee et al, which explored potential surrogate end points in RCTs of aggressive and indolent non-Hodgkin's lymphoma (NHL), concluded that PFS was strongly correlated with OS and was considered as a better surrogate for OS than other surrogates explored[39]. The analyses conducted involved a SLR of RCTs in previously untreated aggressive NHL with ≥100 patients in each arm or untreated indolent NHL with ≥75 patients. Nonparametric Spearman's rank correlation coefficient was used as a measure of correlation between the surrogate endpoints explored and 5-year OS. Overall EFS (event free survival) and PFS were strongly correlated with 5-year OS and statistically significant differences in EFS and PFS at 3 years predicted differences in OS after 5 years. It was

recommended that PFS was a better surrogate for OS due to issues with inconsistent definitions of EFS and 'included' events which may implicate the power of a trial.

In addition to this analysis, as part of the bortezomib submission (TA370), where the immaturity of OS within the LYM-3002 trial was of concern, and PFS was considered as a surrogate for OS, a SLR was conducted that assessed the use of surrogate outcomes for OS in MCL. Two studies were included within the SLR[38]. [redacted]

Further still PFS has been used a surrogate endpoint in prior NICE appraisals in MCL (TA370).

C14. Page 130. Why were PFS follow-up costs modelled according to best overall response? Would this response be maintained over the entire progression-free period?

Feedback from expert clinicians at a recent advisory board suggested that the level of resource use encountered by patients was dependent upon their best overall response categorised as; stable disease, complete response and partial response. The reason given was that patients who respond will be visited on a routine basis whereas patients who do not respond would be monitored more frequently with monitoring frequency being dependent upon the site and symptoms of residual disease. Additionally bone marrow exams are conducted to confirm response, this is not necessary for patients who do not respond. Transfusions are also likely to be required less frequently for responders.

Whilst the level of response may not be maintained over the entire progression-free period, the monitoring schedule is determined according to the patient's initially assessed best overall response. Patients are not re-assessed to down-grade their level of response over time but are rather assessed to determine whether or not their disease is progressing; this is most often a result of the occurrence of progression related symptoms.

C15. Page 132. Both "Method 1 – fixed PPS" and "Method 2 – sequential approach" are referred to as the base case. However, in the results section of the company submission (page 166), only Method 1 is presented as the base case. Please confirm that Method 1 (fixed PPS) is the base case and that Method 2 (sequential approach) should be considered as a scenario analysis.

The fixed PPS approach was the basecase used to inform the cost-effectiveness model, and the sequential approach was included as a scenario analysis.

C16. Page 136. The CS refers to a *"fixed PPS period",* however from scrutiny of the model it appears that it is the risk of death conditional on prior progression that is fixed, rather than the sojourn time in the post-progression state. Did you intend to assume a fixed post-progression sojourn time for all treatment groups?

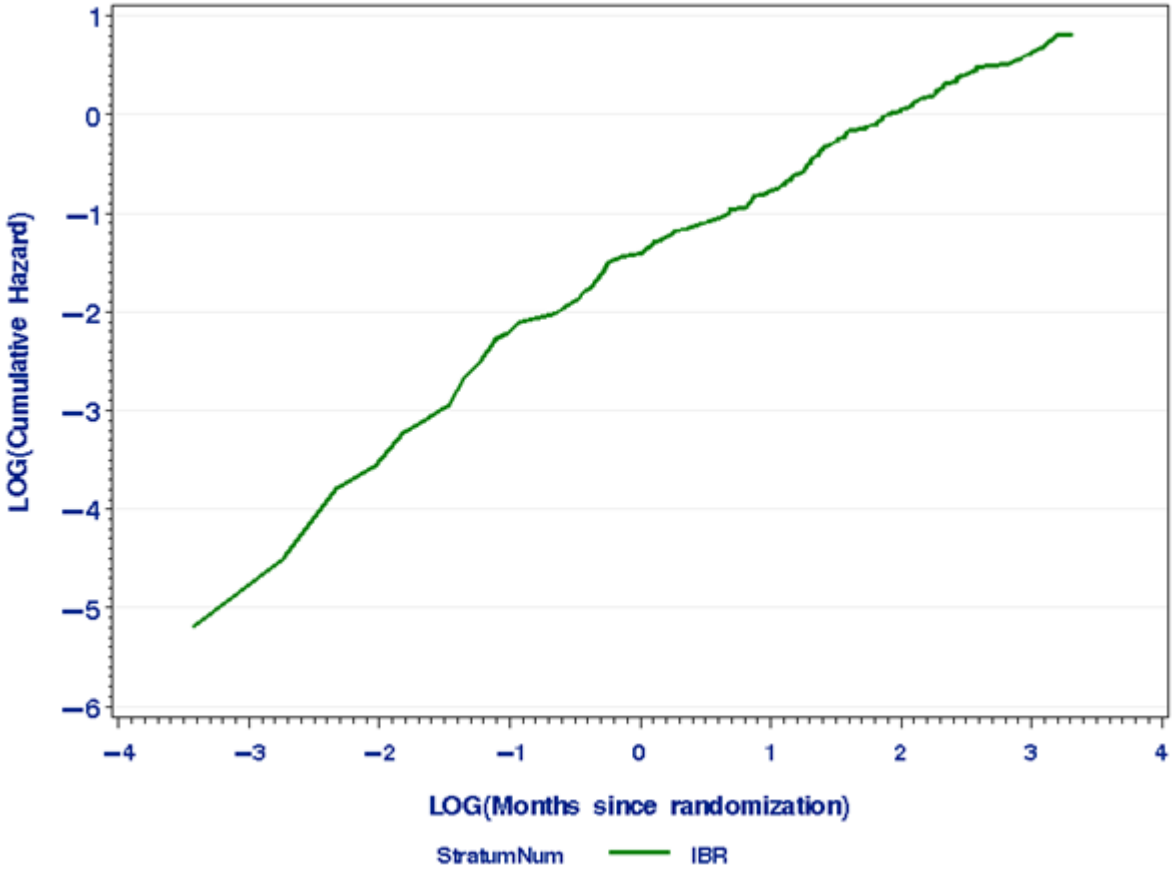
The fixed PPS period does indeed refer to a constant risk of death for all patients in the post-progression heath state. The rate is fixed because it assumes the same rate of death in both arms within the model and does not vary over time. The rate of death was derived from an

exponential curve fit PPS data. It was not intended that the model would assume a fixed sojourn time in PPS for all treatment groups.

C17. PRIORITY. Page 142. The company submission states "A constant rate of mortality of 10.83% per cycle was assumed to avoid the requirement to use tunnel states to track patient movements into PPS." Please clarify whether the hazard rate for post-progression mortality appears to be time-dependent and if so, please justify why time-dependent hazards have not been included in the model.

The model does not consider time-dependent hazards as the evidence does not indicate that the mortality risk is time dependent. This is shown by the log-cumulative hazard plot shown in Figure 5 (also reported within Appendix 15 of the submission), which shows a fairly straight line with a gradient of approximately 1 indicating that the use of an exponential curve is justified.

Figure 5: Log-cumulative Hazard Plot: PPS from pooled ibrutinib data



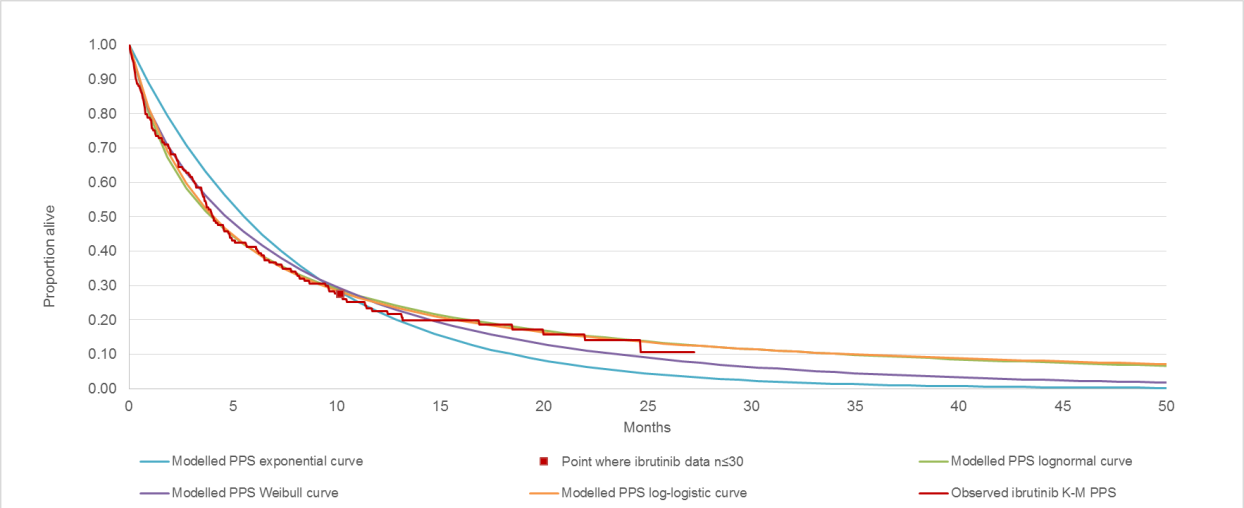
In addition to this, other parametric curves were assessed and were not vastly dissimilar from the exponential curve in terms of the mean survival projected (as shown below in Table 17), indicating that applying a constant rate of mortality is an appropriate simplification to avoid the requirement for the use of time dependent hazards which would necessitate the implementation of tunnel states within the economic model. Of the four parametric curves fitted, the log-normal and log-logistic functions shown in the figure below are clinically implausible due to their long-tails which appear to asymptote at around the 8% mark i.e. a patients remain alive indefinitely if they survive for 40 months, which is clearly implausible.

For the two remaining parametric curves the mean time spent in PPS is 8.03 months for the exponential and 9.21 months for the Weibull, which is not vastly dissimilar and alongside the visual fit, indicates that the exponential curve may be a more conservative approach to modelling PPS. The impact of increasing PPS within the economic model by using Weibull instead of Exponential is shown in Table 17. This increase in PPS reduces the risk of mortality in the PPS health state from 10.83% in the base case to 9.45%. Overall this has minimal effect on the ICER with an increase of £739 from £100,647 to £101,386. This small increase is a result of the slightly larger than proportional increase in QALYs gained within the R-CHOP arm which is a result of more patients progressing on R-chemo.

Table 17: Cost-effectiveness results of reducing PPS mortality to represent the mean PPS using the Weibull curve. No discount (error corrected)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (QALYs)
Ibrutinib	[redacted]	[redacted]	[redacted]	£95,136	1.23	0.93	£102,456
R-CHOP	[redacted]	[redacted]	[redacted]				

Figure 6: Ibrutinib pooled data: PPS parametric curve fits



C18. PRIORITY. Please justify exclusion of subsequent-line therapy costs from the health economic model.

Subsequent treatment was not included within the economic analysis for two reasons:

1. The subsequent treatments received by patients in the pooled dataset were not standard UK practice and therefore not relevant for this submission, for example the use of bendamustine as a subsequent therapy was quite common within the trial
2. Including subsequent treatment has a very limited impact to the results as the added costs are incurred in both arms. Adding this component was considered as adding complexity to the analysis unnecessarily.

Scenario analysis was conducted which considered the use of FCR (which is reasonably reflective of UK current practice based upon advisory board feedback) as a subsequent therapy cost for all patients upon progression within both arms of the model. As shown in Section 5.8.3 of the submission document, this scenario reduces the incremental costs by £1,582 (with no discount) and the corresponding ICER by £1,689 (£100,647 to £98,958), a decrease of approximately 1.7% suggesting that the model base case is a conservative assumption and that, as expected, the inclusion of subsequent treatment costs has limited impact on the overall cost-effectiveness of ibrutinib.

C19. PRIORITY. Please provide evidence of individual-level surrogacy (i.e. individual-level correlation) of PFS for overall survival using the data from RAY (MCL3001), SPARK (MCL2001) and PCYC1104.

As shown in Table 18 both Pearsons and Spearman correlation coefficients are provided indicating a strong statistically significant individual-level correlation between PFS and OS using the ibrutinib pooled dataset and within all individual studies.

Table 18: Correlation of OS and PFS within the ibrutinib clinical trial data

	Pearson		Spearman	
	Correlation coefficients	p-value	Correlation coefficients	p-value
Pooled	0.75538	0.0001	0.7483	0.0001
PCYC1104	0.85451	0.0001	0.81996	0.0001
SPARK (MCL2001)	0.69521	0.0001	0.74015	0.0001
RAY (MCL3001)	0.89917	0.0001	0.87575	0.0001

Survival modelling

C20. PRIORITY. Why was a treatment switching analysis not presented for the RAY data to adjust for confounding due to TEMS patients crossing over to ibrutinib? Is such an analysis planned?

Janssen attempted to adjust for the confounding effect of the 22.3% of patients in the TEM arm crossing over to ibrutinib in the RAY (MCL3001) study. Preliminary exploration has been conducted for three methods as suggested in the NICE DSU Guidance[42].

- Inverse Probability Censoring Weights (IPCW): Janssen believe that this method is not appropriate here as the relevant time-dependent variables were not consistently captured throughout the clinical trial, therefore not enough information was available to properly estimate the weights described above and deal with censoring-related selection bias. Variables which have not been collected post progression which would be expected to be predictive of prognosis include ECOG status, quality of life (measured using the EQ-5D), creatinine clearence, Beta-2 Microglobulin, hemoglobin, lymphocytes and leukocytes
- 2-stage approach: this approach assumes that there is a “secondary baseline”- e.g. disease progression – upon which all control arm patients equally have an opportunity to switch; however, a relatively large amount of time (mean 209 days) passed between patients’ progression and treatment switching on average. It cannot

therefore be assumed that there is no time dependent confounding between the time of disease progression and the time of treatment switch

- Janssen therefore believe that the rank-preserving structural failure time (RPSFT) method is the only method potentially suited considering the dataset type. The strongest assumption required for RPSFT is that there is a common treatment effect regardless of whether a patient received ibrutinib as part of the ibrutinib arm or post TEM. It is not possible to fully test this assumption and there is a rationale both for and against this assumption holding:
    - For: KM data (Figure 7) showing outcomes for ibrutinib from baseline indicate similar outcomes to switchers measured from the point of crossover; it should be noted that there is a high likelihood of selection bias in the analysis presented which is unadjusted. Adjustment to test this further cannot be fully carried out due to lack of recording of many prognostic variables post progression
    - Against: the number of prior lines of therapy appears to be a treatment effect modifier based upon post-hoc analysis conducted with treatment effects and outcomes in the ibrutinib arm appearing different for patient with 1 prior line versus 1+ prior lines.

[redacted]

Results of the RPSFT analysis are reported in Table 19.

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]		

When interpreting the results of this crossover analysis it should be borne in mind that a large proportion of patients received subsequent treatment outside of formal crossover in the RAY (MCL3001) study, especially in the TEM arm. Most of these patients received treatments that are not used in UK clinical practice and may have impacted patients' survival. Unfortunately it was not possible to adjust for this subsequent use outside of formal crossover meaning that OS results should be interpreted with caution within the context of NICE's decision problem and are not considered suitable for direct use in the economic model (see answer to question C12).

C21. Page 137. The company submission states *"Based upon the log-cumulative hazard plot which indicated that the use of a standard parametric curve was appropriate…"* The plot presented in Appendix 15 appears to show log(-log($S(t)$)) vs log(t) for PFS. This is not appropriate for assessing accelerated failure time models. Please present the appropriate plots for the log logistic and log normal survivor functions.

Please find below the QQ plot for PFS from the observed pooled ibrutinib data. If the use of an accelerated failure time model was appropriate then we would expect a QQ plot to show a straight line at a 45 degree angle. As Figure 7 shows, the line is not 45 degrees, and therefore the use of the log-normal or log-logistic survivor functions is not considered appropriate. The same applies for the time on treatment data observed for the pooled ibrutinib data as shown in Figure 8.

Figure 8: QQ-plot for PFS

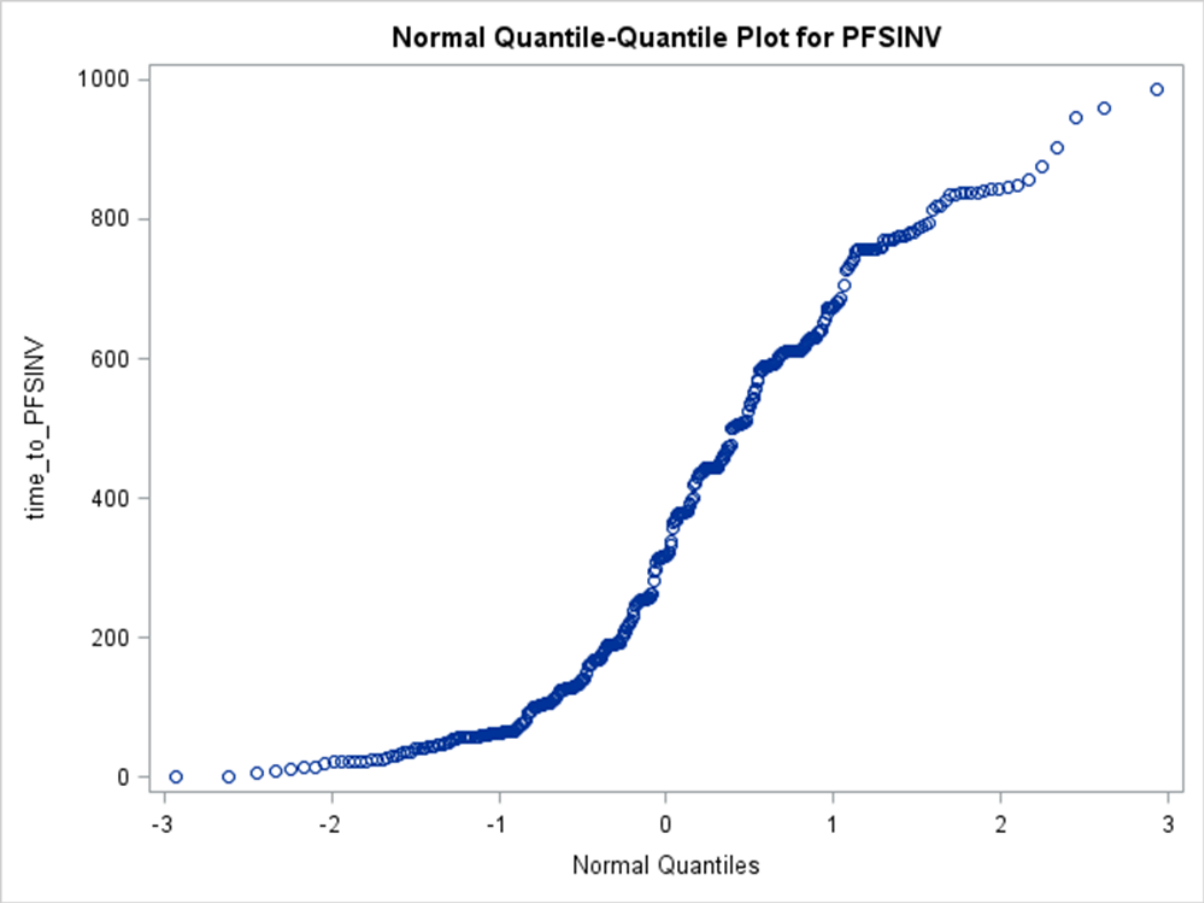
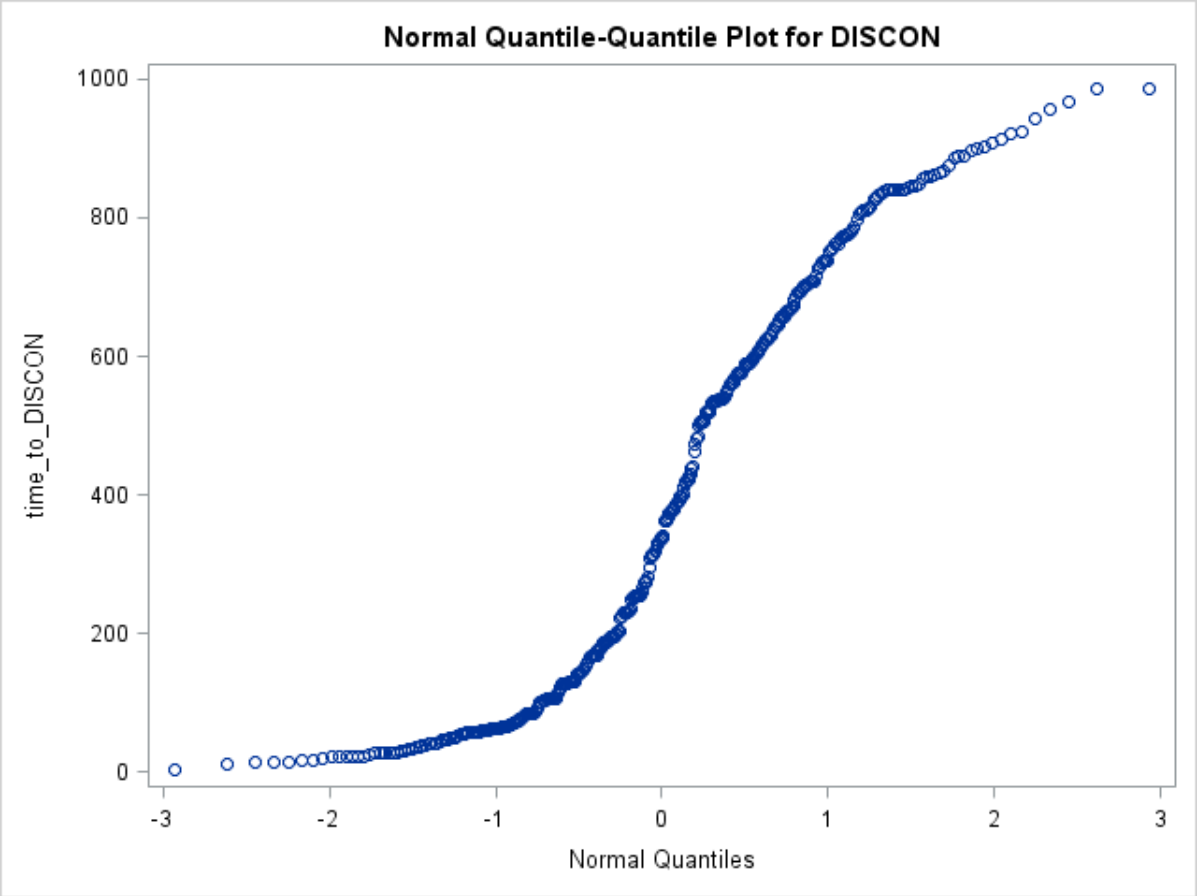


Figure 9: QQ plot for Time on treatment



In addition to the QQ plots explored, log cumulative hazard plots are presented below using time, as opposed to the log of time, for PFS (as shown below in Figure 10) and time on treatment (Figure 11). These plots do not show straight lines indicating that the use of the Gompertz curve is equally not appropriate within this analysis.

Figure 10: Log-cumulative hazard plot for PFS

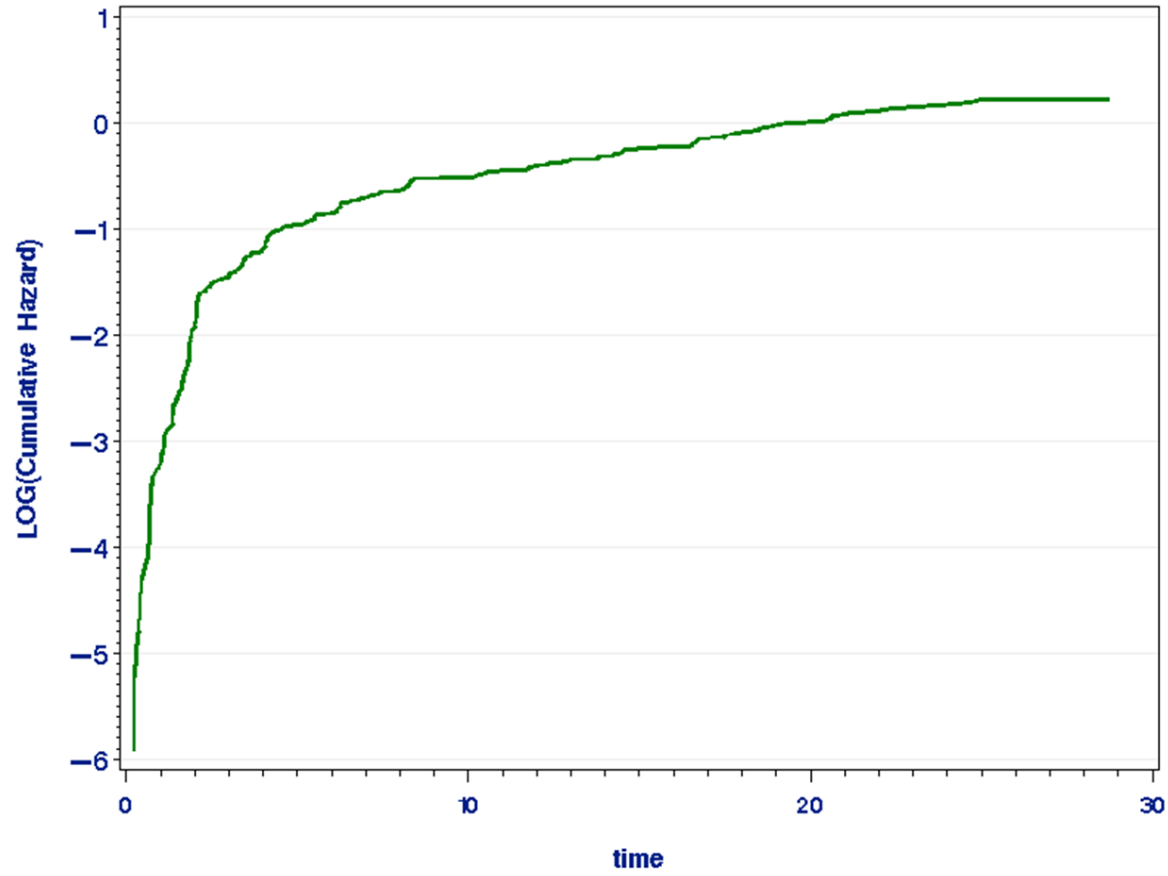
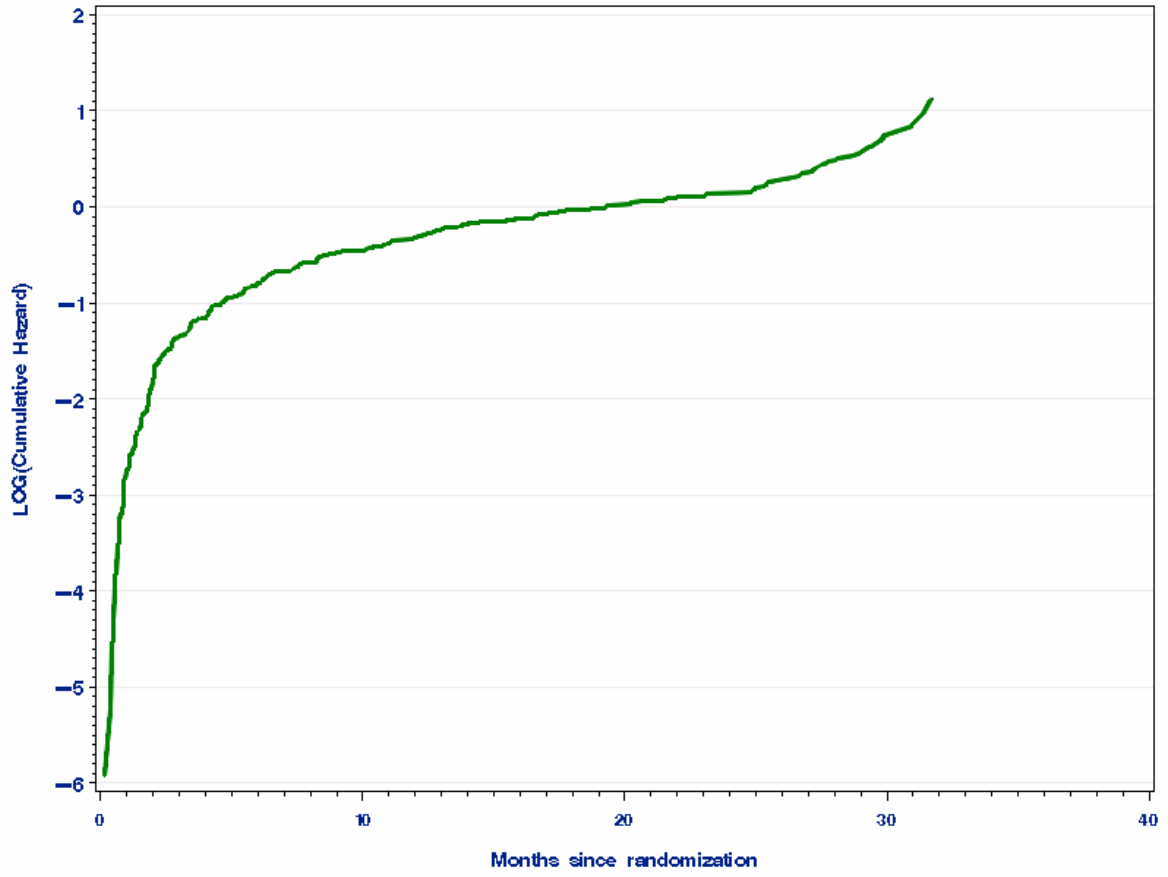


Figure 11: Log-cumulative hazard plot for time on treatment

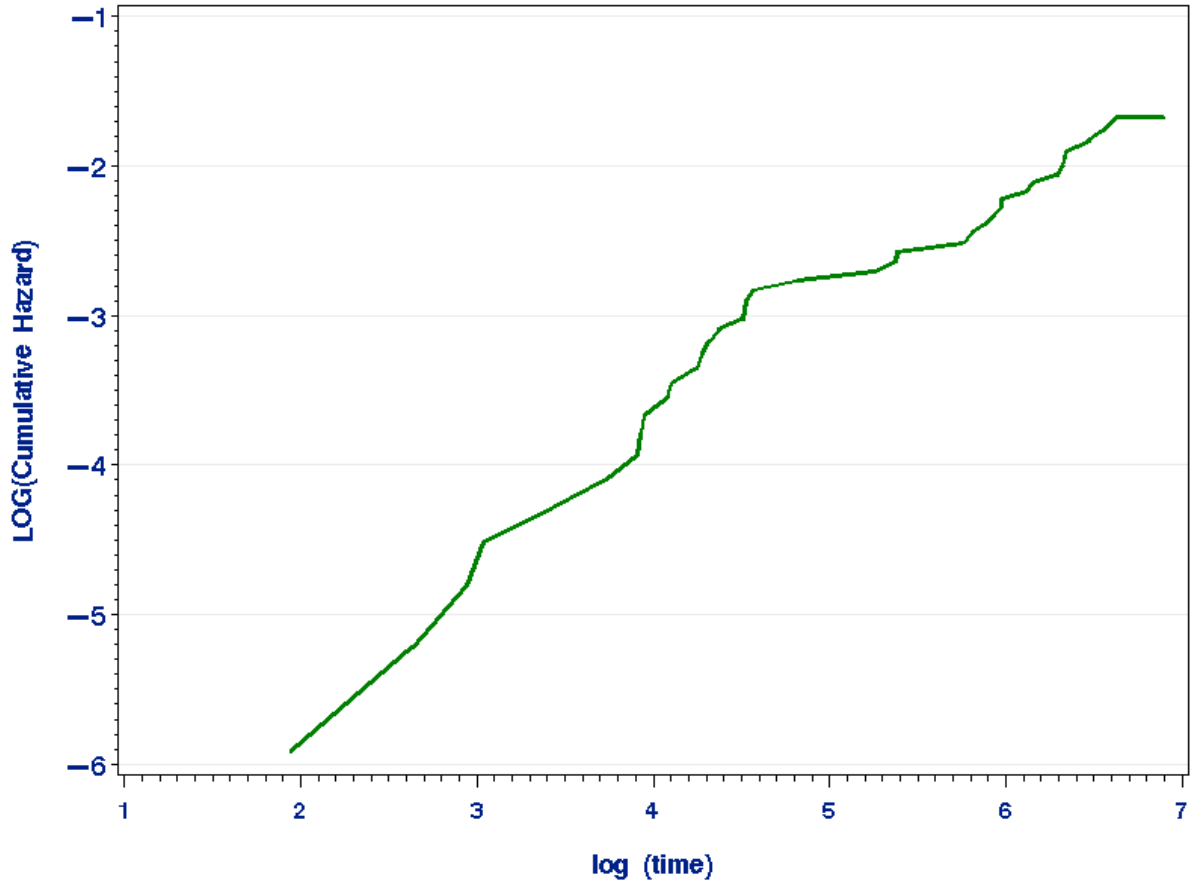


C22. PRIORITY. Page 141. The model assumes a fixed rate of death for patients whilst in the progression-free state (pre-progression mortality). This appears to assume that the hazard of pre-progression death is proportional to the hazard of progression. Please provide evidence from the ibrutinib studies which supports this assumption.

Mortality in the pre-progression health state is modelled based on the number of deaths during PFS observed within the pooled ibrutinib data, and the observed data for TEM which informed the comparator arm. The mean follow up time was multiplied by the total N in each circumstance (370 for ibrutinib and 141 for R-chemo). The mean mortality rate per cycle was then estimated by dividing the number of PFS events by the total follow up time. The mortality rate was assumed constant throughout the time frame based on the available evidence.

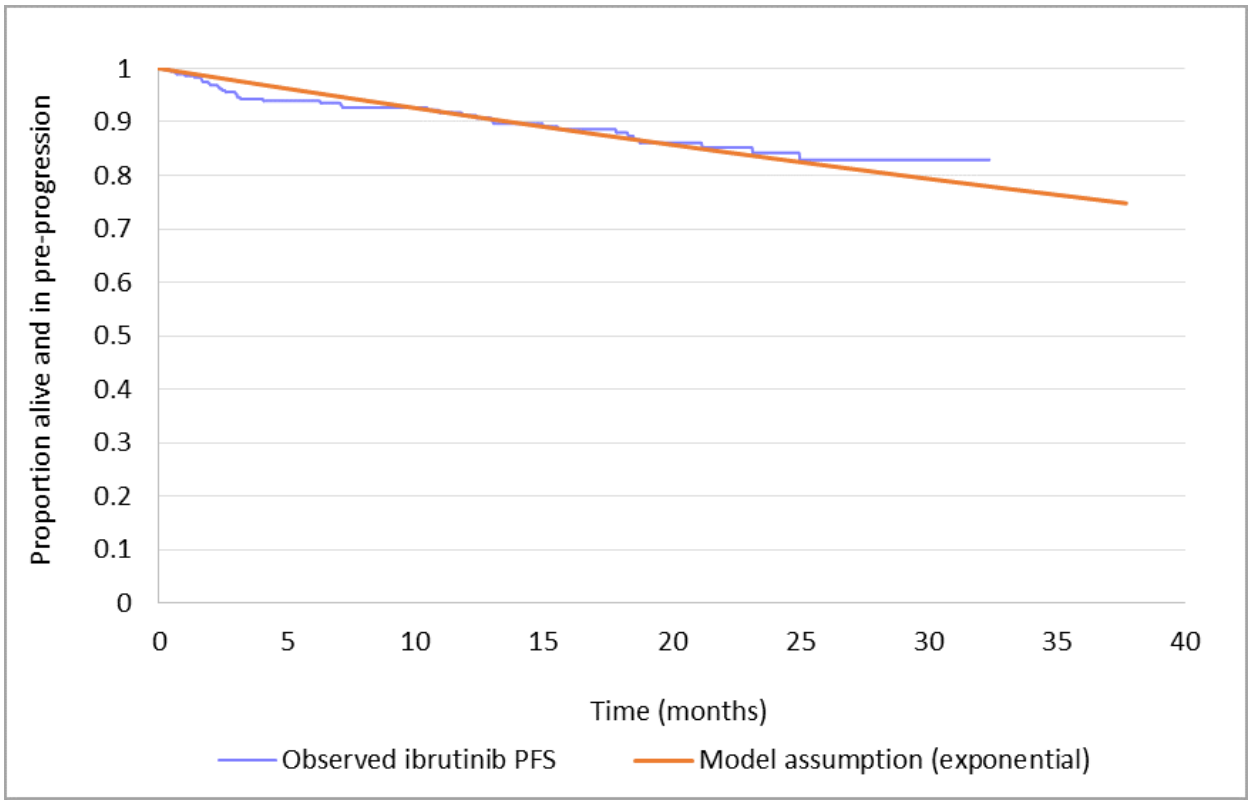
As shown in the log-cumulative hazard plot in Figure 12, applying an exponential distribution is appropriate in this analysis given the approximately straight line shown within the log-cumulative hazard plot (with a gradient of around 1). This indicates that the use of an exponential function applying a constant rate of pre-progression mortality is an appropriate methodology to model death during PFS.

Figure 12: Log-cumulative hazard plot - pre-progression mortality



In addition to this there were very low numbers of patients that experienced death during PFS (38 in the ibrutinib arm within the pooled data of 370 patients and 19 within the TEM arm from RAY (MCL3001)) (n=141), shown in the parametric curves in Figure 13 for the ibrutinib pooled data. This low number of events suggests that using more complicated methodology would not be supported by the available evidence.

Figure 13: Pre-progression mortality observed in pooled ibrutinib data



C23. PRIORITY. Pages 155-156, Figure 36. Given that the Kaplan-Meier curve presented in Figure 36 appears to be complete (with no right censoring), please explain why a parametric curve was fitted to the time on treatment data. Please comment on the apparently poor fit of the parametric curve. Please also comment on why the observed hazard of discontinuing ibrutinib increases sharply at around 27 months.

Parametric curves were fit to time on treatment data as the data were not complete. Ninety four out of the 370 patients within the pooled dataset were right censored.

The use of fitted curves avoids making unjustified model assumptions about long-term discontinuation rates based on the small patient numbers at latter time points still at risk in K-M data. As shown in Figure 14, the parametric curves appear have a fairly good visual fit to the data until approximately 27 months which is where the patient numbers still at risk for ibrutinib drops below 30, and therefore may be considered 'unstable'. This is a result of the low patient numbers remaining on treatment within the trial due to right censoring.

It should be noted that the use of parametric curves produces a longer estimate of time on treatment, as patients are projected to remain on treatment longer after the K-M curve meets the x-axis, and therefore assigns a greater cost to the ibrutinib arm, however, we do consider this to be a more methodologically correct approach. The impact of this has been explored in scenario analysis which uses the time on treatment K-M curve directly within the model rather than fitting parametric curves. The results of this adjustment are shown in Table 20, and, as would be expected, show a decrease in the total costs (with no discount) to both arms of the model £116,649 to £99,120 in the ibrutinib arm and £22,411 to £21,850 in the R-chemo arm, reducing the ICER from £100,647 within the initial base case to £83,028.

Figure 14: Time on treatment curves to pooled ibrutinib data

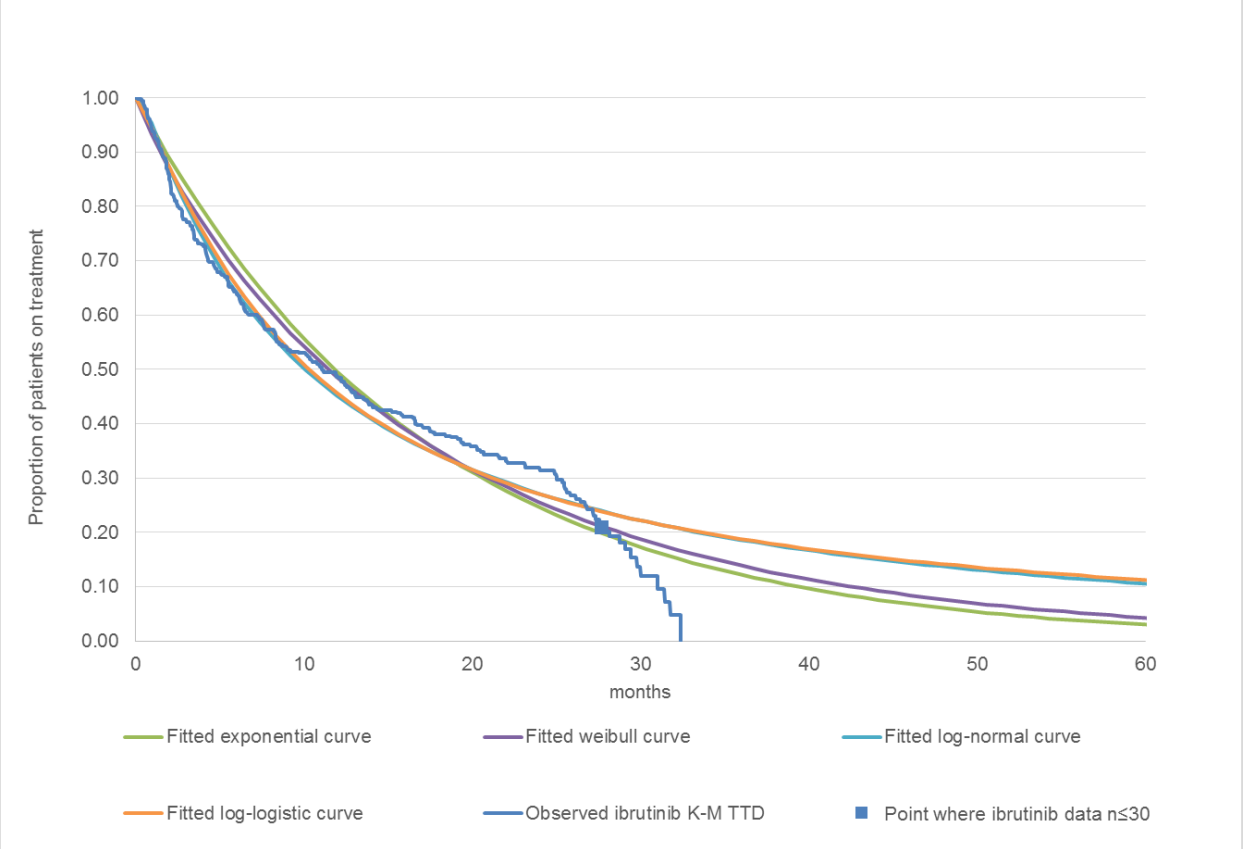


Table 20: Cost-effectiveness results using K-M data to inform time on treatment. No discount, error corrected

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (QALYs)
Ibrutinib	[redacted]	[redacted]	[redacted]	£78,264	1.23	0.93	£84,096
R-CHOP	[redacted]	[redacted]	[redacted]				

C24. Pages 137 and 155. Please clarify why the generalised gamma, generalised F and Gompertz curves were not fitted to the available time-to-event data for the outcomes of PFS and time to treatment discontinuation.

The Gompertz distribution differs from the Weibull distribution because it has a log-hazard function which is linear with respect to time, whereas the Weibull distribution is linear with respect to the log of time. Log-cumulative hazard plots (now provided in answer to question C19) show that the assumption of linearity with respect to time is not appropriate therefore the Gompertz distribution was not considered to represent an improvement to the survival curve fits already presented.

The generalised gamma distribution was not fitted originally as there was concern that use of a 3-parameter distribution might lead to too much weight being placed upon the observed

data (over-fitting) without due consideration to the clinical validity of longer term extrapolation.

The generalised F distribution is rarely used within economic models submitted to NICE and not recommended within the NICE DSU guidance. SAS software was used to produce the survival analysis presented within this submission; we are unaware of a package to produce this function within SAS.

For the purposes of thoroughness, analysis is presented below included the Gompertz and generalised gamma curve fits.

AIC and BIC statistics for the Gompertz and gamma curves compared to the curve fits already presented are shown in Table 21 and Table 22. For both PFS and time on treatment (ToT) the Gompertz curve has the highest AIC and BIC statistics indicating that it is statistically the worst fit. The generalised gamma curve provides a good statistical fit to both ToT and PFS.

Figure 15 and Figure 16, however, show that PFS curves using the generalised gamma and Gompertz functions both produce clinically implausible estimates of the time spent in PFS for patients with R/R MCL; these functions project longer PFS than the log-normal and log-logistic functions which clinicians did not consider to be plausible[31]. For ToT the curve fits are more in line with the other parametric models.

Figure 15: PFS curve fits to observed ibrutinib data

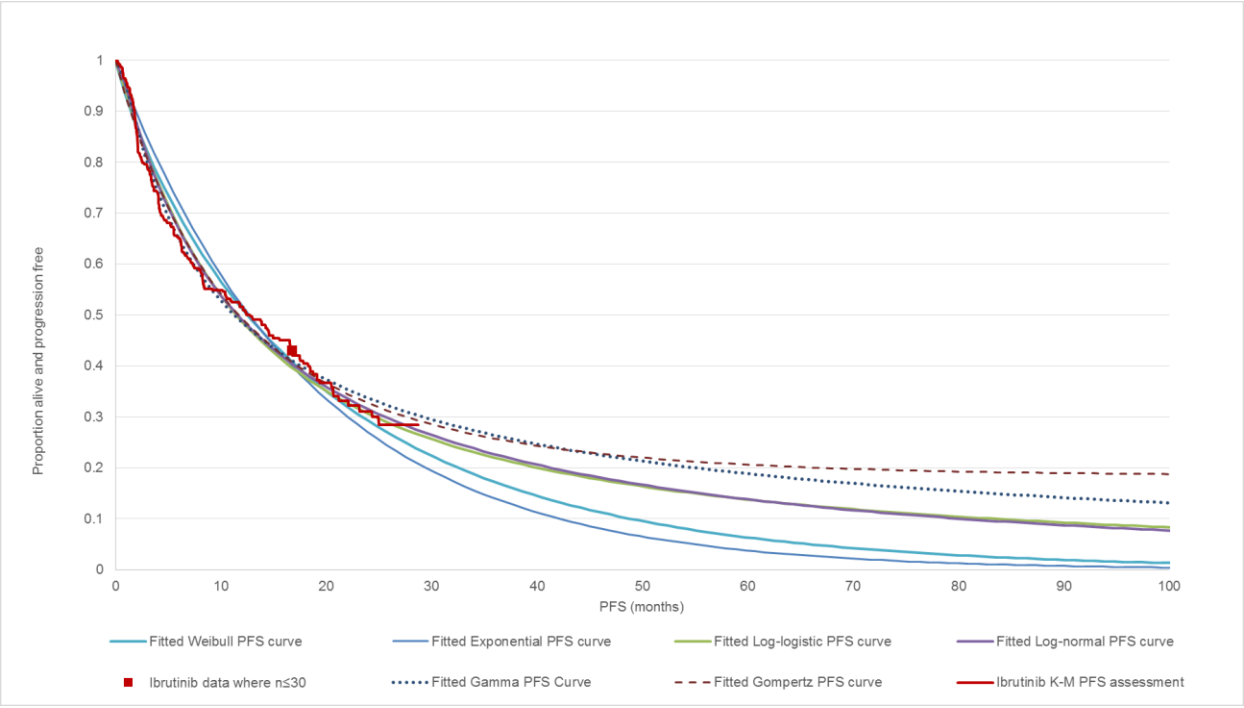


Table 21: AIC / BIC statistics for PFS data

	Weibull	Log Normal	Exponential	Log Logistic	Generalised Gamma	Gompertz
AIC	1058.355	1033.88	1061.221	1044.983	1031.28	1692.22
BIC	1066.182	1041.707	1065.134	1052.81	1043.02	1700.05

Figure 16: ToT curve fits to observed ibrutinib data

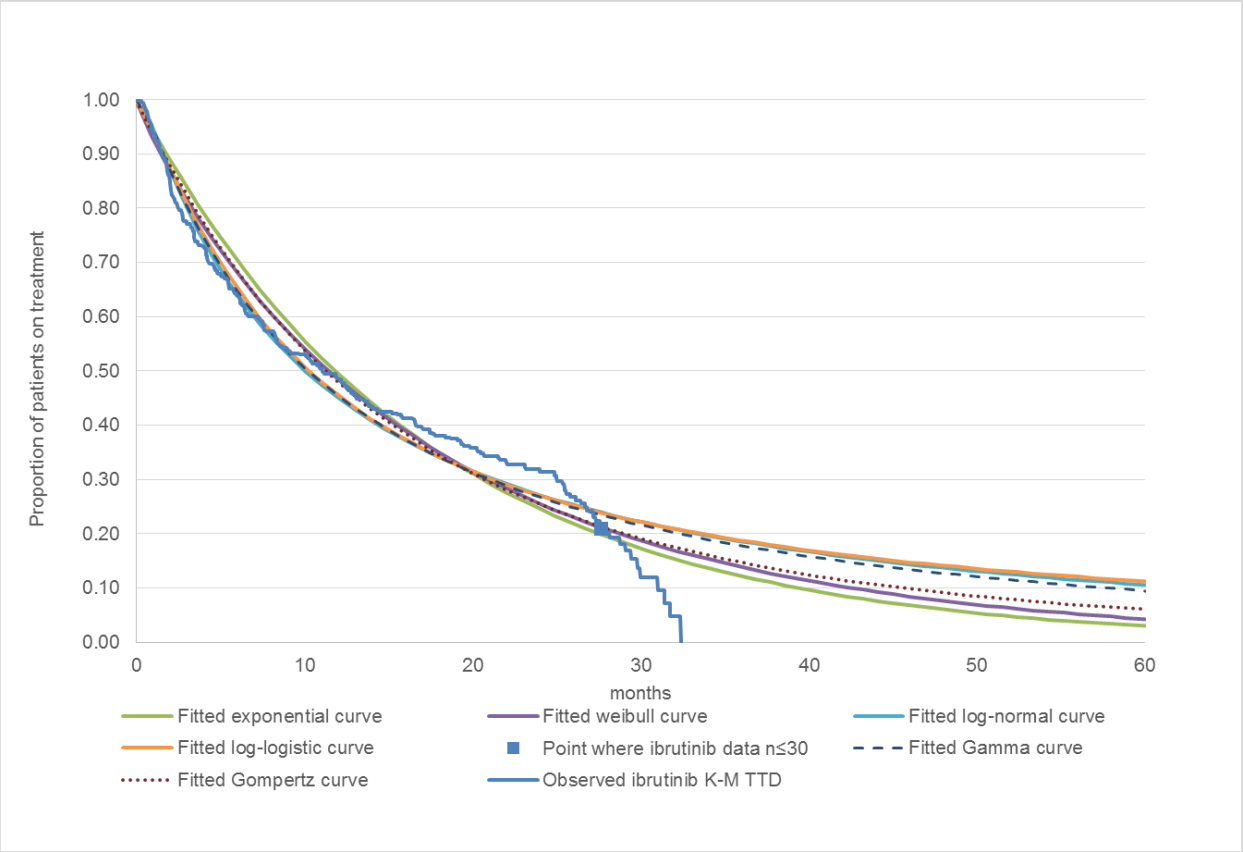


Table 22: AIC / BIC statistics for ToT data

	Weibull	Log Normal	Exponential	Log Logistic	Generalised Gamma	Gompertz
AIC	1165.331	1156.509	1166.49	1167.094	1158.118	2119.957
BIC	1173.158	1164.336	1170.404	1174.921	1169.859	2127.784

Table 23 shows the results of using the generalised gamma curves to inform PFS and ToT curves to inform the cost-effectiveness model. Within this scenario the total QALYs gained increases from 0.94 in the base case to 1.62, and incremental costs using no discount increase from £95,233 to £120,118. The ICER in this scenario falls from £101,709 in the revised base case to £74,298.

Table 23: Cost-effectiveness results using the generalised gamma curve to inform PFS and ToT. No discount, error fixed

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (QALYs)
Ibrutinib	[redacted]	[redacted]	[redacted]	£120,118	2.46	1.62	£74,298
R-CHOP	[redacted]	[redacted]	[redacted]				

Table 24 shows the results of the when Gompertz curves are used to inform PFS and ToT. Within this scenario the incremental QALYs increase from 0.94 in the base case approach (using a Weibull curve) to 1.94, and incremental costs increase from £95,233 to £107,782. The corresponding ICER falls from £101,709 in the base case analysis to £55,596.

Table 24: Cost-effectiveness results using the Gompertz curve to inform PFS and ToT. No discount, error fixed

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (QALYs)
Ibrutinib	[redacted]	[redacted]	[redacted]	£107,782	3.09	1.94	£55,596
R-CHOP	[redacted]	[redacted]	[redacted]				

C25. Pages 141-143. Please clarify why only the exponential model was fitted to the available time-to-event data for pre-progression mortality.

See C22

C26. Pages 141-143. Please clarify why only the exponential model was fitted to the available time-to-event data for post-progression mortality.

See C17

C27. Given that the comparative effectiveness of ibrutinib versus chemotherapy is modelled on the basis of a relative hazard ratio, please comment on the validity of applying hazard ratios to accelerated failure time survivor functions.

The application of hazard ratios to accelerated failure time models, whilst technically incorrect, is common practice where inputs are only available from NMA in the form of HRs. It should be noted that the impact of this simplification is limited within this submission as the Weibull distribution can be parameterised either as a proportional hazards model or an accelerated failure time model. Therefore there is no issue caused by applying a HR to the Weibull curves which are used within the model base case. Given the clear issues with clinical plausibility of the log-logistic and log-normal functions fitted to the PFS curves for ibrutinib (and the generalised gamma curve presented in answer to question C24) we would consider the issue of the validity of application of HRs to these curves to be a secondary

consideration when assessing their relevance. Within the timeframe available we have not been able to find any evidence on the potential impact of applying HRs, rather than assuming proportional odds, for accelerated failure time models with which to fully assess the potential for bias.

The inappropriateness of the use of accelerated failure time models (outside of potential issues applying HRs to them) is further supported by the QQ-plots shown in answer to question C21 (Figure 7 and Figure 8) which indicate that the log-normal and log-logistic models are not appropriate in this setting, shown by their skewed line.

C28. Please clarify why a scenario using only the RAY (MCL3001) trial, rather than the pooled dataset, was not presented in the health economic analysis.

Pooling the ibrutinib data seemed a more appropriate approach for a number of reasons: first of all the evidence base of using the three trials includes a higher number of patients. Further to this, the pooled dataset included the more mature Phase II datasets. The evidence suggests that there is limited difference between the RAY (MCL3001) dataset and the pooled dataset in terms of median PFS (14.59 and [redacted] respectively) and restricted mean PFS calculated based upon within trial data analysis (15.28 and [redacted] respectively).

Questions relating to the model

C29. Worksheet “Cost derivation”, cell B2. Please clarify why the model refers to “Scottish tariffs”.

This cell is not applicable to the health-economic model and should be ignored. Costs in the model are informed from NHS reference costs 2014/2015.

C30. Worksheet “PFS Curve fits to KM data.” Please comment on the poor fit of the log logistic survivor function in the graph.

The sheet ‘PFS Curve fits to KM data’ is used to graphically visualise the fit of the different parametric curves to the KM data and not to inform the model calculations. The poor log-logistic parametric curve is due to an error in the formula used to calculate the log-logistic function.

For example:

Cell F12 currently reading:
=1/(1+EXP(-$F$6*(1/$F$7))*B12)^(1/$F$7)

Should read:
= 1/(1+EXP(-$F$6*(1/$F$7))*(B12)^(1/$F$7))

As this sheet isn’t used to inform any model calculations, this error will not affect any model outcomes.

C31. PRIORITY. Given that the sequential method attempts to model ibrutinib->R-CHEMO versus R-CHEMO, please explain why when the sequential method is selected, the mean survival gain for ibrutinib remain unchanged, yet the R-CHEMO survival decreases.

The sequential approach does not apply any increased survival benefit from additional treatment within the ibrutinib arm as the PPS data from the ibrutinib pooled dataset already incorporates the use of subsequent therapies. Therefore instead of increasing survival in the ibrutinib arm, the survival of R-chemo is decreased to reflect the fact that, unlike within the ibrutinib arm, if no further effective R-chemos can be used, as is often the case within current UK clinical practice, there can be no benefit associated with an additional line of treatment (i.e. PPS will be shorter).

As such, the ibrutinib arm within the economic analysis still has the same health outcomes as in the Fixed PPS approach, but it incorporates the costs associated with subsequent LOTs (assuming all patients receive R-chemo and this has the same impact on PPS as the subsequent therapies received by patients in the ibrutinib clinical trials).

The PPS for ibrutinib is metaphorically split into two sections: the PFS for R-chemo treatment and the PPS of subsequent R-chemo treatment. As the mean PFS time for R-chemo post ibrutinib is calculated based on a constant rate of progression from the exponential distribution (15.6%), the risk of death during PPS once patients are unable to receive additional lines of effective R-chemo is therefore re-estimated, and increases to reflect a lower survival that would be expected for patients with fewer remaining treatment options available to them. This increased risk of death in PPS once patients are unable to receive additional lines of effective R-chemo is applied to both model arms.

C32. Worksheet “Parameters”, cell Q28. Why is no uncertainty around the compliance rate assumed?

Dosing compliance should have been varied within the sensitivity analysis and the omission was an oversight. This parameter should have been varied with a mean of 94% and a SD of 9.59. Analysis presented within the revised appendix includes variation around this parameter.

C33. Worksheet “AE”. With reference to the ibrutinib studies, please comment on the validity of the assumption that adverse events occur only once during the first cycle.

The totality of AEs which occurred within the clinical trial are modelled as a lump sum cost within the first model cycle as a simplifying assumption. This simplifying assumption would appear appropriate based upon the data available for AEs of interest as the majority of AEs occur within the first 5 (28-day) cycles of treatment within the clinical trial (see Table 25). In fact no AEs within the categories included within the economic model were recorded after cycle 18 of the clinical trial, despite treatment continue for up to 35 cycles for some patients.

Table 25: Total number of Grade ≥3 AEs within the Ibrutinib pooled dataset for each cycle (28days)

Cycle	Neutropenia	Anaemia	Pneumonia	Leukopenia	Febrile neutropenia	Infection	Major bleeding	Atrial fibrilation	Tumour lysis syndrome	Leukostasis	Lymphocytosis	Renal failure	Cytomegaloviru s (CMV) reactivation	Abnormal liver function test
1	12 (3.3%)	15 (4.1%)	4 (1.1%)	0 (0.0%)	4 (1.1%)	1 (0.3%)	1 (0.3%)	2 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
2	14 (4.1%)	2 (0.6%)	8 (2.4%)	2 (0.6%)	3 (0.9%)	0 (0.0%)	3 (0.9%)	4 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	14 (4.6%)	3 (1.0%)	4 (1.3%)	3 (1.0%)	2 (0.7%)	0 (0.0%)	4 (1.3%)	2 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.7%)	0 (0.0%)	0 (0.0%)
4	12 (4.2%)	1 (0.4%)	2 (0.7%)	1 (0.4%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	22 (8.2%)	3 (1.1%)	5 (1.9%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	3 (1.1%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
6	8 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.8%)	3 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
7	7 (2.9%)	3 (1.3%)	2 (0.8%)	0 (0.0%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
8	8 (3.6%)	4 (1.8%)	4 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
9	5 (2.4%)	1 (0.5%)	2 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
10	2 (1.0%)	1 (0.5%)	3 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
11	4 (2.0%)	2 (1.0%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
12	2 (1.1%)	2 (1.1%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
13	5 (2.7%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	0 (0.0%)
14	6(3.4%)	0(0.0%)	0(0.0%)	1 (0.6%)	1 (0.6%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
15	2 (1.2%)	1 (0.6%)	3 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
16	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
17	3 (1.9%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
18	2 (1.3%)	2 (1.3%)	2 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.7%)	1 (0.7%)	0 (0.0%)	0 (0.0%)

C34. Worksheet “Parameters”, cells D28:D29. Please justify the assumption of equal relative dose intensity in both the ibrutinib and R-CHEMO groups. Why were other external data not used to inform this parameter for the R-CHEMO group?

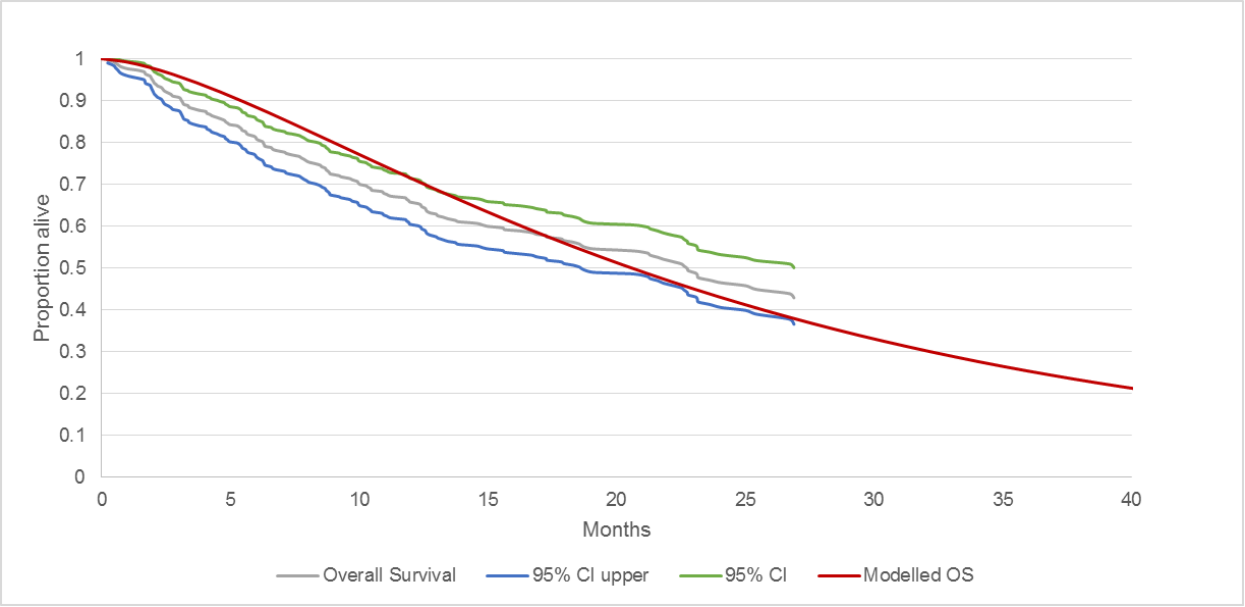
The only external evidence available in relation to the dosing intensity of R-chemo groups is that from TA370 for first-line MCL, where the relative dose intensity was reported from the LYM3002 trial which compared VR-CAP to R-CHOP. For the treatments common to both comparators (rituximab, cyclophosphamide, doxorubicin and prednisone), dose intensity was high at 93% or higher for each common component. Dosing intensity was slightly lower at 80% for vincristine[38]. Overall, with figures not too dissimilar, applying an equal relative dosing intensity of 94% represented a justifiable assumption considering that data are not available with which to make a more informed assumption within the correct treatment setting.

C35. PRIORITY. Worksheet “Clinical Inputs” overall survival graph. Please comment on the discrepancy between the model predicted overall survival and the observed Kaplan-Meier curve for ibrutinib.

As is often the case when a state transition model is used rather than a partitioned survival model the final projections for OS do not represent a completely pleasing fit to the OS curve observed within the clinical trial. The strengths and weaknesses of state transition models compared to partitioned survival models and validity of the partitioned survival model approach is currently the subject of considerable debate among health economists and will be the subject of forthcoming NICE DSU guidance. In the absence of this guidance being available we would like to comment that whilst there is some discrepancy between the K-M and the fitted curve the scale of discrepancy is not large and estimates of survival for patients receiving ibrutinib are conservative in the long-term compared to the observed data.

The K-M data from the pooled ibrutinib dataset although immature, was plotted with 95% confidence intervals to test how the models predicted OS using the PFS+PPS approach compared. As shown in Figure 17, after the initial 10 month period where the model slightly over predicts OS outside of the confidence interval, the overall survival then falls to within the 95% CI of the K-M data, compensating with slight under-prediction.

Figure 17: Ibrutinib modelled PFS+PPS against observed OS



Given the issues with the ibrutinib and comparator data available for OS (detailed in answer to question C12) we would maintain that the benefits of the use of the PFS + PPS approach, in terms of allowing sensible assumptions to be made around PPS, outweigh issues of discrepancy between projections and the K-M data.

Section D: Data request

D1. Please provide estimates of EQ-5D utilities for the progression-free and post-progression states for the TEMS group in the RAY (MCL3001) trial.

EQ-5D utilities are provided for the progression-free and post-progression states using IRC assessment and mixed model analysis in Table 26. Progression status was not significant at the 5% level in this analysis (mean difference 0.077, p value = 0.0835) as we would expect due to the low number of observations available in the post-progression state (n=24).

Table 26: EQ-5D utilities using IRC assessment and mixed model analysis

	n	Mean utility	SE	95% CI
Pre-progression	427	0.732	0.018	0.697 – 0.767
Post progression	24	0.655	0.044	0.568 – 0.742

D2. Please provide individual patient-level survival data for overall survival for ibrutinib from RAY (MCL3001), SPARK (MCL2001) and PCYC1104. Please present the equivalent data for TEMS from RAY (MCL3001). If possible, apply crossover adjustment methods to the data from RAY (MCL3001).

Survival data are provided in the excel file for ibrutinib in RAY (MCL3001), SPARK (MCL2001) and PCYC1104 and TEMS in RAY (MCL3001). Adjusted data can be provided for the RPSFT method if required by the ERG based upon the answer to question C20.

Appendix

1 Base-case results (No PAS)

Results presented within this section are at list price for ibrutinib. Economic analysis incorporating the current simple PAS is presented in Appendix 2.

1.1 *Base-case incremental cost effectiveness analysis results*

Base case results of the economic comparison between ibrutinib and R-CHOP discounted at 3.5% for costs and QALYs over the 15-year time horizon are presented in Table 1.

Ibrutinib was estimated to generate an additional 1.23 life years and 0.94 QALYs. This represents a substantial improvement to both length and QoL for patients with an extremely poor prognosis. The mean life years estimated for patients treated with ibrutinib are over double compared to what estimated for R-chemo.

Table 1: Base case discounted results, ibrutinib versus R-CHOP

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Ibrutinib	[redacted]	[redacted]	[redacted]	£95,233	1.23	0.94	£101,709
R-CHOP	[redacted]	[redacted]	[redacted]				

ICER: incremental cost-effectiveness ratio, QALYs:, quality-adjusted life years, R-CHOP: rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone

1.1.1 *Clinical outcomes from the model*

Table 2 summarises the median results estimated by the CEA in comparison to median results observed in the ibrutinib pooled dataset for the key clinical outcomes. The model predicted the median PFS accurately and predicted the median OS conservatively. The median OS predicted within the model for R-chemo is relatively high compared to the OS information available from published data sources indicating that a highly conservative comparison of the relative effectiveness of ibrutinib to R-chemo has been presented.

Table 2: Summary of model results compared with clinical data (months)

Outcome	Ibrutinib pooled dataset	Ibrutinib model results	R-chemo literature information	R-chemo model results
Median PFS	[redacted]	12.88	1.9 from Hess, 2009[35] 2.8 in Skåne registry[43]	2.76
Median OS	[redacted]	20.24	8.4 in HMRN[44] 9.7 in Hess, 2009[35] 5.2 in Skåne registry[43]	10.12

NE: not evaluable, OS: overall survival, PFS: progression-free survival, R-chemo: rituximab in combination with chemotherapy, HMRN: Haematological Malignancy Research Network

1.1.2 *Disaggregated results of the base case incremental cost effectiveness analysis*

Table 3 summarises the total QALYs for both arms of the base case model, disaggregated by the model health states. Table 4 summarises the total life years accrued over the time

horizon for both arms of the model. As expected, the majority of the difference between the two model arms is observed in the pre-progression health state. Table 5 shows the predicted total incremental costs for ibrutinib versus R-CHOP. The majority of the costs are incurred within the pre-progression health state, and represent the drug costs associated with treating patients with R/R MCL. Table 6 shows these data further split by the category of cost incurred within the model.

Table 3: Base case: total discounted QALYs gained by health state

	QALY ibrutinib	QALY R-CHOP	Increment
PFS	[redacted]	[redacted]	0.99
PPS	[redacted]	[redacted]	-0.05
Total	[redacted]	[redacted]	0.94

QALY: quality-adjusted life year, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone, PFS: progression-free survival, PPS: post-progression survival

Table 4: Base case: total undiscounted LYs gained by health state

	LY ibrutinib	LY R-CHOP	Increment
PFS	[redacted]	[redacted]	1.29
PPS	[redacted]	[redacted]	-0.06
Total	[redacted]	[redacted]	1.23

LY: life year, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone, PFS: progression-free survival, PPS: post-progression survival

Table 5: Base case: total discounted costs accrued in each health state

	Costs ibrutinib	Costs R-CHOP	Increment
PFS	[redacted]	[redacted]	£96,212
PPS	[redacted]	[redacted]	-£979
Total	[redacted]	[redacted]	£95,233

LY: life year, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone, PFS: progression-free survival, PPS: post-progression survival

Table 6: Base case: category of discounted costs accrued within the model

Item	Cost ibrutinib	Cost R-CHOP	Increment
PFS drug cost	[redacted]	[redacted]	£92,573
PFS administration cost	[redacted]	[redacted]	-£1,427
PFS routine follow up	[redacted]	[redacted]	£5,152
AE cost	[redacted]	[redacted]	-£86
Subsequent treatment	[redacted]	[redacted]	£0
PPS routine follow up cost	[redacted]	[redacted]	-£693
Terminal care cost	[redacted]	[redacted]	-£286
Total costs	[redacted]	[redacted]	£95,233

AE: adverse event, PFS: progression-free survival, PPS: post-progression survival, R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

1.2 *Sensitivity analyses*

1.2.1 *Probabilistic sensitivity analysis*

Probabilistic sensitivity analysis (PSA) was performed within the CEA for 1,000 iterations of ibrutinib versus R-CHOP, randomly sampling parameters within their chosen distributions. This analysis demonstrates the impact of parameter uncertainty within the economic model. The results of this analysis are presented in Figure 1 which shows the incremental costs and QALYs for each iteration. Incremental QALYs range from approximately 0.6-1.4, while incremental costs range from £80,000 to £120,000. The largest spread of uncertainty was across the x axis reporting the incremental QALYs. Overall the average incremental QALYs gained from ibrutinib was 0.94 with a mean incremental cost of £96,103, resulting in a mean probabilistic ICER of £101,453. The overall average results were very close to the deterministic base case results (0.94 and £95,697 incremental QALYs and costs respectively), indicating that there is no bias in the deterministic ICER caused by skewed uncertainty within the model parameters.

Based on the 1,000 iterations performed within the PSA, a cost-effectiveness acceptability curve (CEAC) was constructed and is presented in Figure 2. This graph shows the likelihood that each treatment is the most cost-effective option at different willingness to pay (WTP) thresholds.

Figure 1: Cost-effectiveness plane from 1,000 PSA iterations

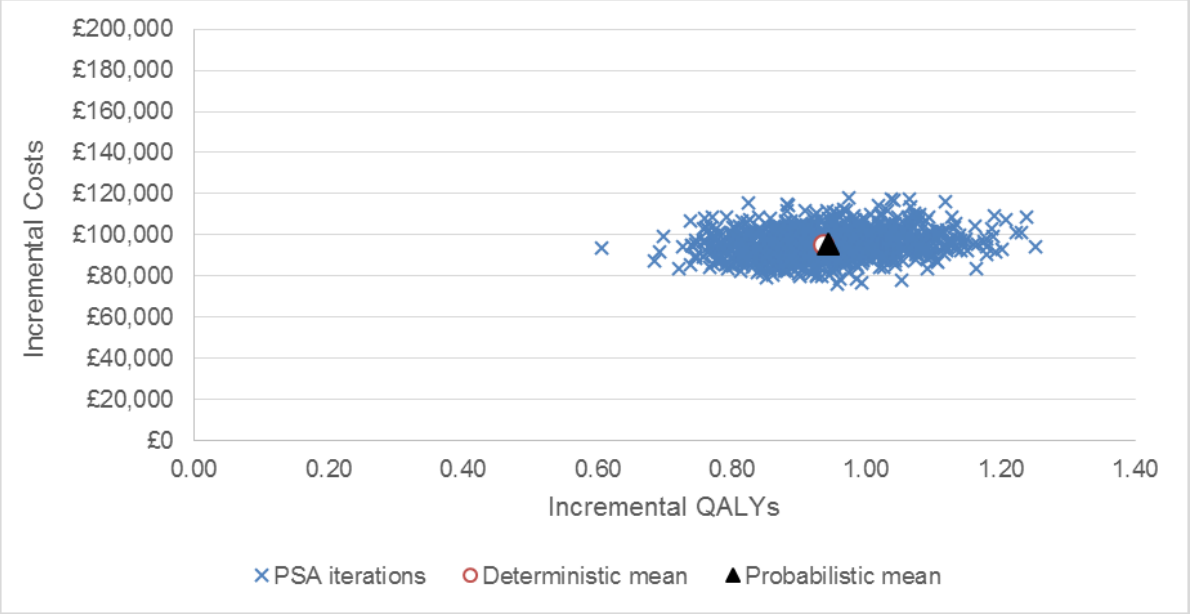
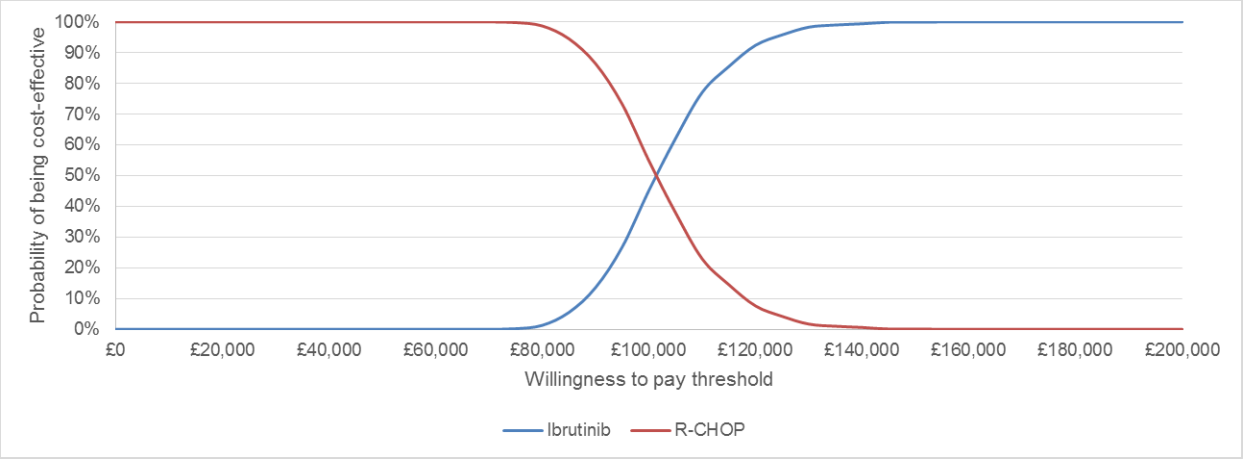


Figure 1: Incremental cost-effectiveness acceptability curve



1.2.2 ***Deterministic sensitivity analysis***

Figure 3 presents a tornado diagram showing the parameters with the greatest impact on the net monetary benefit (NMB) of ibrutinib, with descending sensitivity.

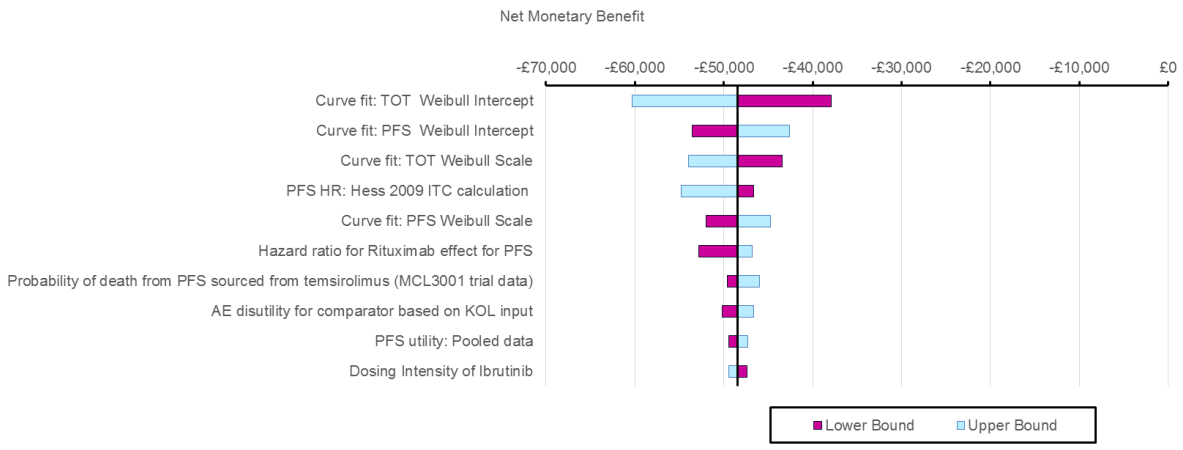
The NMB was calculated as:

$$NMB = (WTP \times Incremental\ QALYs) - Incremental\ Costs$$

The WTP was set at £50,000/QALY, as ibrutinib meets the *end-of-life* criteria in this indication (see Section 4.14.3).

NMB was used in order to account for any issues which may arise as a result of dominant or dominated results where negative ICERs are created. Where the NMB is positive, ibrutinib represents a cost-effective treatment based on a WTP threshold of £50,000 per QALY. Figure 3 shows the ten most influential parameters. The NMB was most sensitive to the uncertainty within the curve fit parameters for TOT and PFS. Parameters informing the HR for comparative efficacy were also influential within the CEA as would be expected. The utility data informing the model were also influential, with both the PFS utility and the disutility associated with R-chemo appearing within the top 10 parameters.

Figure 3: Tornado diagram



1.2.3 ***Scenario analysis***

Table 7 shows the results of the extensive scenario analyses performed which tested the structural uncertainty within the model and are described in Section 5.6. Overall the model was most sensitive to the PPS assumed for the R-chemo arm. Within the PPS scenario a HR was applied to the PPS for R-chemo that reduced the time spent in PPS. The HR selected minimised the difference between the median OS within the model and the median survival reported within the HMRN data (which was estimated to be 8.4 months for patients on second line treatment regimens)[44].

The model was also sensitive to the dataset used to inform PFS of R-chemo. Testing the PFS of TEM from RAY (MCL3001) as a proxy for R-chemo increased the ICER as the estimate used to inform R-chemo here was higher than the one in the base case. It should be noted that no evidence is available regarding the comparative effectiveness of TEM and R-chemo.

In general, results from scenario analyses were consistent with the base case results, demonstrating the minimal amount of uncertainty in the key assumptions.

Table 7: Scenario analyses conducted within the economic model

Scenario	Ibrutinib			R-CHOP			Incremental outcomes			
	Total Costs	Total QALYs	Total LYs	Total Costs	Total QALYs	Total LYs	Inc. Costs	Inc. QALYs	Inc. LYs	ICER
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£95,233	0.94	1.23	£101,709
Comparator efficacy HR for PFS using TEM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£94,909	0.93	1.22	£102,241
Time horizon: 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£95,256	0.94	1.24	£101,653
Time horizon: 20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£96,558	0.94	1.23	£103,124
Comparator: R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£93,065	0.94	1.23	£99,394
Comparator FCR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£94,291	0.94	1.23	£100,704
Comparator RC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£95,257	0.94	1.23	£101,735
Treatment mix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£95,233	0.94	1.23	£101,709
No wastage included	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£95,659	0.94	1.23	£102,164
Utility decrement for R-chemo based on Schenkel *et al.* 2014	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£95,233	0.93	1.23	£102,892
No age-adjusted utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£95,233	0.95	1.23	£100,384
Sequential approach (OS ibrutinib = PFS ibrutinib + PFS R-chemo + PPS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£107,462	1.08	1.43	£99,566
Including FCR as subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£93,651	0.94	1.23	£100,020
PFS curve: exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£90,779	0.83	1.06	£108,934
PFS curve: log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£124,731	1.30	1.88	£96,005
PFS curve: log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£131,215	1.32	1.93	£99,415
Risk of death during PFS for R-chemo assumed equal to ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£94,986	0.92	1.21	£103,542

Scenario	Ibrutinib			R-CHOP			Incremental outcomes			
	Total Costs	Total QALYs	Total LYs	Total Costs	Total QALYs	Total LYs	Inc. Costs	Inc. QALYs	Inc. LYs	ICER
Response rates of R-chemo equal to TEM response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£94,779	0.94	1.23	£101,224
Response rates of R-chemo equal to response in Hess, 2009 Y	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£94,318	0.94	1.23	£100,733
Response rates of R-chemo equal to ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£95,337	0.94	1.23	£101,820
No benefit from rituximab in PFS HR (rituximab HR = 1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£97,020	1.00	1.35	£97,023
Rituximab PFS HR applied to Hess, 2009 ITC = 0.75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£95,644	0.95	1.26	£100,358
Rituximab PFS HR applied to Hess, 2009 ITC = 0.89	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£96,471	0.98	1.32	£98,163
Rituximab PFS HR applied to Hess 2009 ITC = 1.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£99,032	1.05	1.44	£94,312
Applying a HR to PPS of R-chemo to adjust survival to be as close as possible to HMRN anticipated survival (8.4 months for patients on 2nd line treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£147,936	1.87	2.64	£79,128

HR: hazard ratio, PFS: progression-free survival, TEM: temsirolimus, R-CVP: rituximab + cyclophosphamide + vincristine + prednisone, FCR: fludarabine + cyclophosphamide + rituximab, RC: rituximab + cytarabine, R-chemo: rituximab-based chemotherapy, OS: overall survival, ITC: indirect treatment comparison, PPS: post-progression survival, HMRN: haematological malignancy research network, QALY: quality-adjusted life year, LY: life year, Inc: incremental

1.2.4 *Summary of sensitivity analyses results*

PSA indicates that the results obtained within the base case were robust to parameter uncertainty, with average PSA results very similar to the deterministic results. The model results showed that the majority of uncertainty lays within the estimated QALYs, however, in all cases a substantial QALY improvement was expected for ibrutinib compared to R-chemo (QALY gains expected to lie between 0.6 and 1.4).

Key uncertainties within the model parameterisation surrounded the parametric curve fits to TOT and PFS and the HR assumed for comparative efficacy within the model. Within scenario analysis the model was also sensitive to the PPS assumed for R-chemo, with the ICER reducing when HMRN data were used to inform PPS. The model was also sensitive to the dataset used to inform the PFS of R-chemo, with the use of the TEM arm of RAY (MCL3001) as proxy for R-chemo producing an increased estimate of the ICER.

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

1.3 *Subgroup analysis*

Results of the economic comparison between ibrutinib and R-CHOP for subgroups of 1 prior LOT versus 2+ prior LOTs are presented in Table 8 and Table 9. Substantially higher estimates of LYs and QALYs were produced for ibrutinib in the subgroup of patients only receiving one prior LOT. These results are consistent with the findings of the post-hoc analysis of RAY (MCL3001) presented in Section 4.8.2, clearly demonstrating that an increased benefit is observed when ibrutinib is used early in the treatment pathway for R/R MCL, which were also confirmed in the pooled dataset (Section 4.12.2). In those patients with 1 prior LOT, ibrutinib produces 3.65 LYs, compared to 1.91 LYs in patients with 2+ prior LOTs. This strongly suggests that whilst all R/R MCL patients can benefit from ibrutinib, the benefit is more pronounced the earlier they receive it.

Table 8: Base case discounted results, ibrutinib versus R-CHOP: 1 prior LOT

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Ibrutinib	[redacted]	[redacted]	[redacted]	£145,385	2.34	1.67	£86,851
R-CHOP	[redacted]	[redacted]	[redacted]				
ICER: incremental cost-effectiveness ratio, QALYs:, quality-adjusted life years, R-CHOP: rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone							

Table 9: Base case discounted results, ibrutinib versus R-CHOP: 2 + prior LOTs

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Ibrutinib	[redacted]	[redacted]	[redacted]	£81,046	0.92	0.72	£113,053
R-CHOP	[redacted]	[redacted]	[redacted]				
ICER: incremental cost-effectiveness ratio, QALYs:, quality-adjusted life years, R-CHOP: rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone							

1.4 *Threshold analysis on comparative efficacy*

Due to the paucity of data available to inform the effectiveness of the comparators in the NICE scope, a high level of uncertainty specifically lies within the PFS HR estimate used to inform the comparative effectiveness of R-chemo. As explained in previous sections, this is not an uncertainty that Janssen could have addressed, due to the unlicensed nature of R-chemo. We have therefore presented an extensive analysis below showing how much the estimated benefit of R-chemo (in terms of PFS HR for ibrutinib vs. R-chemo, and the specific HR for the effect of adding rituximab to chemo) would need to increase in order to produce a meaningful increase in the ICER (i.e., how a decrease in the relative benefit of ibrutinib vs. R-chemo impacts the ICER).

Table 10 shows how the ICER changes with an increase in HR of R-chemo (i.e., decreasing the comparative effectiveness of ibrutinib over R-chemo). The analysis shows that the ICER is relatively insensitive to any increase in R-chemo HR. Even when the HR is increased by as much as 90% (HR=0.53) the ICER only increases by 22.79%. This HR of 0.53 could be considered clinically implausible as this would represent a mean PFS for R-chemo of 10.09 months, which is considerably greater than that observed in clinical practice (1.9 months in Hess, 2009 and 2.8 months in Skåne).

A similar conclusion can be drawn from the 'threshold' analysis on the effect of adding rituximab to the HR derived from Hess, 2009 (Table 11). Decreasing the HR of adding rituximab (which increases the overall PFS HR of R-chemo, thus reducing the estimate of comparative efficacy of ibrutinib over R-chemo) does not impact the ICER substantially (for example, a decrease of 45% only raises the ICER by 19.29%). The ICER raises substantially only when unrealistic HRs for the rituximab effect are tested, such as a HR of 0.17, which would mean that rituximab would add an additional benefit of 83% to the one observed in Hess, 2009.

Consequently, these 'threshold' analyses show how, despite there being uncertainty in the estimates of the comparative efficacy of comparators from the NICE scope in this submission, the ICER remains relatively stable.

Table 10: Threshold analysis on the PFS HR of R-chemo

Increase in HR of R-chemo	R-chemo HR	ICER	Increase in ICER
Base case	0.28	£101,709	
15%	0.32	£104,742	2.98%
30%	0.36	£107,802	5.99%
45%	0.41	£112,104	10.22%
50%	0.42	£113,031	11.13%
60%	0.45	£115,954	14.01%
75%	0.49	£120,203	18.18%
90%	0.53	£124,890	22.79%
105%	0.57	£130,068	27.88%
120%	0.62	£137,325	35.02%

Increase in HR of R-chemo	R-chemo HR	ICER	Increase in ICER
135%	0.66	£143,856	41.44%
150%	0.70	£151,139	48.60%
R-chemo: rituximab in combination with chemotherapy, HR: hazard ratio, ICER: incremental cost-effectiveness ratio			

Table 11: Threshold analysis on the PFS HR for the effect of adding rituximab

Increase in HR of the effect of rituximab	Effect of rituximab HR	ICER	Increase in ICER
Base case	**0.69**	£101,709	
-15%	0.59	£104,890	3.13%
-30%	0.48	£110,829	8.97%
-45%	0.38	£121,332	19.29%
-60%	0.28	£147,137	44.67%
-75%	0.17	£338,364	232.68%
R-chemo: rituximab in combination with chemotherapy, HR: hazard ratio, ICER: incremental cost-effectiveness ratio			

2 Cost-effectiveness results using agreed discount price

2.1 *Base-case results: using applied discount*

This section outlines the results of the CEA when using an agreed discount of ibrutinib of [redacted]

2.1.1 *Base-case incremental cost effectiveness analysis results*

Base case results of the economic comparison between ibrutinib and R-CHOP discounted at 3.5% for costs and QALYs over the 15 year time horizon are presented in Table 12.

Ibrutinib was estimated to generate an additional 1.23 life years and 0.94 QALYs. This represents a substantial improvement to both length and QoL for patients with an extremely poor prognosis. The mean life years estimated for patients treated with ibrutinib are over double compared to what estimated for R-chemo. The resulting ICER with the agreed discount is [redacted].

Table 12: Base case discounted results, ibrutinib versus R-CHOP using agreed discount price for ibrutinib

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Ibrutinib	[redacted]	2.28	1.59	[redacted]	1.23	0.94	[redacted]
R-CHOP	[redacted]	1.04	0.65				
ICER: incremental cost-effectiveness ratio, QALYs:, quality-adjusted life years, R-CHOP: rituximab with							

cyclophosphamide, doxorubicin, vincristine and prednisone,

2.1.2 *Disaggregated results of the base case incremental cost effectiveness analysis*

Table 13 summarises the total QALYs for both arms of the base case model, disaggregated by the model health states. Table 14 summarises the total life years accrued over the time horizon for both arms of the model. As expected the majority of the difference between the two model arms is observed in the pre-progression health state. Table 15 shows the predicted total incremental costs for ibrutinib versus R-CHOP. The majority of the costs are incurred within the pre-progression health state, and represent the drug costs associated with treating patients with R/R MCL. Table 16 shows these data further split by the category of cost incurred within the model.

Table 13: Base case: total discounted QALYs gained by health state

	QALY ibrutinib	QALY R-CHOP	Increment
PFS	[redacted]	[redacted]	0.99
PPS	[redacted]	[redacted]	-0.05
Total	[redacted]	[redacted]	0.94

QALY: quality-adjusted life year, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone, PFS: progression-free survival, PPS: post-progression survival

Table 14: Base case: total undiscounted LYs gained by health state

	LY ibrutinib	LY R-CHOP	Increment
PFS	[redacted]	[redacted]	1.29
PPS	[redacted]	[redacted]	-0.06
Total	[redacted]	[redacted]	1.23

LY: life year, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone, PFS: progression-free survival, PPS: post-progression survival

Table 15: Base case: total discounted costs accrued in each health state

	Costs ibrutinib	Costs R-CHOP	Increment
PFS	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

LY: life year, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone, PFS: progression-free survival, PPS: post-progression survival

Table 16: Base case: category of discounted costs accrued within the model

Item	Cost ibrutinib	Cost R-CHOP	Increment
PFS drug cost	[redacted]	[redacted]	[redacted]
PFS administration cost	[redacted]	[redacted]	[redacted]
PFS routine follow up	[redacted]	[redacted]	[redacted]
AE cost	[redacted]	[redacted]	[redacted]
Subsequent treatment	[redacted]	[redacted]	[redacted]
PPS routine follow up cost	[redacted]	[redacted]	[redacted]

Terminal care cost	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
AE: adverse event, PFS: progression-free survival, PPS: post-progression survival, R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone			

2.2 ***Sensitivity analyses***

2.2.1 ***Probabilistic sensitivity analysis***

PSA was performed within the CEA for 1,000 iterations of ibrutinib versus R-CHOP, randomly sampling parameters within their chosen distributions. This analysis demonstrates the impact of parameter uncertainty within the economic model. The results of this analysis are presented in Figure 4, which shows the incremental costs and QALYs for each iteration. Incremental QALYs range from approximately 0.6-1.4, while incremental costs range from [redacted] to [redacted]. The largest spread of uncertainty was across the x axis reporting the incremental QALYs. Overall the average incremental QALYs gained from ibrutinib was 0.94 with a mean incremental cost of [redacted], resulting in a mean probabilistic ICER of [redacted]. The overall average results were very close to the deterministic base case results (0.94 and [redacted] incremental QALYs and costs respectively), indicating that there is no bias in the deterministic ICER caused by skewed uncertainty within the model parameters.

Based on the 1,000 iterations performed within the PSA, a CEAC was constructed and is presented in Figure 5. This graph shows the likelihood that each treatment is the most cost-effective option at different WTP thresholds.

[redacted]

[redacted]

2.2.2 ***Deterministic sensitivity analysis***

Figure 6 presents a tornado diagram showing the parameters with the greatest impact on the net NMB of ibrutinib, with descending sensitivity.

The NMB was calculated as:

$$NMB = (WTP \times Incremental\ QALYs) - Incremental\ Costs$$

The WTP was set at £50,000/QALY, on the assumption that ibrutinib meets the *end-of-life* criteria in this indication (see Section 4.14.3).

As for the results with no discount, NMB was used in order to account for any issues which may arise as a result of dominant or dominated results where negative ICERs are created. Where the NMB is positive, ibrutinib represents a cost-effective treatment based on a WTP threshold of £50,000 per QALY. Figure 6 shows the ten most influential parameters. The NMB was most sensitive to the uncertainty within the curve fit parameters for TOT and PFS. Parameters informing the HR for comparative efficacy were also influential within the CEA as would be expected. The utility data informing the model were also influential, with both the PFS utility and the disutility associated with R-chemo appearing within the top 10 parameters.

[redacted]

2.2.3 ***Scenario analysis***

Table 17 shows the results of the extensive scenario analyses performed which tested the structural uncertainty within the model and are described in Section 5.6. Overall the model was most sensitive to the PPS assumed for the R-chemo arm. Within scenario testing PPS a

[redacted]

HR was applied to the PPS for R-chemo that reduced the time spent in PPS. The HR selected minimised the difference between the median OS within the model and the median survival reported within the HMRN data (which was estimated to be 8.4 months for patients on second line treatment regimens)[44].

The model was also sensitive to the dataset used to inform PFS of R-chemo. Testing the PFS of TEM from RAY (MCL3001) as proxy for R-chemo increased the ICER as the estimate used to inform R-chemo here was higher than the one in the base case. It should be noted that no evidence is available regarding the comparative effectiveness of TEM and R-chemo.

In general, results from scenario analyses were consistent with the base case results, meaning that there is not a great deal of uncertainty in key assumptions.

Table 17: Scenario analyses conducted within the economic model

Scenario	Ibrutinib			R-CHOP			Incremental outcomes			
	Total Costs	Total QALYs	Total LYs	Total Costs	Total QALYs	Total LYs	Inc. Costs	Inc. QALYs	Inc. LYs	ICER
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£70,522	0.94	1.23	£75,318
Comparator efficacy HR for PFS using TEM data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£70,253	0.93	1.22	£75,681
Time horizon: 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£70,541	0.94	1.24	£75,279
Time horizon: 20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£71,847	0.94	1.23	£76,732
Comparator: R-CVP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£68,354	0.94	1.23	£73,002
Comparator FCR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£69,580	0.94	1.23	£74,312
Comparator RC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£70,546	0.94	1.23	£75,343
Treatment mix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£70,948	0.94	1.23	£75,773
No wastage included	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£70,522	0.94	1.23	£75,318
Utility decrement for R-chemo based on Schenkel *et al.* 2014	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£70,522	0.93	1.23	£76,194
No age-adjusted utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£70,522	0.95	1.23	£74,336
Sequential approach (OS ibrutinib = PFS ibrutinib + PFS R-chemo + PPS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£82,751	1.08	1.43	£76,671
Including FCR as subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£68,940	0.94	1.23	£73,628
PFS curve: exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£66,914	0.83	1.06	£80,296
PFS curve: log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£93,071	1.30	1.88	£71,636

Scenario	Ibrutinib			R-CHOP			Incremental outcomes			
	Total Costs	Total QALYs	Total LYs	Total Costs	Total QALYs	Total LYs	Inc. Costs	Inc. QALYs	Inc. LYs	ICER
PFS curve: log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£97,926	1.32	1.93	£74,194
Risk of death during PFS for R-chemo assumed equal to ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£70,275	0.92	1.21	£76,605
Response rates of R-chemo equal to TEM response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£70,068	0.94	1.23	£74,833
Response rates of R-chemo equal to response in Hess, 2009	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£69,607	0.94	1.23	£74,341
Response rates of R-chemo equal to ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£70,626	0.94	1.23	£75,429
No benefit from rituximab in PFS HR (rituximab HR = 1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£72,309	1.00	1.35	£72,311
Rituximab PFS HR applied to Hess, 2009 ITC = 0.75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£70,933	0.95	1.26	£74,429
Rituximab PFS HR applied to Hess, 2009 ITC = 0.89	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£71,760	0.98	1.32	£73,019
Rituximab PFS HR applied to Hess 2009 ITC = 1.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£74,321	1.05	1.44	£70,779
Applying a HR to PPS of R-chemo to adjust survival to be as close as possible to HMRN anticipated survival (8.4 months for patients on 2nd line treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£110,949	1.87	2.64	£59,345

HR: hazard ratio, PFS: progression-free survival, TEM: temsirolimus, R-CVP: rituximab + cyclophosphamide + vincristine + prednisone, FCR: fludarabine + cyclophosphamide + rituximab, RC: rituximab + cytarabine, R-chemo: rituximab-based chemotherapy, OS: overall survival, ITC: indirect treatment comparison, PPS: post-progression survival, HMRN: haematological malignancy research network, QALY: quality-adjusted life year, LY: life year, Inc: incremental

2.2.4 *Summary of sensitivity analyses results*

PSA indicates that the results obtained within the base case where fairly robust to parameter uncertainty, with average PSA results very similar to the deterministic results. The model results showed that the majority of uncertainty lies within the estimated QALYs, however, in all cases a substantial QALY improvement was expected for ibrutinib compared to R-chemo (QALY gains expected to lie between 0.6 and 1.4).

Key uncertainties within the model parameterisation surrounded the parametric curve fits to TOT and PFS and the HR assumed for comparative efficacy within the model. Within scenario analysis the model was also sensitive to the PPS assumed for R-chemo, with the ICER reducing when HMRN data were used to inform PPS. The model was also sensitive to the dataset used to inform the PFS of R-chemo, with the use of the TEM arm of RAY (MCL3001) as proxy for R-chemo producing an increased estimate of the ICER.

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

2.3 *Subgroup analysis*

Results of the economic comparison between ibrutinib and R-CHOP for subgroups of 1 prior LOT versus 2+ prior LOTs are presented in Table 18 and
Table 19. Substantially higher estimates of LYs and QALYs were produced for ibrutinib in the subgroup of patients only receiving one prior LOT. These results are consistent with the findings of the post-hoc analysis of RAY (MCL3001) presented in Section 4.8.2, clearly demonstrating that an increased benefit is observed when ibrutinib is used early in the treatment pathway for R/R MCL, which were also confirmed in the pooled dataset (Section 4.12.2). In those patients with 1 prior LOT, ibrutinib produces 3.65 LYs, compared to 1.91 LYs in patients with 2+ prior LOTs. This strongly suggests that whilst all R/R MCL patients can benefit from ibrutinib, the benefit is more pronounced the earlier they receive it.

Table 18: Base case discounted results, ibrutinib versus R-CHOP: 1 prior LOT

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Ibrutinib	[redacted]	[redacted]	[redacted]	£108,398	2.34	1.67	£64,755
R-CHOP	[redacted]	[redacted]	[redacted]				
ICER: incremental cost-effectiveness ratio, QALYs:, quality-adjusted life years, R-CHOP: rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone							

Table 19: Base case discounted results, ibrutinib versus R-CHOP: 2 + prior LOTs

	Costs	Life years	QALYs	Incremental			ICER
				Costs	Life years	QALYs	
Ibrutinib	[redacted]	[redacted]	[redacted]	£59,685	0.92	0.72	£83,256
R-CHOP	[redacted]	[redacted]	[redacted]				
ICER: incremental cost-effectiveness ratio, QALYs:, quality-adjusted life years, R-CHOP: rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone							

2.4 *Threshold analysis on comparative efficacy*

A similar analysis as the one reported in Section 5 was performed using the discounted price of ibrutinib.

Table 20 shows how the ICER changes with an increase in HR of R-chemo (i.e., decreasing the comparative effectiveness of ibrutinib over R-chemo). The analysis shows that the ICER is relatively insensitive to any increase in R-chemo HR. Even when the HR is increased by as much as 90% (HR=0.53) the ICER only increases by 21.21%. This HR of 0.53 could be considered clinically implausible as this would represent a mean PFS for R-chemo of 10.09 months, which is considerably greater than that observed in clinical practice (1.9 months in Hess, 2009 and 2.8 months in Skåne).

A similar message is given by the 'threshold' analysis on the effect of adding rituximab to the HR derived from Hess, 2009 (Table 21). Decreasing the HR of adding rituximab (which increases the overall PFS HR of R-chemo, thus reducing the estimate of comparative efficacy of ibrutinib over R-chemo) does not impact the ICER substantially (for example a decrease of 45% only raises the ICER by 17.90%). The ICER raises substantially only when unrealistic HRs for the rituximab effect are tested, such as a HR of 0.17, which would mean that rituximab would add an additional benefit of 83% to the one observed in Hess, 2009.

Thus these 'threshold' analyses show how, despite there being uncertainty in the estimates of the comparative efficacy of comparators from the NICE scope in this submission, the ICER remains relatively stable.

Table 20: Threshold analysis on the PFS HR of R-chemo

Increase in HR of R-chemo	R-chemo HR	ICER	Increase in ICER
Base case	**0.28**	£75,317	
15%	0.32	£77,348	2.70%
30%	0.36	£79,428	5.46%
45%	0.41	£82,385	9.38%
60%	0.45	£85,054	12.93%
75%	0.49	£88,013	16.86%
90%	0.53	£91,291	21.21%
105%	0.57	£94,922	26.03%
120%	0.62	£100,027	32.81%
135%	0.66	£104,629	38.92%
150%	0.70	£109,769	45.74%

R-chemo: rituximab in combination with chemotherapy, HR: hazard ratio, ICER: incremental cost-effectiveness ratio

Table 21: Threshold analysis on the PFS HR for the effect of adding rituximab

Increase in HR of the effect of rituximab	Effect of rituximab HR	ICER	Increase in ICER
Base case	**0.69**	£75,317	
-15%	0.59	£77,447	2.83%
-30%	0.48	£81,506	8.22%
-45%	0.38	£88,801	17.90%
-60%	0.28	£106,944	41.99%
-75%	0.17	£242,503	221.97%

R-chemo: rituximab in combination with chemotherapy, HR: hazard ratio, ICER: incremental cost-effectiveness ratio

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Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ibrutinib for treating relapsed or refractory mantle cell lymphoma [ID753]

Thank you for agreeing to make a submission on your organisation's 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 submission, 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: , submitting on behalf of:

Name of your organisation: NCRI-ACP-RCP-RCR

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

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ibrutinib for treating relapsed or refractory mantle cell lymphoma [ID753]

What is the expected place of the technology in current practice?

Mantle Cell Lymphoma is an aggressive form of Non Hodgkin Lymphoma that predominantly affects older patients with a median age at presentation of over 70 years in the UK. Following front line treatment with immuno-chemotherapy most patients achieve a remission, but there is an inevitable pattern of relapse with no curative therapy available for the vast majority of patients. For younger patients initial therapy involves a high dose cytarabine based treatment which is consolidated with a stem cell transplant. For patients who are too old to consider transplantation then treatment is with rituximab in combination with CHOP or Bendamustine therapy, followed by rituximab given as maintenance. In those patients too frail to receive such treatment more gentle chemotherapeutic options such as CVP or chlorambucil in combination with rituximab are employed. In general the more intensive the initial therapy used the longer and more complete the remission achieved. However all patients eventually relapse and subsequent therapy becomes more challenging. There is little variation in this general approach across the UK although the use of bendamustine is entirely dependent on its availability through the Cancer Drugs Fund.

At relapse an alternative immuno-chemotherapeutic approach is adopted and in general the response and duration of response is shorter following this. There is no standard of care at this point but a range of options and current guidelines (UK, European and American) simply list a number of these. In the case of a very young and fit patient an allogeneic transplant can be considered at relapse and this is curative in around 30-40%.

In the setting of relapsed MCL there are 4 novel agents that have a licence for use across the world; Bortezomib, lenalidomide, temsirolimus and Ibrutinib. The relative efficacy of these drugs as single agents across comparative trials shows that Ibrutinib is significantly more active with the highest response rate, complete response rate and longest progression free survival[1]. Together with this it has the best side effect profile and with long term use there is no emerging toxicity and over 20% patients remain on drug at 2 years[2]. The drug works in all risk groups and following all prior therapies. Blastoid variant MCL, which is the most aggressive histological sub-type, has a shorter duration of remission following therapy than conventional MCL but it is still more active than any other agent in this setting. Because of the extremely good side effect profile of this agent it can be used in frail elderly patients where the conventional options are the least effective and most toxic. In contrast it can also be used in very young patients as an effective salvage therapy before an allogeneic transplant[3]. The UK guidelines on the management of MCL are currently being updated and will incorporate Ibrutinib into recommended therapies for relapsed disease.

This treatment is very easy to deliver but requires supervision through secondary care preferably through a specialist lymphoma clinic.

Ibrutinib is currently only available through the CDF in its licensed indication and as such is not available throughout the UK.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ibrutinib for treating relapsed or refractory mantle cell lymphoma [ID753]

The advantages and disadvantages of the technology

Ibrutinib is the most active agent yet seen in the context of relapsed MCL and combined with its excellent side effect profile it should replace all other available therapies. From an efficacy and quality of life perspective one of our experts notes it is the most impressive agent he has ever used in clinical or research practice in over 20 years as a consultant and there are no clinical scenarios where this approach would not apply. Data will be presented later this year (European Haematology Association annual meeting) that will clearly demonstrate that the outcomes with ibrutinib are significantly better when it is used at first rather than later relapse. This is a pooled analysis of the 3 trials that have used Ibrutinib as a single agent in relapsed MCL.

The only clinical issue with the use of this drug it that it increases bruising and bleeding and as such needs to be withheld around operative procedures and needs to be used cautiously with any form of anti-coagulation. There are no particular testing requirements for these patients and monitoring for response is no different to that used with conventional therapies.

Of interest ibrutinib was made available on a compassionate use basis prior to the CDF availability. 156 patients received therapy for MCL in the UK and I have collected real world data (completely independently from the drug company) on a significant number of those patients. This data is being presented next week at the British Society of Haematology annual meeting[4] and rather surprisingly shows that the responses and toxicities observed in a non trial population is identical to that seen in the phase II studies. The abstract and database can be made available after it has been presented if required.

Implementation issues

If this agent were made available following a NICE appraisal there would be near universal uptake in the setting of relapsed MCL. There would not be any need for any specific education as the drug has been widely used via the expanded access programme from Janssen and the CDF.

Equality

There are no issues relating to equality with this agent or appraisal.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ibrutinib for treating relapsed or refractory mantle cell lymphoma [ID753]

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David Tucker[(1)], Elisabeth Vandenberghe[(2)], Nick Morley[(3)], Kristian Bowles[(4)], Simon Rule[(1)].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Ibrutinib for treating relapsed or refractory mantle cell lymphoma [ID753]

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, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

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 length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Bloodwise

Your position in the organisation: Head of Patient Experience

Brief description of the organisation: Bloodwise's mission is to beat all blood cancers – stopping people from dying, improving the lives of everyone affected by blood cancer, and where possible preventing people getting blood cancer in the first place. We do this by funding world leading research, supporting all those affected by blood cancer, and campaigning for improvements in care and services.

We are entirely funded by voluntary donations.

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?

Mantle cell lymphoma is a rare and incurable form of NHL. It affects nearly twice as many men than women and is more common in the over 60 age group. It can be very aggressive but can also behave in a more indolent fashion.

Patients frequently present with painless swelling in their lymph nodes but symptoms also include weight loss, fevers, night sweats, nausea and vomiting, heartburn or stomach pains.

If the condition is indolent patients may go through a period of watch and wait with the psychological implications of having cancer but not being treated, however the majority of patients will require treatment, often many treatments over time. Treatment is usually combination chemotherapy +/- rituximab, with

the considerable side effect profile that goes with this. Younger and /or fitter patients may have very intensive chemotherapy followed by stem cell transplant which can increase response times.

The patient quote below is typical of the experience of living with MCL:

“Before beginning the treatment, in addition to my high white blood cell count I was feeling tired and moderately unwell all the time. I was anaemic because of the decreasing amount of red blood cells and I had lost a lot of weight over the previous two years. My glands were significantly and visibly enlarged and a scan had shown my spleen and other internal glands were also enlarged to extent of needing treatment.”

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.

Ideally, patients and carers would want a good response to treatment, with long remission times and as good a quality of life as possible. Patients have cited reducing side effects and the speedy reductions in symptoms as being important, particularly fatigue and pain caused by swelling of organs and glands.

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?

Current treatment for Mantle cell lymphoma requires multiple visits to hospital. Patients usually receive intravenous chemotherapy with the numerous side effects that go with treatment, ongoing support and numerous practical difficulties associated with multiple hospital trips.

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.

Patients report a number of advantages to this treatment. The following patient quote is typical of the feedback we received from patients:

"I took my first dosage of ibrutinib and within two days the glands in myneck had visibly reduced. This continued and within a matter of weeks my glands were back to nearly their normal size. These results were also reflected in my blood test results. I also instantly felt much more energised and generally more like I felt before I had MCL. I suffered very few side effects and none of them significant. Diarrhoea and a minor skin reaction were the only noticeable side effects and after a couple of weeks they both subsided."

This patient's views on side effects were echoed by many others.

Patients have also cited the advantage of ibrutinib being an oral treatment that can be taken at home as a significantly benefit compared to other treatment options that require multiple hospital treatments for chemotherapy, with all the side effects that can bring.

Overall, the common thread through all responses we received from patients is that ibrutinib allowed them to live their life normally without invasive treatment or side effects that often accompany alternative treatment options.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

This is an oral medication, that patients can take at home, reducing the need to hospital visits and day case or in patient stays. Allowing patients the comfort and privacy of remaining in their own homes was also frequently mentioned. Ibrutinib has significantly less and more tolerable side effect profile in the majority of users again reducing the need and cost of medical intervention.

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.

None from patient responses we received.

5. What do patients and/or carers 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)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- 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 patients or carers have about current NHS treatments in England.

As previously stated, current NHS treatments often involve multiple hospital visits and significant side effects. There are no treatments available that rival ibrutinib for its management of both these problems.

Please list any concerns patients or carers have about the treatment being appraised.

None – side effects were reported as minor and overcome within two weeks.

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.

None.

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.

Are there any groups of patients who 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

Is your organisation 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 patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Patients both on clinical trials and receiving ibrutinib out of the trial setting have reported positive responses and experiences of this treatment, as set out in this response.

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.

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?

No

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)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having 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 treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

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.

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 provides significant improvement in treatment, side effects and overall patient experience. There is nothing currently available that provides the benefits offered by ibrutinib.

Are there any other issues 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.

- Ibrutinib is regarded by patients as step change in the way MCL is treated, significantly out-performing current treatments.
- Patients report a rapid reduction in symptoms, such as swelling, pain and fatigue, allowing many to return to their normal life very quickly.
- As an oral treatment that can be taken at home, there are significant benefits for patients compared to current therapies, which involve multiple hospital visits.
- The side effects of ibrutinib are mild and generally only last for around a couple of weeks. This is a significant improvement on current chemotherapy treatment.

Appendix K – clinical expert statement declaration form

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

INSERT TITLE

Please sign and return via NICE Docs/Appraisals.

Formatted: Highlight

I confirm that:

- I agree with the content of the submission provided by **[insert name of nominating organisation]** and consequently I will not be submitting a personal statement. Royal College of Physicians

Name: .....

Signed: .....

Date: 3.8.16

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

[

Ibrutinib for treating relapsed or refractory mantle cell lymphoma [ID753]

]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by Bloodwise and consequently I will not be submitting a personal statement.

Name:

Signed:

Date: 14 July 2016

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Ibrutinib for treating relapsed or refractory mantle cell lymphoma [ID753]

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, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

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 length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Lymphoma Association

Your position in the organisation: Chief Executive

Brief description of the organisation:

About the Lymphoma Association

The Lymphoma Association is a national charity registered in England and Wales and in Scotland.

Our primary aim and objective is to provide information, advice, support and training to everyone affected by lymphoma. We work throughout the UK, publishing leading, quality-assured written information on lymphoma, and providing a national helpline, a network of support groups and a buddy scheme. We are also in the process of developing a survivorship and well-being programme specifically designed for those with lymphoma. We also provide education and training courses for healthcare professionals, as part of their CPD.

About this submission

In compiling this patient organisation submission, we gathered information from our network of patients and carers who are linked to us through our role as a national lymphoma information, support and training charity in the UK, and via access to international networks as part of our membership of the global Lymphoma Coalition. We have access to people affected by lymphoma via our national helpline, network of support groups, buddy schemes, programme of conferences and events, the readers of our "Lymphoma Matters" magazine, people who contribute to our online forums, and via the circulation of surveys/feedback forms.

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?

Although mantle cell lymphoma might appear to be a low grade, indolent lymphoma, it can often act more like a high grade, aggressive lymphoma, growing quickly and is also likely to relapse after it has been treated.

The commonest symptom of mantle cell lymphoma is one or more swollen lymph nodes (glands) – in the neck, armpit or groin. Often other areas are affected too by the time mantle cell lymphoma is diagnosed. This means patients might have other symptoms depending on which areas of their body are affected, eg, bone marrow (which can stop enough normal blood cells being made, causing anaemia, which might lead to severe tiredness or shortness of breath, or bruising or bleeding); the bloodstream; bowel (which may lead to diarrhoea); spleen; and tonsils.

With those patients on "watch and wait", they report a good quality of life and minimal symptoms. For those with more advanced disease, their quality of life is more significantly affected. Such patients report fatigue, loss of appetite, weight loss, fever, night sweats, nausea, vomiting, indigestion, abdominal pain, bloating diarrhoea, enlarged tonsils, and muscle/joint pain. Some patients also highlight difficulties with vision, concentration, anxiety, depression, insomnia, intimacy and mood swings.

> *"I was so tired I could not go to work. I had a low-grade fever. I would go to bed at 7. I was losing weight... I felt bloated all of the time. Night sweats caused me to not sleep well. I went to bed early. I slept but it was not a restful sleep, it was a disturbed sleep and I would get up sweaty and here I was thinking it was menopause kicking in. I could not go to work because I was so anaemic. I had nausea and thought I had the flu. I only showed up to work 5-6 times the month before I was diagnosed."*
>
> [Woman, aged 57]

Additional complications sometimes also reported include frequent infections (due to compromised immunity), shortness of breath, easy bruising, small intestine polyps, gastrointestinal, pulmonary and central nervous system complications (due to extranodal MCL), renal failure (due to obstruction caused by tumour) and difficulty breathing (caused by tumour obstruction of the airway).

> *"Anxiety and depression; muscular, joint and bone pain; regular sinus and lung infections; severe cramps; loss of muscle and muscle weakness; vision reduced; memory loss; slow in dealing with tasks; reduced reaction time; reduced sexual desire; occasional headaches."*
>
> [Man, aged 55-64]

> "*My husband had to have trach installed for about 7 wks before the chemo treatments began because he had a tumour in his throat that cut off his air flow.*"
>
> [Spouse of patient]

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.

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?

Given that most forms of MCL have to be treated as an aggressive cancer via traditional chemotherapy regimes, that outcomes are generally poor compared to many other forms of lymphoma, and that treatment options are limited, the disease is an extremely difficult one to cope with for patients, their carers and friend and families. While current treatments can work initially, patients with MCL will usually relapse after treatment, with in most cases periods of remission becoming shorter.

Patients we have heard from commonly referenced treatment with R-CHOP, Bendamustine, Rituximab maintenance and stem cell transplants, while some people also mentioned BEAM, FCR and Bortezomib, among others. In relation to current treatments, patients have reported both positive (ie, disease control) and negative side effects (ie, disease progression); adverse events; and the discontinuing of treatments due to the side effects.

The current treatment options available for many are said to be associated with increased toxicity, lower tumour-reduction capability, and unpleasant side-effects.

> *"CHOP-R sent me to the hospital 4 to 6 times with febrile neutropenia. High dose chemo, radiation and stem cell made me violently ill and weak. Nausea, pain in the chest, incontinence stool, blisters in the mouth, hair loss, loss of appetite, major weight gain with the steroids. Loss of mobility, severe fatigue, low platelets. Rituximab - severe fatigue each session, nausea, loss of mobility."*
>
> [Female; 55-64]

A significant proportion of carers (up to a half) also report the significant impact that current treatments have on day-to-day life. This can significantly affect the patients' and carers' ability to travel, to spend time with family and friends, to concentrate, to fulfill family obligations, to complete household chores, to exercise and to work and to contribute financially to household expenses/work. For carers, the impact tends to be greater in most of these areas for those who are not retired.

> *"The side effects of the chemo have robbed me of the man that I married. He is constantly fatigued, to the point of being zombie like after noon. So difficult to watch the fatigue, etc."*
>
> [Spouse of patient, aged 55-64]

"My husband is no longer able to do MOST things. Simple things such as showering needs assistance. Mentally he is a complete and total stranger to me. Very withdrawn, angry. He has no desire for ANYTHING. I am the sole caregiver and I have to do all appointments and meds, nobody helps me. I spend probably 30+ hours a week just on him, plus work full time."

[Spouse of patient, aged 45-54]

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 MCL patients' quality of life and experience of care. Many people with MCL will be aware of the treatment being available in the US and will know it 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 chemotherapty regimes), and has limited and manageable side-effects and a well-tolerated toxicity profile, it seen as a step-change in the management of MCL.

Most patients with experience of ibrutinib, state that the side effects are mild with minimal tolerability issues (far less so that 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.

"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]

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

It would present major options and hope for patients and carers. The fact that ibrutinib 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.

"*Yes. I love the fact that I can take a pill at home. I call it my magic pill.*"

[Woman, aged 77; previous treatment R-CHOP]

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 that we have highlighted in some of our previous answers.

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.

Unaware of any significant differences of opinion.

5. What do patients and/or carers 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)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- 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 patients or carers have about current NHS treatments in England.

The main concerns patients or carers have are threefold:

- That some of the current treatments have a high toxicity profile.
- That they have an increased range of side-effects and after effects, with a corresponding impact on quality of life.
- That they may not be as effective in bringing about fuller and longer remissions than new and more innovative treatments.

Please list any concerns patients or carers have about the treatment being appraised.

The list price of the current treatment is a significant disadvantage. This becomes an increased disadvantage where patients are prescribed the treatment for long periods of time.

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.

Unaware of any significant 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.

Older patients, particularly those with co-morbidities, who might not be fit enough for some of the current treatments may benefit more than other patients due to ibrutinib's reduced toxicity profile.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Can't think of any.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐ Yes X☐ No

If you answered 'no', please skip the rest of section 7 and move on to

section 8.

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.

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 (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having 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 treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

If the treatment is not approved for use on the NHS, then older people may be disadvantaged, as they will potentially have reduced access to effective treatments with reduced toxicity profiles, compared to younger people.

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.

None of which we're aware

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.

This treatment is innovative and a step-change in management because it has a new mode of action and appears effective for this patient group, whose options may previously have been quite limited. Patients will also potentially benefit hugely from the fact that it is an oral therapy, which generally seems to be well tolerated in comparison to the alternatives.

Are there any other issues that you would like the Appraisal Committee to consider?

No

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- As MCL can be an aggressive and challenging form of lymphoma, with limited effective treatment options and often poor outcomes, ibrutinib offers patients and their carers/families real hope for the future.
- Current chemotherapy and radiotherapy regimes have higher toxicity profiles, are generally less effective and have a range of difficult side-effects, creating significant challenges for patients and carers with a significant effect on their quality of life.

- In contrast, ibrutinib is an innovative treatment and represents a step-change in the management of MCL. With good tolerability and reduced side effects, the treatment appears to deliver improved efficacy, a better quality of life and long-term hope - all of which are applicable to both patients and their carers, families and friends.
- The oral nature of the treatment, and the fact that it can be administered at home, deliver huge personal and professional benefits.
- The one big disadvantage of the treatment is its price.

Ibrutinib for treating relapsed or refractory mantle cell lymphoma: A Single Technology Appraisal

Produced by School of Health and Related Research (ScHARR), The University of Sheffield

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21st June 2016

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Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Emma Simpson and Eva Kaltenthaler summarised and critiqued the clinical effectiveness data reported within the company's submission. Paul Tappenden and Daniel Pollard critiqued the health economic analysis submitted by the company. Mark Clowes critiqued the company's search strategies. Jean Sanderson critiqued the statistical analysis contained within the company's submission. David Meiklejohn and Nick Morley 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

AE	Adverse event
AFT	Accelerated failure time
AIC	Akaike Information Criterion
ALT	Alanine transaminase
SGPT	Serum glutamic-pyruvic transaminase
ASCT	Autologous stem cell transplant
AUC	Area under the curve
BCSH	British Committee for Standards in Haematology
BIC	Bayesian Information Criterion
BR / R-bendamustine	Bendamustine and rituximab
BSA	Body surface area
BSC	Best supportive care
BTK	Bruton's tyrosine kinase
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLL	Chronic Lymphocytic Leukaemia
CMU	Commercial Medicines Unit
CMV	Cytomegalovirus
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company's submission
CSR	Clinical study report
CT	Computed tomography
CUP	Compassionate use programme
DARE	Database of abstracts of reviews of effects
dL	Decilitre
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAP	Early Access Programme
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EMA	European Medicines Agency
Embase	Excerpta Medica Database
eMit	Electronic market information tool
EoL	End of life
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer quality of life questionnaire
EORTC-8D	European Organisation for Research and Treatment of Cancer 8 Dimensions
EQ-5D-5L	Euroqol EQ-5D 5-level
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-Lym	Functional Assessment of Cancer Therapy - Lymphoma
FCR	Fludarabine cyclophosphamide and rituximab
FE	Fixed effects
FMC	Fludarabine, cyclophosphamide and mitoxantrone
FR	Fludarabine plus rituximab

HIV	Human immunodeficiency virus
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IPCW	Inverse Probability of Censoring Weights
IQR	Inter-quartile range
IRC	Independent review committee
ITC	Indirect treatment comparison
ITT	Intention to treat
i.v.	Intravenous
LD	Lymphocyte depletion
LOT	Line of therapy
LS	Least squares
MCL	Mantle cell lymphoma
Medline	Medical Literature Analysis and Retrieval System Online
mg	Milligram
MIMS	Monthly Index of Medical Specialties
MIPI	Mantle Cell Lymphoma International Prognostic Index
N/A	Not applicable
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not evaluable
NED	No evidence of disease
NHL	Non-Hodgkin's lymphoma
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
o.d	Once daily
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
p.o.	Per os
PAS	Patient access scheme
PEP-C	Prednisone, etoposide, procarbazine, and cyclophosphamide
PFS	Progression-free survival
PHEDRA	Platform for Haematology in EMEA: Data for Real World Analysis
PPS	Post-progression survival
PR	Partial response
PrI	Predictive interval
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
QoL	Quality of life
R/R MCL	Relapsed/refractory mantle cell lymphoma
RC	Rituximab and cytarabine
R-Cbl / R-chlorambucil	Rituximab and chlorambucil
R-chemo	Rituximab plus chemotherapy
R-CHOP	Rituximab, cyclophosphamide, vincristine and prednisolone
RCT	Randomised controlled trial
R-CVP	Rituximab, cyclophosphamide, vincristine and prednisolone

R-DHAP	Rituximab, dexamethasone, cytarabine and cisplatin
RDI	Relative dose intensity
RE	Random effects
R-FCM	Rituximab, fludarabine, cyclophosphamide and mitoxantrone
RPSFT	Rank preserving structural failure time
SD	Standard deviation
SE	Standard error / stable disease
SF-36	Short Form 36 Items
SF-6D	Short Form 6 Dimensions
sMIPI	Simplified Mantle Cell Lymphoma International Prognostic Index
SmPC	Summary of product characteristics
TA	Technology appraisal
TE	Treatment effect
TEM	Temsirolimus
TSD	Technical Support Document
TTD/D	Time to treatment discontinuation or death
UK	United Kingdom
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale
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

Mantle cell lymphoma (MCL) is a B-cell malignancy with unique biological, pathological and clinical features. It comprises approximately 3-10% of all non-Hodgkin lymphomas (NHLs). MCL typically arises in older adults, with a median age of presentation of between 60 and 65 years of age. The majority of patients (approximately 75%) with MCL are male. The disease is extremely rare: the company's submission (CS) states that there will be an estimated 356 patients with relapsed/refractory mantle cell lymphoma (R/R MCL) in England, Wales and Northern Ireland in 2017. MCL is characterised by an aggressive clinical disease course, but features a pattern of resistant and relapsing disease which thereby renders it incurable with standard therapy. Prognosis for patients with MCL is very poor compared with other forms of NHL. Within the R/R MCL population, after excluding patients for whom autologous stem cell transplantation (ASCT) is a treatment option, median survival following first relapse is reported to be approximately 1-2 years. The CS suggests that expected survival for the R/R MCL population is likely to be below 1 year. One clinical advisor to the Evidence Review Group (ERG) suggested that expected survival in this population is less than 1 year whilst the other suggested that expected survival is 1-2 years.

The decision problem required an assessment of the clinical effectiveness and cost-effectiveness of ibrutinib compared with established clinical management for the treatment of adult patients with R/R MCL.

Ibrutinib is a first-in-class Bruton's tyrosine kinase (BTK) inhibitor. Ibrutinib holds a European marketing authorisation for the treatment of patients with R/R MCL, chronic lymphocytic leukaemia (CLL) and Waldenström's macroglobulinaemia (WM). Within its R/R MCL indication, ibrutinib is administered orally at a recommended dose of 560mg (four 140mg capsules) once daily (o.d.). 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. Ibrutinib is available in packs of 90 capsules or 120 capsules. As of June 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 CS, the company is currently in the process of agreeing a further confidential commercial access arrangement with NHS England; details of the commercial access arrangement were not agreed at the time of this assessment.

The population defined in the final NICE scope relates to adults with R/R MCL; this is in line with the marketing authorisation for ibrutinib. This also reflects the populations recruited into the RAY

(MCL3001), SPARK (MCL2001) and PCYC1104 studies included in the company's systematic review of clinical effectiveness and the population reflected in the pooled ibrutinib dataset used to inform the company's health economic model.

The final NICE scope defines the relevant comparator as established clinical management without ibrutinib, including: (i) rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP); (ii) rituximab, cyclophosphamide, vincristine and prednisolone (R-CVP); (iii) fludarabine cyclophosphamide and rituximab (FCR), and; (iv) rituximab and cytarabine (RC). The company's clinical effectiveness review did not identify any studies which included head-to-head comparisons of ibrutinib versus any of these comparators; the only comparative study of ibrutinib in the R/R MCL population was the RAY (MCL3001) study which compared ibrutinib versus temsirolimus (TEM). The CS includes an indirect comparison which compares ibrutinib versus physician's choice of single-agent chemotherapy. The company's health economic model includes a further indirect comparison which attempts to adjust for the effect of rituximab, based on data from the Haematological Malignancy Research Network (HMRN). Owing to a lack of evidence, the effectiveness of all rituximab plus chemotherapy (R-chemo) options are assumed to be equivalent. The company's base case model evaluates ibrutinib versus R-CHOP. A separate scenario analysis is presented comparing ibrutinib followed on progression by R-CHOP versus R-CHOP alone. In addition, the CS includes a blended comparison of ibrutinib versus a mix of R-CHOP, R-CVP and FCR.

The outcomes reported in the company's clinical effectiveness review includes all outcomes listed in the final NICE scope. Outcomes are presented for individual studies (RAY [MCL3001], SPARK [MCL2001] and PCYC1104) and for a pooled dataset which combines all three ibrutinib studies. The company's indirect comparison of ibrutinib versus physician's choice of single-agent chemotherapy was undertaken for the outcomes of overall survival (OS), progression-free survival (PFS) and overall response rate (ORR). The company's indirect comparison of ibrutinib versus R-chemo was undertaken only for the endpoint of PFS.

The CS argues that NICE's End of Life criteria are relevant to this appraisal. Ibrutinib is currently available through the Cancer Drugs Fund (CDF) for the R/R MCL indication. The company requests the opportunity to remain on the CDF in order to collect further evidence to reduce the level of uncertainty that currently exists.

1.2 Summary of clinical effectiveness evidence submitted by the company

Clinical effectiveness data were taken from three studies, comprising one randomised controlled trial (RCT) (RAY [MCL3001]) and two single-arm studies (PCYC1104 and SPARK [MCL2001]). One

additional non-ibrutinib study (OPTIMAL) was included for the indirect comparison of ibrutinib versus single-agent chemotherapy.

At the time of the company's submission, the median OS was not reached in the ibrutinib arm of the RAY (MCL3001) study (n=139) or in the SPARK (MCL2001) study (n=120). In Study PCYC1104 (n=111), median OS was 22.5 months.

Median PFS for ibrutinib-treated patients was 14.6 months in the RAY (MCL3001) study, 13.0 months in the final analysis of Study PCYC1104, and 10.5 months in the SPARK (MCL2001) study. In the RAY (MCL3001) study, median PFS within the TEM arm was 6.2 months; this was significantly worse than for the ibrutinib arm (hazard ratio [HR]=0.43, 95% confidence interval [CI] 0.32; 0.58; $p<0.0001$). Overall response rates (ORR) assessed by independent review committee (IRC) were similar for ibrutinib-treated patients across studies (71.9% in RAY [MCL3001], 69% in Study PCYC1104 and 69% in SPARK [MCL2001]). In RAY (MCL3001), there was a significant advantage for ibrutinib over TEM (ORR 40.4%, odds ratio [OR]=3.98, 95% CI 2.38, 6.65, difference in ORR $p<0.0001$).

Health-related quality of life (HRQoL) was measured by Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym) in the RAY (MCL3001) and SPARK (MCL2001) studies. The percentage of patients reporting clinically meaningful improvement was 61.9% in ibrutinib-treated patients in the RAY (MCL3001) study, and [redacted] in the SPARK (MCL2001) study. Within RAY (MCL3001), significantly fewer TEM-treated patients reported clinically meaningful improvement (35.5%, $p<0.0001$).

Across studies, the most common adverse events (AEs) for ibrutinib (≥20% of patients) were: diarrhoea; cough; fatigue; thrombocytopenia; neutropenia; peripheral oedema; nausea; muscle spasms, and; pyrexia.

The company's indirect comparison of ibrutinib versus single-agent chemotherapy suggests that ibrutinib is associated with a slower rate of disease progression compared with single-agent chemotherapy (HR=0.19, 95% CI 0.10, 0.36) and a survival benefit (HR=0.61, 95% CI 0.34, 1.10), although the result for OS is inconclusive as it did not reach statistical significance at the 95% level. Rituximab is used in routine clinical practice in England, therefore to account for the differential effectiveness of using rituximab alongside chemotherapy, the company performed an additional adjustment to the HR for PFS. The adjusted HR for PFS for ibrutinib versus R-chemo was estimated to be 0.28.

SUPERSEDED
See erratum

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG does not believe that any relevant studies have been omitted from the CS. Studies presented were relevant to the population, intervention and outcomes of the decision problem. The CS did not identify any RCTs which included head-to-head comparisons of ibrutinib versus comparators listed in the final NICE scope. TEM, the comparator in the RAY (MCL3001) trial, is not used in UK practice.

The populations of the three included trials reflect the demographic characteristics of the R/R MCL population that would be eligible for ibrutinib treatment. However, in practice, patients may have more co-morbidities than trial patients. Studies were international, with a small proportion of patients from the UK, and thus there may be differences between the treatment pathways of trial patients and those in current practice in England.

One included ibrutinib study was an RCT, whereas the others adopted lower quality study designs. All three included ibrutinib studies were open-label and therefore were subject to bias. However, all studies addressed the issue of measurement bias for the primary outcome by having an assessment of the primary outcome by IRC.

All three studies were sufficiently large to be adequately powered for their primary endpoint of PFS (RAY [MCL3001]) or ORR (PCYC1104, SPARK [MCL2001]). OS was not adequately powered, and may have been influenced by subsequent therapies.

The TEM arm in the RAY (MCL3001) study had better outcomes than the TEM arm in the OPTIMAL study, and was also better than data reported within the HMRN audit. There is uncertainty regarding how much of this difference is due to TEM treatment, differences in populations between trials and routine practice, and the use of other therapies.

The company adopted a two stage approach to estimate treatment effects for ibrutinib versus R-chemo. The ERG considers that a single stage approach using random effects NMA would provide a better representation of the uncertainty in the resulting treatment comparisons. Based on the ERG's additional analyses, ibrutinib is associated with a slower rate of disease progression, compared to R-chemo, but with considerable uncertainty (random effects HR=0.27, 95% CrI 0.06, 1.26). The estimated median HRs for OS for ibrutinib versus R-chemo range from 0.98 to 1.96, depending on the data source used for the rituximab arm of the network. Due to concerns regarding the evidence used to inform the indirect comparisons, the results of the indirect comparison should be interpreted with caution.

1.4 Summary of cost effectiveness submitted evidence by the company

The CS includes a systematic review of published economic evaluations of treatments for R/R MCL together with a *de novo* health economic evaluation of ibrutinib versus R-chemo in adult patients with R/R MCL.

The company's review of existing economic evaluations did not identify any studies relating to ibrutinib in the R/R MCL indication. However, during the course of the assessment, the ERG identified one study (Peng *et al*) which modelled the effectiveness of ibrutinib versus rituximab plus bendamustine (R-bendamustine), fludarabine, cyclophosphamide and mitoxantrone (FMC) and TEM, based on a partitioned survival approach. This study reported estimated incremental health gains of 0.86 to 0.92 life years gained (LYGs) and 0.70 to 0.72 quality-adjusted life years (QALYs) gained for ibrutinib. In addition, the documentation provided alongside the CS included an unpublished economic evaluation of ibrutinib versus TEM, R-bendamustine and R-CHOP using registry data from the Skåne registry in Sweden; this analysis also adopted a partitioned survival approach. The ERG considers that these models could have been further developed to inform the appraisal**.**

The company's *de novo* economic model adopts a Markov approach to estimate the costs and health outcomes for ibrutinib versus R-chemo from the perspective of the NHS and Personal Social Services (PSS) over a 15-year (lifetime) horizon. The base case compares ibrutinib versus R-CHOP; scenario analyses are also presented for ibrutinib versus R-CVP, FCR, RC, and a blended comparison of all four R-chemo options. Separate subgroup analyses are presented for patients who have received one prior line of therapy (LOT) and for patients who have received ≥2 prior LOTs. The company's base case model includes three health states: (i) progression-free; (ii) post-progression, and; (iii) dead. The model also implicitly includes a further partition between patients who are progression-free and on treatment and those who are progression-free after discontinuation of treatment, based on TTD/D data. Transitions between states are modelled according to a 28-day cycle length (195 cycles). Within the ibrutinib group, health state transitions are modelled using parametric survivor functions fitted to data on pre-progression-mortality (exponential model), PFS (Weibull model), and post-progression survival (PPS, exponential model) from the pooled ibrutinib dataset. TTD/D is also modelled using a parametric survivor function (Weibull model), but does not impact on transitions. The benefits of ibrutinib versus R-chemo are modelled using a treatment effect derived from an indirect comparison based on the RAY (MCL3001) trial (ibrutinib versus TEM), the OPTIMAL trial (TEM versus physician's choice single-agent chemotherapy) and the HMRN audit (R-chemo versus chemo). This HR for PFS is applied to the PFS and TTD/D curves for ibrutinib. Health utilities for the progression-free and post-progression states were derived from RAY (MCL3001) and SPARK (2001) studies; a disutility associated with R-chemo toxicity was derived from clinical opinion. The company's model includes costs associated with drug acquisition, drug administration, follow-up, management of AEs,

best supportive care (BSC) and death. Resource use was estimated using a survey of actively practicing NHS haematologists and oncologists and was assumed to include full blood counts, X-rays, blood glucose tests, lactate dehydrogenase, lymphocyte counts, bone marrow exams, consultations with a haematologist, non-surgical inpatient visits, biopsies, blood transfusions and platelet infusions. Unit costs were taken from the Monthly Index of Medical Specialties (MIMs), the Commercial Medicines Unit (CMU) electronic market information tool (eMit) and NHS Reference Costs.

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 R-CHOP; the incremental cost-effectiveness ratio (ICER) for ibrutinib versus R-CHOP is expected to be £76,014 per QALY gained. The results of the deterministic model are similar, with ibrutinib yielding an ICER of £75,317 per QALY gained compared with R-CHOP. Assuming a willingness-to-pay (WTP) threshold of £50,000 per QALY gained, the company's base case model suggests that the probability that ibrutinib produces more net benefit than R-CHOP is approximately zero.

Across all but one of the company's scenario analyses, the ICER for ibrutinib versus R-chemo was greater than £70,000 per QALY gained. The only exception to this relates the analysis in which the modelled OS for R-CHOP is "calibrated" against the HMRN OS estimate of 8.4 months by adjusting the post-progression mortality rate in this group only (ICER=£59,345 per QALY gained). The ERG notes that this is an analysis in the 1 prior LOT subgroup rather than the base case population. The ERG also notes that the choice of comparator regimen does not have a material impact upon the company's deterministic ICER for ibrutinib.

The company's subgroup analysis according to number of prior LOTs indicates the potential for an improved cost-effectiveness profile for ibrutinib. Within the subgroup of patients who have received only one prior LOT, the probabilistic version of the company's model suggests that ibrutinib is expected to generate an additional [redacted] QALYs at an additional cost of [redacted] per patient; the corresponding ICER is £65,977 per QALY gained. Within the subgroup of patients who have received two or more prior LOTs, ibrutinib is expected to produce and additional [redacted] QALYs at an additional cost of [redacted] per patient; the corresponding ICER is £84,263 per QALY gained.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG critically appraised the company's economic analysis and double-programmed the deterministic version of the company's model. No programming errors were identified in the base case model, however some programming mistakes were identified in the implementation of the company's sequential 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) concerns regarding the constraints and assumptions imposed by the company's Markov model approach, particularly surrounding the use of PPS rather than OS as a model input; (ii) uncertainty surrounding the relative benefits of ibrutinib relative to current treatments for R/R MCL used in the NHS; (iii) the use of parametric survival curves to model TTD/D rather than the Kaplan-Meier curves; (iv) questionable assumptions regarding HRQoL; (v) discrepancies between the model-predicted and observed OS for ibrutinib, and; (vi) uncertainty surrounding the company's subgroup analysis based on the number of prior LOTs.

The ERG undertook two sets of exploratory analyses. The first set of exploratory analyses ("Set A") involved amending the parameter values of the company's submitted model. The ERG's preferred analysis within Set A involved using the ERG's network meta-analysis (NMA) derived HR for PFS, the use of the Kaplan-Meier curve for TTD/D for ibrutinib and the truncation of the R-chemo QALY loss upon treatment discontinuation. The second set of exploratory analyses ("Set B") involved amending the structure of the company's model such that OS was used as an input and PPS at any time t was defined as $S(t)_{OS}$-$S(t)_{PFS}$; this is analogous to a partitioned survival model. This structural amendment of the model allowed for the exploration of the impact of applying alternative HRs for OS for ibrutinib versus R-chemo, including those derived from the ERG's random effects NMAs.

The ERG's exploratory analyses based on the company's model structure (Set A) suggest the following:

- The impact of using the HR for PFS from the ERG's NMA had a negligible impact upon the cost-effectiveness of ibrutinib versus R-CHOP (ICER=£75,094 per QALY gained).
- The use of the Kaplan-Meier curves for TTD/D improves the cost-effectiveness of ibrutinib versus R-chemo; within this analysis the ICER was estimated to be £61,472 per QALY gained.
- The truncation of the R-chemo disutility upon treatment discontinuation increased the ICER for ibrutinib versus R-CHOP to £77,111 per QALY gained.
- The ERG's preferred analysis, which includes all three amendments results in a probabilistic ICER for ibrutinib versus R-CHOP of £63,340 per QALY gained.
- The use of alternative utility values for the progression-free and post-progression states within the ERG's preferred analysis produced ICERs for ibrutinib versus R-CHOP ranging from £59,952 to £60,417 per QALY gained.
- The analyses in which rituximab is excluded from the comparator regimen produced ICERs ranging from £64,727 to £69,054 per QALY gained.
- Within the LOT=1 subgroup, the ERG's preferred analysis suggests that the ICER for ibrutinib versus R-CHOP is £44,711 per QALY gained. This is considerably lower than the

ICER for the overall population, but may be subject to confounding due to the *post hoc* definition of the subgroup and bias due to the poor fit of the PFS function.

The ERG's exploratory analyses based on the partitioned survival model structure (Set B) suggest that irrespective of whether the rituximab effect is estimated using data reported by Forstpointner *et al*, the HRMN audit, or both, ibrutinib is expected to be dominated. This is likely to be a consequence of problems in robustly estimating treatment effects for OS given the available evidence.

1.6 ERG commentary on the robustness of evidence submitted by the company

Strengths

The ERG considers that it is unlikely that any other trials of ibrutinib relevant to the final NICE scope were missed. The included studies administered ibrutinib in line with its marketing authorisation. Studies included independent blinded assessment of primary outcome measures (PFS or ORR) and were adequately powered for their primary outcomes.

The company's base case health economic model was implemented without programming errors, although there is ambiguity regarding the duration over which the disutility of R-chemo was intended to have been applied.

Weaknesses and areas of uncertainty

The evidence base is subject to a number of weaknesses. In particular:

- There were no head-to-head trials comparing ibrutinib with any of the comparators listed in the final NICE scope.
- The comparator used in the ibrutinib RCT, and the comparators from the indirect comparison, were not reflective of clinical practice in England.
- The ibrutinib studies were open-label.
- Treatment pathways in studies may not reflect UK practice, including subsequent anticancer therapies.
- There were few UK patients in the trials.
- The RAY (MCL3001) RCT had not reached median OS at the time of the company's submission.
- Subsequent anticancer therapies may have affected OS estimates, thereby increasing uncertainty.
- The company's model is subject to a number of uncertainties. Some of these are an inevitable consequence of the limited clinical evidence available, whilst others are consequence of the restrictions and assumptions of the company's model structure and use of evidence.

The CS suggests four areas in which further data collection may reduce uncertainty: (i) the final datacut of the RAY (MCL3001) study (expected during the first quarter of 2017); (ii) new analyses of the HRMN audit; (iii) the Janssen "PHEDRA initiative" (Platform for Haematology in EMEA: Data for Real World Analysis), and; (iv) a further prospective longitudinal study using an alternative preference-based measure of HRQoL. The key uncertainty surrounding the cost-effectiveness of ibrutinib relates to its OS gain relative to R-chemo. The ERG's threshold analyses using the exploratory partitioned survival model consistently suggest that irrespective of the true value of the HR for PFS and the source of utility values, the HR for OS necessary for ibrutinib versus R-CHOP to have an ICER below £50,000 per QALY gained is around 0.39-0.40. Other things being equal, this would require the final datacut of the RAY (MCL3001) study to report an HR for ibrutinib versus TEM of 0.31. The ERG considers this outcome to be unlikely.

2. BACKGROUND

This chapter presents a brief summary and critique of the company's description of relapsed or refractory mantle cell lymphoma (R/R MCL) and treatments currently available for its management. Where appropriate, the information provided in the company's submission[1] (CS) has been augmented using current clinical guidelines and other literature.[2-4]

2.1 Critique of company's description of underlying health problem

MCL is a B-cell malignancy with unique biological, pathological and clinical features. It comprises approximately 3–10% of all non-Hodgkin lymphomas (NHLs).[5] The diagnosis of MCL is established according to the criteria of the World Health Organization (WHO) classification of haematological neoplasms, requiring the detection of cyclin D1 expression or the t(11;14) translocation in the context of a mature B-cell proliferation.[2, 5] MCL typically arises in older adults, with a median age of presentation of between 60 and 65 years of age. The majority of patients (approximately 75%) with MCL are male. The disease is extremely rare: according to the CS[1] (page 40), there will be an estimated 356 patients with R/R MCL in England, Wales and Northern Ireland in 2017. The rarity of the disease means there is a paucity of randomised controlled trial (RCT) data to determine treatment decisions and to inform this appraisal.

According to the CS,[1] the most common signs of MCL are: lymphadenopathy (swelling of the lymph nodes, which is usually widespread at diagnosis); splenomegaly (enlargement of the spleen, leading to abdominal pain or fullness); bone marrow infiltration (and consequently anaemia, low platelets and low neutrophils), and; leukaemic involvement. Extranodal involvement is also frequent, particularly affecting the gut and liver, and involvement of more than two extranodal sites is observed in 30-50% of patients.[1] Common symptoms are the awareness of enlarged nodes and systemic upset. Approximately 40% of patients with MCL also report "B symptoms"; these include fever, night sweats and weight loss, and can affect patients' health-related quality of life (HRQoL).[1]

Recent guidelines for the diagnosis and management of MCL[3] note that MCL is characterised by an aggressive clinical disease course, but features a pattern of resistant and relapsing disease which thereby renders it incurable with standard therapy. Prognosis for patients with MCL is very poor compared with other forms of NHL.[4] Median survival estimates for the overall MCL population are estimated to be between 4 and 5 years,[6] although both clinical disease course and prognosis are highly heterogeneous and vary widely according to the pathological sub-type of disease. Patients with blastoid variant MCL (comprising approximately 10% of the overall MCL population) typically have a particularly aggressive disease course. Conversely, patients with indolent disease (approximately 10-30% of all MCL patients[3]) have a markedly better prognosis. Overall, after excluding patients for

whom autologous stem cell transplantation (ASCT) is a treatment option, median survival following first relapse of MCL is reported to be approximately 1–2 years.[3] The CS[1] (page 41) suggests a lower estimated survival for the R/R MCL population of less than 1 year. The CS notes that in the Haematological Malignancy Research Network (HMRN) audit dataset,[7] median overall survival (OS) in patients with R/R MCL who achieved a response to first-line treatment (n=57) was 8.4 months, although the Evidence Review Group (ERG) notes considerable skewness caused by censoring; the long tail of the curve indicates that estimated mean survival may be higher. The CS also states that within the OPTIMAL trial,[8] which compared temsirolimus (TEM) versus physician's choice of single-agent chemotherapy in R/R MCL, the observed median survival for the control group was 9.7 months. Clinical advisors to the ERG noted uncertainty surrounding the expected survival duration for patients with R/R MCL: one clinical advisor suggested that expected survival would be 1-2 years, whilst the other clinical advisor suggested that expected survival would likely be below 1 year.

Whilst empirical data specific to MCL are limited, the disease has significant impacts upon HRQoL, in particular for older patients in whom treatment results in considerable toxicity.[4] The CS[1] notes that fatigue and loss of mobility are common problems for patients with MCL and that these adversely affect the patient's ability to perform simple activities of daily living. The ERG notes that the evidence used to support this in the CS is drawn from a review of quality of life studies across all haematological cancers rather than MCL specifically.[9] The CS notes that current treatments for R/R MCL have significant HRQoL impacts due to fatigue and diarrhoea. The CS also argues that the EQ-5D has limited sensitivity to measure fatigue-related quality of life impacts. This has implications for the interpretation of the company's health economic model (see Chapter 5). In addition, the CS also highlights that MCL can have a marked impact upon the HRQoL of carers but notes that there is a dearth of evidence with which to quantify such impacts.

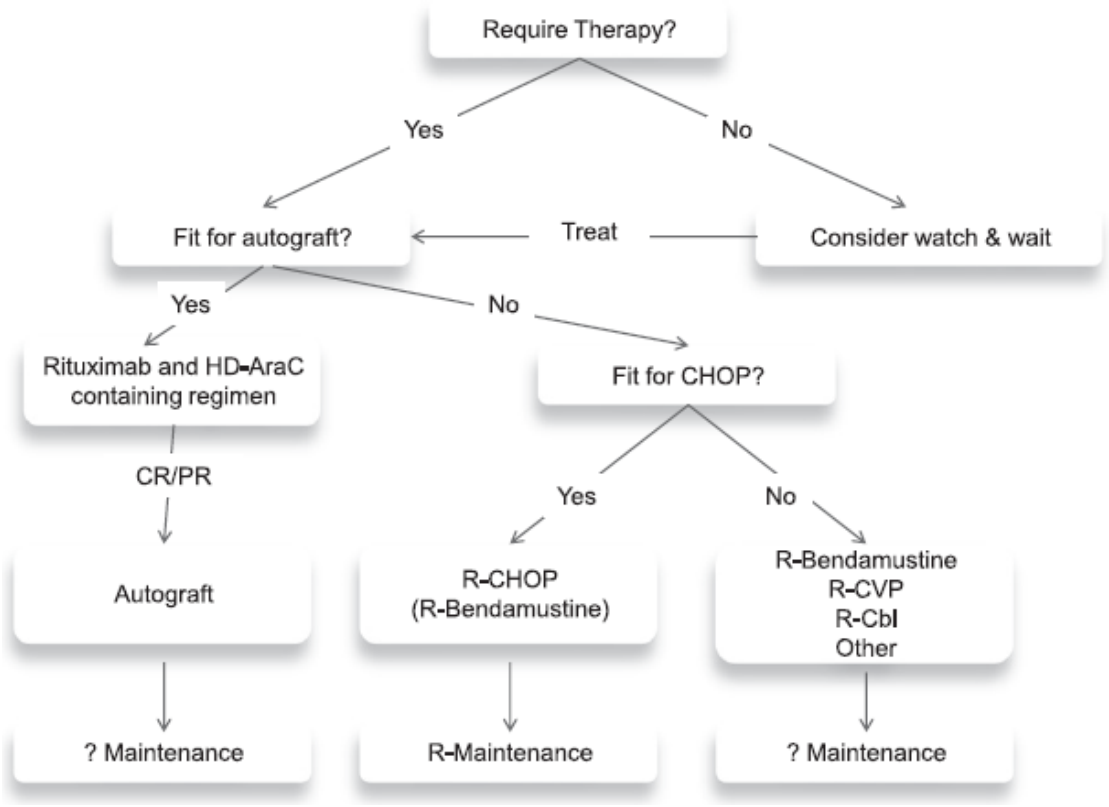
One clinical advisor to the ERG noted that overall, relapsed MCL has a poor outlook and that patients who are not treated usually survive less than one year, whilst those who are treated experience significant treatment-related toxicity often without clinical benefit of much duration before the disease progresses again.

2.2 Critique of manufacturer's overview of current service provision

The CS presents an algorithm describing first-line treatment options for MCL (reproduced from Campo *et al*[4] and provided in Figure 1). It is generally accepted that there is no standard of care for patients with R/R MCL and the disease remains very difficult to manage.[3] There is currently no NICE guidance on any therapy used in the management of R/R MCL. As noted by the CS,[1] the draft NICE Clinical Guideline for NHL[10] states that "*There is no accepted standard of care for patients with*

MCL. The paucity of randomised control data, the relative infrequency of this lymphoma subtype, historical problems in identifying this entity correctly and finding trials with only MCL patients included have all contributed to this." (NICE,[10] page 100). This view is further supported in the CS through reference to the HMRN audit,[7] whereby across the 79 patients who received second-line chemotherapy for R/R MCL, a total of 19 different treatment approaches were used.

Figure 1: Current first-line treatment for MCL (reproduced from Campo *et al*)



HD-AraC – high-dose cytarabine; CHOP - cyclophosphamide, doxorubicin, vincristine and prednisolone; CR/PR – complete response/partial response; R-CHOP – rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; R-bendamustine – rituximab and bendamustine; R-CVP - rituximab, cyclophosphamide, vincristine and prednisolone; R-Cbl – rituximab and chlorambucil

The British Committee for Standards in Haematology (BCSH) guidelines[3] note that the choice of therapy at relapse will be determined by patient age, performance status, bone marrow reserve, initial therapy and history of infections. For patients who have not received transplantation as part of their first-line therapy, but are considered sufficiently fit for such therapy following relapse, ASCT may be considered as a clinical option.[3] However, clinical advisors to the ERG suggested that this is not a common option in the relapsed/refractory setting since most patients suitable for an autograft will have received it in first-line when it is best tolerated and likely to be most effective. For older and/or less fit patients, a range of systemic chemotherapy regimens may be considered (provided the patient is sufficiently fit to receive them). The CS states that treatment typically involves chemotherapy with

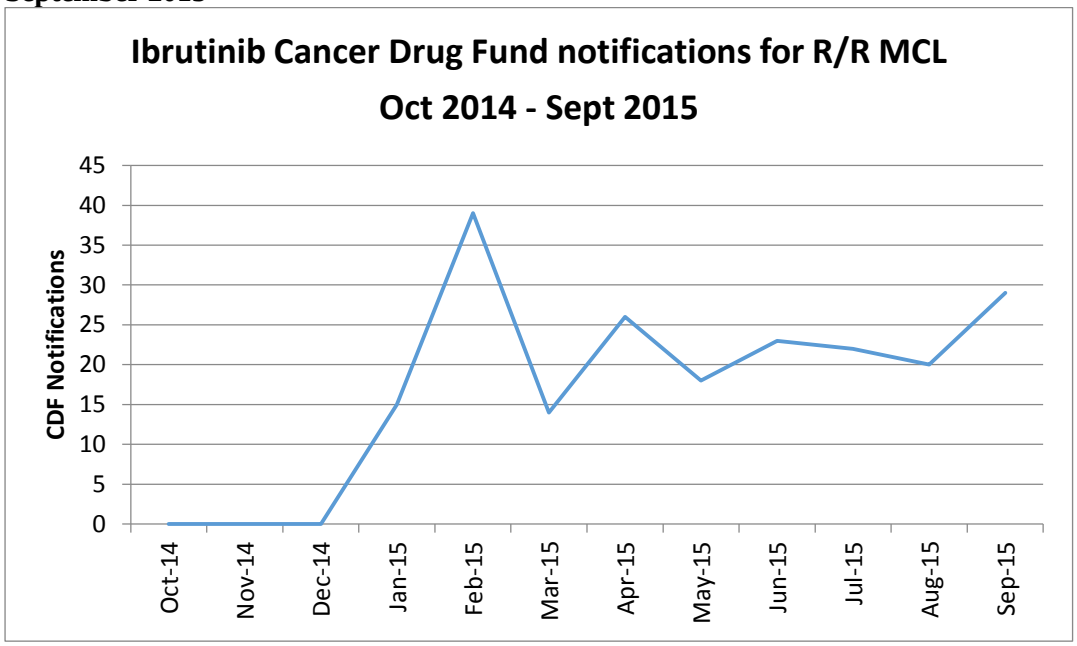
or without rituximab. This may include regimens such as: R-CHOP (rituximab, cyclophosphamide, doxorubicin and vincristine); R-bendamustine (rituximab and bendamustine); FCR (rituximab, fludarabine and cyclophosphamide); R-CVP (rituximab, cyclophosphamide, vincristine and prednisolone), or; R-chlorambucil (rituximab and chlorambucil). With the exception of R-bendamustine and R-chlorambucil, these options are included as the comparators in the final NICE scope,[11] however none of these therapies are specifically licensed in the R/R MCL population. It should also be noted that the European Society for Medical Oncology (ESMO) guidelines[2] discourage the use of R-CVP and FCR due to inferior response rates and long-lasting myelosuppression.

In addition to the rituximab plus chemotherapy (R-chemo) options listed above, the BCSH guidelines[3] state that a number of other regimens have been shown to have activity in the R/R MCL population. These include: (i) bortezomib; (ii) bortezomib-gemcitabine; (iii) bortezomib-rituximab; (iv) TEM; (v) rituximab, fludarabine, cyclophosphamide and mitoxantrone (R-FCM); (vi) fludarabine; (vii) fludarabine-cyclophosphamide; (viii) fludarabine-cyclophosphamide+/-rituximab; (ix) cladribine; (x) gemcitabine-dexamethasone; (xi) gemcitabine-dexamethasone-cisplatin; (xii) lenalidomide; (xiii) thalidomide-rituximab, and; (xiv) PEP-C/thalidomide/rituximab. Where the patient has received one previous line of treatment, a different regimen would typically be chosen following relapse.[3] Whilst the ESMO guidelines[2] recommend targeted therapies such as TEM, bortezomib and lenalidomide, the CS argues that these therapies are not available in usual clinical practice in England: TEM is not currently used, bortezomib is recommended only in untreated MCL and lenalidomide is available only via a compassionate use programme (CUP).[1]

Current use of ibrutinib

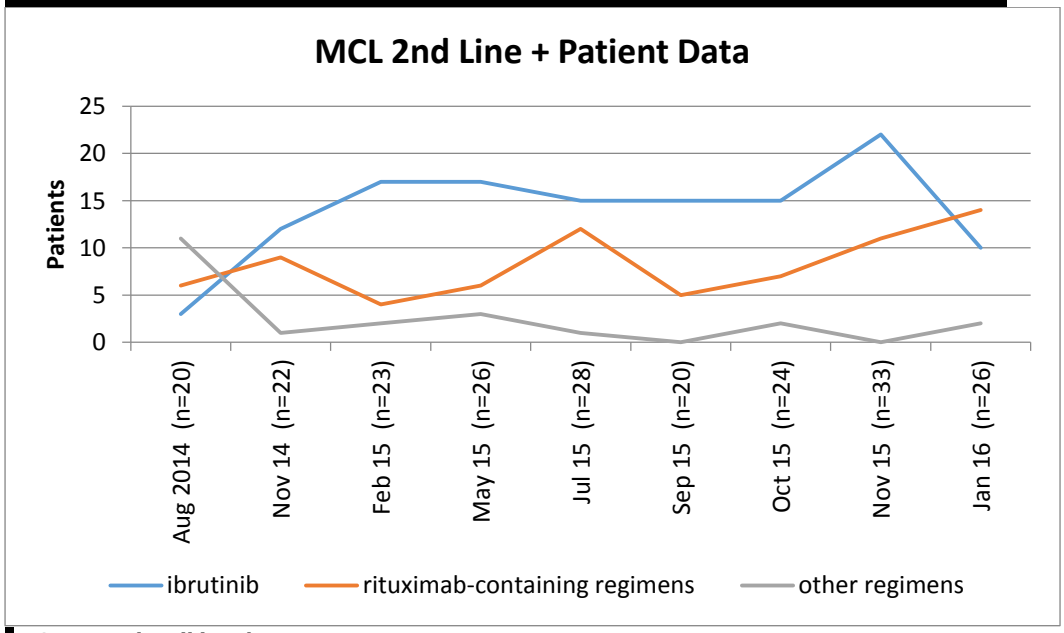
The CS notes that ibrutinib has been available via CUPs and through the Cancer Drugs Fund (CDF) (since January 2015). Figure 2 presents the number of new CDF notifications for ibrutinib within the R/R MCL indication.[12, 13] Figure 3 presents market research data reported in the CS on the use of second- and subsequent-line therapies in MCL.[1] [redacted]

Figure 2: Analysis of ibrutinib CDF notifications for R/R MCL from October 2014 to September 2015



CDF – Cancer Drugs Fund; R/R MCL – relapsed/refractory mantle cell lymphoma

[redacted]



MCL – mantle cell lymphoma

[redacted]

Clinical advisors to the ERG noted that adding rituximab to chemotherapy was likely to offer a small benefit compared with the use of chemotherapy alone. This is supported by the findings of an RCT[14] which reported a statistically significant OS benefit in the R/R MCL subgroup for R-FCM versus FCM alone (p=0.0042). Clinical advisors to the ERG also commented that the benefit of R-chemo would to be expected to reduce with increasing lines of therapy. In addition, the clinical advisors

agreed that whilst TEM (the comparator in the only RCT of ibrutinib in R/R MCL[15]) is the only treatment specifically licensed for use in R/R MCL, it is not a relevant comparator for ibrutinib as it is not currently available on the NHS (TA207 was terminated as the company did not submit evidence[16]). Despite not being available in clinical practice, TEM is considered to be more effective than treatments currently used in England. The clinical advisors stated that whilst other therapies may potentially be used in the R/R MCL population, for example, bortezomib and lenalidomide, these are also not relevant comparators as they are not available in England, except in very small numbers of patients via individual funding requests.

The clinical advisors to the ERG suggested that the most relevant comparator for ibrutinib for patients with R/R MCL who are not refractory to rituximab would be R-bendamustine, although one advisor noted that other R-chemo options may be used (e.g. R-CHOP, R-CVP, FCR or RC). They also noted that outcomes for R-bendamustine and R-CHOP were likely to be similar. One advisor also noted that the likely pathway for the first-line treatment of MCL in older patients is R-chemo followed by rituximab maintenance followed on progression by further chemotherapy; consequently, some patients in the R/R MCL population may not receive rituximab. The ERG's clinical advisors also commented that R/R MCL patients who are still fit enough to receive active chemotherapy may receive additional lines of treatment after progression on second-line therapy; this is not directly reflected in the company's base case health economic analysis (see Chapter 5).

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[11] and addressed in the CS[1] is presented in Table 1.

Table 1: 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[11]**
Population	Adults with R/R MCL	Adults with R/R MCL	Same as final NICE scope
Intervention	Ibrutinib	Ibrutinib	Same as final NICE scope
Comparator(s)	Established clinical management without ibrutinib, including: • R-CHOP • R-CVP • FCR • RC	Established clinical management without ibrutinib, including: • R-CHOP • R-CVP • FCR • RC	Same as final NICE scope
Outcomes	The outcomes to be considered include: • Overall survival (OS) • Progression-free survival (PFS) • Overall response rates (ORR) • Duration of response (DOR)/remission • Time to new anti-lymphoma treatment/time to progression • Adverse effects of treatment • HRQoL	The outcomes considered in the CS include: • OS • PFS • ORR • DOR/remission • Time to new anti-lymphoma treatment/time to progression • Adverse effects of treatment • HRQoL Additional outcomes not specified in the scope are presented in CS[1] Table 14	Same as final NICE scope

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from final NICE scope[11]
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 (QALY) • 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 (PSS) perspective	• The economic analysis conforms to the final scope • The outcome measure of the economic analysis is the incremental cost-effectiveness ratio (ICER) • The time horizon considered is 15 years (less than 0.10% of patients in both model groups are alive at this timepoint) • Costs are considered from an NHS and PSS perspective	Same as final NICE scope
Subgroups to be considered	None detailed	Subgroup analysis provided for R/R MCL patients who have received: • 1 prior line of therapy (LOT) • >1 prior LOT	Feedback from clinical experts has indicated that these subgroups are relevant to explore. Evidence supports increased efficacy of ibrutinib when used at earlier lines of treatment.
Special considerations including issues related to equity or equality	None detailed	N/A	N/A

R/R MCL - relapsed/refractory mantle cell lymphoma; R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CVP - rituximab, cyclophosphamide, vincristine and prednisolone; FCR - fludarabine, cyclophosphamide, rituximab; RC - rituximab and cytarabine; OS - overall survival; PFS - progression-free survival; ORR - overall response rates; DOR - duration of response; HRQoL - health-related quality of life; QALY - quality-adjusted life year; PSS - Personal Social Services; ICER - incremental cost-effectiveness ratio; LOT – line of therapy

3.1 Population

The population defined in the final NICE scope[11] relates to adults with R/R MCL. This is in line with the marketing authorisation for ibrutinib detailed in the Summary of Product Characteristics (SmPC).[17] This also reflects the populations recruited into the RAY (MCL3001), SPARK (MCL2001) and PCYC1104 studies included in the company's systematic review of clinical effectiveness evidence. The ERG notes that the populations recruited into the three ibrutinib studies differ in terms of eligibility criteria with SPARK (MCL2001) requiring all patients to have prior bortezomib therapy, and PCYC1104 not requiring prior rituximab treatment. At baseline, patients in the SPARK (MCL2001) study had higher Eastern Cooperative Oncology Group (ECOG) status than the other studies, and the single-arm studies had fewer patients with only one prior line of therapy (LOT) than the RAY (MCL3001) RCT.

Whilst not discussed in the CS, the clinical advisors to the ERG noted that the distinction between "relapsed" and "refractory" disease relates principally to time since last treatment, but that in practice the terms tend to be interchangeable. If the disease returns more than 6 months after response to chemotherapy, the patient would be considered relapsed. If the patient does not respond to chemotherapy, or relapses very early, they would be considered refractory.

3.2 Intervention

The intervention under appraisal is ibrutinib (Imbruvica®). Ibrutinib is a first-in-class Bruton's tyrosine kinase (BTK) inhibitor. Within its R/R MCL indication, ibrutinib is administered orally at a recommended dose of 560mg (four 140mg capsules) once daily (o.d.). Ibrutinib received orphan status from the European Medicines Agency (EMA) for its MCL indication in April 2012. Full marketing authorisation was granted by the EMA in October 2014. Ibrutinib also holds a European marketing authorisation for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy, or in first-line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy, and for the treatment of 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.[17]

The SmPC[17] recommends that treatment with ibrutinib should continue until disease progression or until the therapy is no longer tolerated by the patient. 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 once daily 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.[17] 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 moderate CYP3A4 inhibitors.[17]

Ibrutinib is available in packs of 90 capsules or 120 capsules. As of June 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).[18] 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.[17] 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 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.[17]

3.3 Comparators

The final NICE scope[11] defines the relevant comparator as established clinical management without ibrutinib, including: (i) rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP); (ii) rituximab, cyclophosphamide, vincristine and prednisolone (R-CVP); (iii) fludarabine cyclophosphamide and rituximab (FCR), and; (iv) rituximab and cytarabine (RC).

The company's review of clinical effectiveness (see CS,[1] Section 4) did not identify any studies which included head-to-head comparisons of ibrutinib versus any of the comparators listed in the final NICE scope.[11] The only comparative study of ibrutinib in the R/R MCL population is the RAY (MCL3001) RCT which compared ibrutinib versus TEM.[15] The CS[1] includes an indirect comparison which compares ibrutinib versus physician's choice of single-agent chemotherapy.[8] A further indirect comparison was undertaken to adjust for the addition of rituximab to chemotherapy, based on data

from the HMRN audit.[7] The company's clinical review reports only on the comparison of ibrutinib versus single-agent chemotherapy. The company's health economic model includes an estimate of the effectiveness of ibrutinib versus R-chemo by synthesising the hazard ratio (HR) generated from the indirect comparison of ibrutinib versus single-agent chemotherapy with the HR describing the benefit of adding rituximab to chemotherapy.[1] Owing to a lack of evidence, the company's health economic analysis assumes that all R-chemo options are equivalent in terms of clinical effectiveness. The company's base case model evaluates ibrutinib versus R-CHOP. A separate scenario analysis is presented comparing ibrutinib followed on progression by R-CHOP versus R-CHOP alone. In addition, the CS includes a blended comparison of ibrutinib versus a mix of R-CHOP, R-CVP and FCR. Further scenario analyses are presented comparing ibrutinib versus R-CHOP, R-CVP, FCR and RC individually.

3.4 Outcomes

The final NICE scope[11] lists the following outcomes:

- Overall survival (OS)
- Progression-free survival (PFS)
- Overall response rates (ORR)
- Duration of response (DOR)/remission
- Time to new anti-lymphoma treatment/time to progression
- Adverse effects of treatment
- HRQoL.

The CS reports outcomes for ibrutinib for all of these endpoints. Outcomes are presented for individual studies (RAY [MCL3001], SPARK [MCL2001] and PCYC1104) and for a pooled dataset which combines all three ibrutinib studies. The company's indirect comparison of ibrutinib versus single-agent chemotherapy is presented for the outcomes of OS, PFS and ORR. The company's indirect comparison of ibrutinib versus R-chemo was undertaken only for the endpoint of PFS.

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 R-chemo for the treatment of adults with R/R MCL. The company's health economic analysis is detailed and critiqued in Chapter 5.

3.6 Subgroups

The final NICE scope[11] did not specify any subgroups of patients with R/R MCL. The company's clinical effectiveness review includes an analysis of outcomes according to number of prior LOTs;

this analysis is presented for two subgroups: LOT=1 and LOT≥2. Within the company's clinical review, subgroup analysis of PFS and OS by LOT is presented for the RAY (MCL3001) study and for the pooled ibrutinib dataset. The company's health economic analysis also includes a separate subgroup analysis according to number of prior LOTs using the pooled ibrutinib dataset.[19]

3.7 Special considerations

The CS states that ibrutinib *"provides an effective treatment option for all R/R MCL patients including those who cannot receive cytotoxic therapies due to their advanced age, performance status, comorbidities or fitness"* (CS,[1] page 44). The CS also notes that equality issues which may currently exist for older, frailer patients would be alleviated through the use of ibrutinib and that the oral administration of ibrutinib allows an effective treatment option to be given to patients that may not have local access or transport to an appropriate infusion unit. One clinical advisor to the ERG stated that ibrutinib would be well tolerated by patients who would never be candidates for most chemotherapy options.

The CS claims that ibrutinib meets NICE's criteria for a life-extending therapy given at the end of life;[20] the evidence used to support this claim is discussed further in Chapter 7 of this report.

The ERG notes that in the foreword to the CS, the company requests the opportunity to remain on the CDF in order to collect further evidence to reduce the level of uncertainty that currently exists regarding ibrutinib. The implications of this are discussed in Chapter 5 of this report.

4. CLINICAL EFFECTIVENESS

This chapter presents a review of the clinical effectiveness evidence for ibrutinib for treating R/R MCL. Section 4.1 presents a critique of the company's systematic review of clinical effectiveness. Section 4.2 presents the results of the ibrutinib studies included in the CS. Sections 4.3 and 4.4 discuss the company's indirect comparisons. Section 4.5 reports the results of additional analyses undertaken by the ERG. Conclusions on the clinical effectiveness of ibrutinib are summarised in Section 4.6.

4.1 Critique of the methods of review(s)

4.1.1 Searches

The company conducted a systematic review of published clinical studies (RCTs and non-randomised studies) in R/R MCL in June 2015, including an update of searches previously undertaken in May 2014. Section 4.1.2 of the CS[1] states that the review will be updated again in June 2016. Since the results are not yet available, they cannot be considered as part of the current submission. In response to a request for clarification from the ERG regarding the outdated searches (see clarification response,[21] question B4), the company updated the searches in May 2016 and provided a PRISMA flowchart with the details of their most recent findings.

Searches were run on all of the core databases recommended for reviews of interventions (Medline, Embase, Cochrane CENTRAL) including pre-indexing "in-process" records where available. However, the searches did not include "e-pub ahead of print" records within PubMed; this may explain why a relevant clinical modelling study (Peng *et al*[22]) was not identified for inclusion in the review (see Section 5.1).

Rather than naming ibrutinib and its comparators, the searches were structured around the condition (MCL) and the treatment stage (salvage chemotherapy; 2nd or 3rd line etc.). This allows for the identification of any clinically tested intervention in the relevant population.

Broadly speaking, the searches appear to be competent, using a combination of subject headings and free text search strings; however, there are some examples of redundant repetition. For example, in the original Embase search from 2014 (see CS,[1] Appendix 3, Table 96), there are search strings for both "mantle cell lymphoma" and the combination of "mantle cell" and "lymphoma". It is unnecessary to include both since the latter string is much more sensitive and would retrieve everything found by the exact phrase search. There are similar instances of repetition later in the search (e.g. "refractory or refractor*", searched for both with and without chemotherapy and alternative 'treatment' terms).

Limits were applied in order to restrict results to clinical trials and reviews. However, no limits were applied to the most recent results in order to maximise recall. Proceedings from relevant oncology, haematology and pharmacoeconomics conferences (2013-2015 and 2016, where available) were examined in an attempt to identify studies not yet reported in the peer-reviewed literature, however the search strategies used are not reproduced in the CS. Bibliographies of included studies were also reviewed. In response to a request for clarification from the ERG (see clarification response,[21] question B1), the company confirmed that no forward citation tracking was conducted using included studies.

Overall, the ERG is satisfied that no relevant empirical clinical studies of ibrutinib would have been missed by the company's searches.

4.1.2 Inclusion criteria and study selection

Study selection is described in the CS[1] Section 4.1.3 (page 47). The CS describes an appropriate two stage study selection process involving two independent reviewers using pre-specified inclusion and exclusion criteria. Any discrepancies between reviewers were reviewed by a third reviewer; the ERG considers this to reflect good practice. The inclusion and exclusion criteria, as presented in the CS, are reproduced in Table 2. The ERG notes that the table includes text relating to "Review of full texts only". It is therefore unclear whether or not the inclusion criteria for sifting titles and abstracts were different from those used for full text sifting.

Table 2: Inclusion/exclusion criteria used for ibrutinib study selection (reproduced from CS Table 11)

	Inclusion criteria	**Exclusion criteria**
Population	R/R MCL patients	Patients without at least 85% R/R MCL, i.e. studies involving treatment-naïve MCL patients, other lymphoma subtypes, or patients receiving first-/front-line therapies
Intervention	Review of full texts only Ibrutinib monotherapy Ibrutinib combination therapy BR R-CHOP Fludarabine + cyclophosphamide ± mitoxantrone (FC ± M) Fludarabine + (bendamustine or cisplatin or chlorambucil or rituximab or cyclophosphamide) Chlorambucil + rituximab Bortezomib monotherapy ± rituximab Bleomycin monotherapy Vinblastine monotherapy Dacarbazine monotherapy TEM monotherapy Doxorubicin monotherapy Rituximab monotherapy R-DHAP ± low-dose aracytine Lenalidomide monotherapy Rituximab and cytarabine (RC) Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CVP)	No treatment of interest (for example, radioimmunotherapy, 'watch and wait'/no treatment, prophylactic or palliative care alone)
Comparators	*Review of full texts only* Any of the above interventions	
Outcomes	Efficacy Overall response: number of patients Complete response (CR): number of patients Partial response (PR): number of patients Stable disease: number of patients Progressive disease: number of patients Unconfirmed CR or nodular PR: number of patients Minimal residual disease Response duration: in months Time to first response: in weeks Time to progression: in weeks PFS: in months OS: in months Treatment-related death: number of patients Overall death: number of patients Event-free survival (EFS): in months Time to treatment failure: in months Safety Grade 3, 4, or 3/4 safety endpoints (each outcome definition was to be captured as	Publications that did not report safety outcomes, or efficacy outcomes for R/R MCL Articles investigating *in vitro*, animal, foetal, molecular, genetic, pathologic, or pharmacokinetic/pharmacodynamic outcomes without outcomes of interest reported

	Inclusion criteria	Exclusion criteria
	reported; the number of patients was to be captured or calculated from a percent for each outcome unless otherwise specified) Infusion-related complications Anaemia/haemoglobin Febrile neutropenia Infection-related Leukopenia Lymphocytes abnormal Neurotoxicity Neutropenia Pain Peripheral oedema Thrombocytopenia	
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 abstract published in English Comparative studies with fewer than 10 patients per treatment group in at least two treatment arms or single-arm studies with fewer than 10 patients
Language	English language	Non-English-language

R/R MCL – relapsed/refractory mantle cell lymphoma

The ERG notes that non-English language studies were excluded from the company's review; this could have resulted in relevant studies being missed. The company's PRISMA diagram (see CS,[1] Figure 6) states that only one publication was excluded because it was not published in English.

The inclusion and exclusion criteria for the population specified in the CS are appropriate and reflect the decision problem outlined in the final NICE scope[11] (see Table 1) in that the population covered patients with R/R MCL. Studies with less than 85% of patients with R/R MCL were excluded. Given the lack of data for this patient population, it would have useful to assess other RCTs of ibrutinib which may have included subgroup data reported separately for patients with R/R MCL. During the clarification process, the ERG requested that the company provide a list of studies including subgroups of patients with R/R MCL treated with ibrutinib. In response, the company stated that *"no studies were excluded where results for R/R MCL subgroups were reported separately (provided there were at least 10 patients with MCL in each treatment arm). The 85% criterion was only applied to studies of mixed populations for which results were not reported separately"* (Clarification response,[21] question B5).

With regard to the intervention, studies of ibrutinib monotherapy and combination therapy were included. The company's search was not limited by comparators. In addition to those listed in the final NICE scope,[11] several additional comparator therapies were listed under the inclusion criteria. This is appropriate when populating an indirect comparison and/or network meta-analysis (NMA).

On the whole, the outcomes listed in the final NICE scope[11] are included in the inclusion criteria for the review; however, HRQoL is not listed. Also, the exclusion criteria state that studies were excluded if they did not report safety or efficacy outcomes. It is thus unclear whether studies only reporting HRQoL would be excluded. There is no indication that studies reporting only HRQoL outcomes were excluded, although the company's PRISMA diagram states that seven studies were excluded on the basis of outcomes reported (see CS,[1] Figure 6). The other efficacy outcomes listed in the final NICE scope[11] are all included in the CS (Table 11), although some have been renamed and some additional outcomes have been included, such as: complete response; partial response; stable disease; progressive disease; unconfirmed complete response or nodular partial response; minimal residual disease; treatment-related death, and; overall death.

For safety outcomes, specific adverse events (AEs) are listed as well as Grade 3, 4 or 3/4 safety endpoints. It is assumed that this refers to any Grade 3, 4 or 3/4 event and is not restricted to the specific events listed in the table. There is no restriction in the NICE scope by type of AE and there is no indication that studies have been excluded from the company's review based on AE reporting, however, as stated above, seven studies were excluded on the basis of outcomes reported (see CS,[1] Figure 6).

Included study designs were not limited to RCTs; this is appropriate given there is very limited RCT evidence for ibrutinib in the treatment of R/R MCL. It is unclear from CS Table 11 if searches for non-RCTs were undertaken for ibrutinib only, or whether non-randomised studies including other interventions may have been considered for indirect comparison. The exclusion criteria state that non-systematic reviews were excluded. It is however unclear whether systematic reviews were included. The text on page 47 of the CS suggests that systematic reviews published after 2011 were reviewed as potential supplemental sources of relevant studies.

The study selection process is described in Section 4.1.4 of the CS. The PRISMA diagram (see CS,[1] Figure 6) states that five studies were excluded on the basis of publication type. It is unclear from CS Appendix 4 (Table 108) which studies were excluded on the basis of study type and which study types were excluded.

The CS describes 29 R/R MCL studies as being included in the systematic review (see CS,[1] Figure 6), including four relevant RCTs and 25 single arm studies. Confusingly, all 29 studies were included in Appendix 4 of the CS (Tables 106 and 107), but were not all included in the systematic review. In response to a request for clarification on this matter (see clarification response,[21] question B6), the company stated that 29 studies met the eligibility criteria. However, of the four RCTs which were deemed eligible for inclusion, two were deemed not relevant and of the 25 non-RCTs, 22 studies were deemed to not be relevant to the decision problem. In Appendix 4 of the CS,[1] it is stated that 28 studies, rather than 29 studies, were included in the review. In response to the ERG's clarification request[21] (question B6), the company stated that this was an error and should refer to 29 studies, as in Figure 6 of the CS. Of the 29 included studies, one RCT of ibrutinib (RAY [MCL3001] - CS,[1] Section 4.2), and two single-arm studies of ibrutinib (PCYC1104 and SPARK [MCL2001] - CS[1] Section 4.11) were actually included in the company's systematic review.

In response to a request for clarification[21] (question B4), the company provided updated database searches which identified 17 studies which met the eligibility criteria. Only two of these were new studies which had not been identified in the original search; both of the new studies were excluded as they related to ibrutinib combination therapy rather than monotherapy.

The four RCTs identified are listed in Table 12 of the CS. Of these, one was the RAY (MCL3001) RCT (the main ibrutinib study), and one further RCT (OPTIMAL,[8] reported by Hess *et al*) was also included in the company's indirect comparison (see Section 4.3). The other two RCTs, SPRINT[23] and the German Low-Grade Lymphoma Study Group trial,[14] are listed in the CS Table 12, but were not included in the company's systematic review as they were not considered relevant to the decision problem.

The RAY (MCL3001) RCT is described in Section 4.3 of the CS. The population and intervention in the RAY (MCL3001) study matches the decision problem set out in the final NICE scope[11] and included relevant outcomes. The comparator in this study was TEM; this is not included in the final NICE scope[11] and is not available in England (as previously discussed in Chapter 3). The RAY (MCL3001) study was used in spite of this due to the lack of data for ibrutinib for patients with R/R MCL. With regard to the two single-arm studies of ibrutinib, PCYC1104 and SPARK (MCL2001), the population, intervention and outcomes are in line with the decision problem set out in the final NICE scope.[11] PCYC1104 and SPARK (MCL2001) did not include a comparator arm. The intervention and comparator used in the OPTIMAL study[8] were not listed in the final NICE scope.[11] Details of the OPTIMAL study can be found on page 82 of the CS.[1]

4.1.3 Critique of data extraction

The company's data extraction methods are described on page 47 of the CS.[1] Data were extracted by one reviewer and checked by another; discrepancies were resolved by a third reviewer. The ERG considers this to reflect good practice. It is however unclear from the CS which data items were extracted and an example data extraction form was not provided. However, all relevant data appear to have been extracted for the RAY (MCL3001), PCYC1104 and SPARK (MCL2001) studies. Some limited information relating to the OPTIMAL trial[8] used in the company's indirect comparison is presented in Table 26 of the CS. For each included study, data were extracted from multiple relevant publications, avoiding double-counting; the ERG also considers this to be good practice. Where possible, the ERG checked data reported in the CS[1] on baseline characteristics and outcomes against published study papers and found the data to be accurate.

4.1.4 Quality assessment of included studies

The company provided a formal appraisal of study quality for the three ibrutinib studies included in the CS[1] (RAY [MCL3001], PCYC1104 and SPARK [MCL2001]). It is unclear from the CS how many reviewers conducted the quality assessment of the included studies. The quality assessment for the RAY (MCL3001) study, an RCT, is provided in CS Section 4.6. Whilst not stated in the CS, the quality assessment criteria used were taken from the Centre for Reviews and Dissemination (CRD) guidelines for undertaking reviews in health care.[24] These are the minimum criteria for the assessment of risk of bias and generalisability in parallel group RCTs as set out in the NICE user guide for company submissions,[25] and their use is appropriate. The company's completed quality assessment is presented together with the ERG's assessment in Table 3.

RAY (MCL3001) quality assessment

In order to assess the quality of the RAY (MCL3001) study, the ERG used Dreyling *et al*[15] supplemented with information from the Clinical Study Report (CSR).[26]

Table 3: Quality assessment for RAY (MCL3001) trial

Quality assessment criteria from NICE CS template (based on CRD report 4)	Company's quality assessment	ERG's quality assessment
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	No	No.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?	No	No Except outcome assessment for PFS (Independent Review Committee [IRC])
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	[redacted]
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

PFS – progression free survival

The ERG agreed with the company's quality assessment of the RAY (MCL3001) study presented in the CS.[1] In the RAY (MCL3001) study, central randomisation was used with a computer generated randomisation schedule. Randomisation was balanced by using randomly permuted blocks and stratified by the number of previous LOTs and prognostic index score;[27] the ERG considers this to be appropriate. Both patients and investigators were unaware of treatment assignment. Blinding of patients and investigators protects against both performance bias and measurement bias.[28] The absence of double blinding in RCTs tends to result in larger treatment effects.[29] Groups appeared to be similar in terms of ECOG performance status, stage of MCL at study entry, and time from initial diagnosis to randomisation. Blinded outcome assessment is rare in oncology trials although its use can enhance bias reduction.[30] The primary endpoint in RAY (MCL3001) was assessed by an IRC masked to study treatment. The CS (Table 15) states the process used for the calculation of study sample size and shows that RAY (MCL3001) was adequately powered for the primary endpoint of PFS. Methods used to handle missing data were not reported in the CS.[1] Dreyling *et al*[15] state that at the time of reporting, 65 (47%) of 139 ibrutinib patients were still on treatment, compared with 15 (11%) of 141 TEM patients. Additionally, more patients discontinued TEM due to investigator decision or patient refusal of treatment (ibrutinib, 4 [3%]; TEM, 22 [16%]). Fewer subjects discontinued drug treatment due to AEs in the ibrutinib arm compared with the TEM arm (6.5% versus 25.5% of subjects). Fewer subjects in the ibrutinib arm required dose reduction compared with the TEM arm (4.3% versus 43.9% of subjects).[1]

PCYC1104 and SPARK (MCL2001) quality assessment

The quality assessment for the two single-arm studies, PCYC1104 and SPARK (MCL2001), was undertaken using the Downs and Black checklist for non-randomised studies.[31] This is an appropriate checklist for this study type. The quality assessment for Study PCYC1104 is provided in Section 4.11.1.5 and Appendix 6 of the CS. The quality assessment for the SPARK (MCL2001) study is provided in Section 4.11.2.5 and Appendix 6 of the CS. The company's completed quality assessment is presented together with the ERG's assessment in Table 4 for Study PCYC1104 and in Table 5 for SPARK (MCL2001). The ERG's assessment of the quality of Study PCYC1104 was based on Wang *et al*.[32]

Table 4: Quality assessment of Study PCYC1104

Criteria from Downs and Black quality assessment checklist	Company's quality assessment	ERG's quality assessment
Is the hypothesis/aim/objective of the study clearly described?	Yes	Yes
Are the main outcomes to be measured clearly described in the introduction or methods section?	Yes	Yes
Are the characteristics of the patients included in the study clearly described?	Yes	Yes
Are the interventions of interest clearly described?	Yes	Yes
Are the main findings of the study clearly described?	Yes	Yes
Does the study provide estimates of the random variability in the data for the main outcomes?	Yes	Yes
Have all important AEs that may be a consequence of the intervention been reported?	Yes	Yes
Have the characteristics of patients lost to follow-up been described?	No	No
If any of the results of the study were based on "data dredging", was this made clear?	Yes	Yes
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	Yes
Were the statistical tests used to assess the main outcomes appropriate?	Yes	Yes
Was compliance with the intervention/s reliable?	Yes	Yes
Were the main outcome measures used accurate (valid and reliable)?	Yes	Yes
Were losses of patients to follow-up taken into account?	Yes	Yes

The ERG's assessment of the quality of the PCYC1104 study is in line with that found in the CS.

The ERG's assessment of the quality of the SPARK (MCL2001) study was based on the CSR[33] as the study has not been published except in abstract form.[34]

Table 5: Quality assessment of SPARK (MCL2001) study

Criteria from Downs and Black	Company's quality assessment	ERG's quality assessment
Is the hypothesis/aim/objective of the study clearly described?	Yes	Yes
Are the main outcomes to be measured clearly described in the introduction or methods section?	Yes	Yes
Are the characteristics of the patients included in the study clearly described?	Yes	Yes
Are the interventions of interest clearly described?	Yes	Yes
Are the main findings of the study clearly described?	Yes	Yes
Does the study provide estimates of the random variability in the data for the main outcomes?	Yes	Yes
Have all important AEs that may be a consequence of the intervention been reported?	Yes	Yes
Have the characteristics of patients lost to follow-up been described?	No	No
If any of the results of the study were based on "data dredging", was this made clear?	Yes	Yes
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	Yes
Were the statistical tests used to assess the main outcomes appropriate?	Yes	Yes
Was compliance with the intervention/s reliable?	Yes	Yes
Were the main outcome measures used accurate (valid and reliable)?	Yes	Yes
Were losses of patients to follow-up taken into account?	Yes	Yes

The ERGs assessment of the quality of the PCYC1104 study is in line with the company's assessment.

The Downs and Black checklist includes 27 questions,[31] 13 of which were not addressed in the company's quality assessment of the PCYC1104 and SPARK (MCL2001) studies. Some of the questions were not considered by the ERG to be relevant as they relate to studies with comparator arms; these are listed below.

1. Have actual probability values been reported for the main outcomes except where the probability value is less than 0.001?
2. Are the distributions of principal confounders in each group of subjects to be compared clearly described?
3. Were the patients in different intervention groups recruited from the same population?
4. Were study subjects in different intervention groups recruited over the same time?
5. Were study subjects randomised to intervention groups?
6. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?

The quality assessment questions addressed in Table 6 were however considered by the ERG to be relevant and should have been included in the company's quality assessment. The ERG's quality assessment of these additional questions for the PCYC1104 and SPARK (MCL2001) studies are presented in Table 6. In both PCYC1104 and SPARK (MCL2001), it is unclear whether or not the patients included were representative of patients with R/R MCL in current clinical practice in England. As described above, blinding is particularly challenging in oncology trials, although no attempts were made to blind those assessing study outcomes.

Table 6: ERG quality assessment of Downs and Black questions not included in the CS

Additional Downs and Black question	PCYC1104	SPARK (MCL2001)
Where the subjects asked to participate in the study representative of the entire population from which they were recruited?	Unclear	[redacted]
Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Unclear	[redacted]
Were the staff, places and facilities where the patients were treated representative of the treatment the majority of patients receive?	Yes	[redacted]
Was an attempt made to blind study subjects to the intervention they have received?	No	[redacted]
Was an attempt made to blind those measuring the main outcomes of the intervention?	No Except outcomes assessment for response rates (IRC)	[redacted]
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Yes	[redacted]
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance <5%?	Yes	[redacted]

PFS – progression-free survival; IRC – independent review committee

OPTIMAL quality assessment

The OPTIMAL RCT (Hess *et al*[8]) was used in the company's indirect comparison described in Section 4.10 of the CS. The CS does not include a quality assessment of this study. The ERG's quality assessment of the OPTIMAL trial based on criteria taken from the CRD guidance[24] is presented in Table 7.

Table 7: Quality assessment of OPTIMAL trial

Quality assessment criteria from NICE guide (based on CRD report 4)	ERG's quality assessment
Was randomisation carried out appropriately?	Unclear
Was the concealment of treatment allocation adequate?	Unclear
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?	No, although independent outcome assessors were used.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

It is unclear from Hess *et al*[8] whether or not randomisation was carried out appropriately or whether allocation concealment was adequate. Although patients and providers were not blinded to treatment allocation, independent outcome assessors were used in the study.

4.1.5 Evidence synthesis

A pooled analysis using individual patient-level data from RAY (MCL3001), PCYC1104 and SPARK (MCL2001) was performed, including 370 patients in order to assess the impact of baseline factors on OS. The methods and results used in this pooled analysis are presented in Section 4.12 of the CS.[1] There are differences in study design across these three studies (one RCT and two single-arm studies) and no discussion or statistical testing of between-study differences was provided in the CS. It is generally not recommended to pool arms across trials. Pooling should be conducted at the treatment effect level, with treatment effects assumed to be combinable but allowing for variations in the baseline response in each trial due to differences in the patient populations. This is not possible for PCYC1104 and SPARK (MCL2001) as the single-arm studies do not provide an estimate of treatment effect. Since the analysis is not used to estimate relative treatment effects, and given the paucity of evidence for ibrutinib in the R/R MCL indication, pooling was considered acceptable by the ERG and their clinical advisors. It is however noteworthy that inclusion criteria differed across the three included studies. In RAY (MCL3001), all patients had received at least one prior rituximab-containing chemotherapy regimen, whilst in Study PCYC1104, patients had received at least one prior treatment. Exposure or not to bortezomib, prior to ibrutinib, was found not to be prognostic which justified the inclusion of the SPARK (MCL2001) study (whereby all patients had received prior bortezomib) in the meta-analysis (see CS,[1] Appendix 10, page 275). The baseline characteristics for all three studies are presented in Table 9. There were other differences between the studies, for

example, there were more men and a lower percentage of patients with ECOG status 0 in SPARK (MCL2001), and a lower percentage of patients with one prior LOT in SPARK (MCL2001) and PCYC1104 than in RAY (MCL3001), as well as differing lengths of time from end of last prior therapy to randomisation (See Table 9).

4.2 Ibrutinib studies in R/R MCL

No RCTs were identified comparing ibrutinib with any of the comparators listed in the NICE scope.[11] The ERG believes that there were no unidentified RCTs with available clinical effectiveness data relevant to the NICE scope.[11] Effectiveness data were taken from three studies of ibrutinib (RAY [MCL3001], PCYC1104, SPARK [MCL2001]). These comprised two single-arm studies and one RCT comparing ibrutinib versus TEM. One other trial (OPTIMAL[8]) was included in the indirect comparison (see Sections 4.3 and 4.4). Additional data on ibrutinib was provided from a CUP.

4.2.1 Clinical effectiveness studies included in the review

Effectiveness data were taken from three studies of ibrutinib for R/R MCL (see Table 8). All three studies used ibrutinib monotherapy within its licensed indication. The single-arm PCYC1104 was the registration trial. SPARK (MCL2001) was a single-arm study investigating ibrutinib following bortezomib therapy. RAY (MCL3001) was a Phase III RCT superiority trial comparing ibrutinib with TEM. In the EU, TEM is the only licensed treatment for R/R MCL.[35]

In the RAY (MCL3001) trial, the primary analysis was conducted at a median follow-up of 20 months; the study was still ongoing at the time at which the CS was submitted to NICE. For Study PCYC1104, data were collected for the primary analysis at a median follow-up 15.3 months, and a long-term extension median follow-up of 26.7 months. For SPARK (MCL2001), the primary analysis was undertaken at a median follow-up of 14.9 months, and the final data analysis was at a median follow-up of [redacted].[36]

Table 8: Characteristics of ibrutinib studies

Trial	Trial design	Sample size	Dates of enrolment	Population	Intervention	Comparator	Outcomes
RAY (MCL3001)	Phase III open-label RCT Multicentre international	280 Allocated to Ibrutinib n=139; TEM n=141	December 2012 – November 2013 (dates assessed for eligibility)	R/R MCL At least one prior R-chemo	Ibrutinib 560mg orally o.d.	TEM (i.v.) days 1, 8 and 15 of 21-day cycles 175 mg first cycle, 75 mg subsequent cycles	Primary PFS (IRC assessed) Secondary OS One year survival rate PFS2, DOR, ORR – CR and PR (IRC assessed) Time to next treatment, FACT-Lym, EQ-5D-5L, AEs
PCYC1104	Single-arm Phase II open-label Multicentre international	115 enrolled (data from n=110 who received drug)	February 2011 – March 2012 (enrolment)	R/R MCL At least one prior treatment	Ibrutinib 560mg orally o.d.	N/A	Primary ORR (PR or CR) investigator assessed Secondary DOR, time to response, PFS, OS, AEs Other ORR and DOR IRC-assessed
SPARK (MCL2001)	Single-arm Phase II open-label Multicentre international	120 enrolled	July 2012 (study initiated)	R/R MCL At least one prior R-chemo and progressed after bortezomib	Ibrutinib 560mg orally o.d.	N/A	Primary ORR (PR or CR) Secondary Time to initial response, DOR, PFS, OS FACT-Lym, EQ-5D-5L, AEs

Taken from CS Table 12, Dreyling et al,[15] CS Table 29, Wang et al 2013,[32] and Wang et al 2014[34]
RCT – randomised controlled trial; TEM – temsirolimus; R/R MCL – relapsed/refractory mantle cell lymphoma; i.v. – intravenous; N/A – not applicable; PFS – progression-free survival; IRC - independent review committee; PFS2 – progression-free survival after next line of therapy; DOR - duration of response; CR – complete response; PR – partial response; AE – adverse event

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Eligibility criteria for all three studies included men and women aged 18 years and over with a confirmed diagnosis of MCL.

Study PCYC1104 (described in CS[1] Table 30 and EMA[37]) included patients with a confirmed diagnosis of MCL with cyclin D1 overexpression or translocation breakpoints at t(11:14), and measurable disease on cross sectional imaging that is ≥2 cm in the longest diameter and measurable in 2 perpendicular dimensions per computed tomography (CT); and had received at least one prior treatment (but no more than 5) for MCL, and documented failure to achieve at least PR with, or documented disease progression after, the most recent treatment regimen, and ECOG performance status of 0-2; adequate organ function; absolute neutrophil count of at least 0.75 x 109 per litre and platelet count of at least 50 x 10^9 per litre, unless the patient had bone marrow involvement by lymphoma; use of contraception for patients of child-bearing age. Patients may or may not have been treated with bortezomib. Patients were classified as either receiving prior bortezomib treatment (≥2 cycles) or not receiving bortezomib treatment (<2 complete cycles or no treatment). Exclusion criteria included: prior chemotherapy or radiation therapy within 3 weeks, prior anticancer antibodies within 4 weeks, radiotherapy within 3 weeks, radio- or toxin-immunoconjugates within 10 weeks or major surgery within 2 weeks of the first dose of the study drug; known central nervous system lymphoma; history of malignancies within 1 year (except for treated basal cell or squamous skin cancer or *in situ* cervical cancer); clinically significant cardiovascular disease or electrocardiogram (ECG) abnormalities, laboratory abnormalities (absolute neutrophil count (ANC) <750 cells/mm^3 (0.75 x 109/L) unless there is documented bone marrow involvement; platelet count <50,000 cells/mm^3 (50 x 109/L) independent of transfusion support unless there is documented bone marrow involvement; serum aspartate transaminase (AST/SGOT) or alanine transaminase/serum glutamic-pyruvic transaminase (ALT/SGPT) ≥3.0 x upper limit of normal (ULN), creatinine >2.0 x ULN); any condition which would impact on absorption of ibrutinib; infection with human immunodeficiency virus (HIV), hepatitis C or hepatitis B or any uncontrolled active systemic infection; pregnancy or breast-feeding.

SPARK (MCL2001) (CS,[1] Table 34) included patients with MCL who had received at least one prior rituximab-containing chemotherapy regimen for MCL; and who progressed after bortezomib therapy; had received at least two cycles of bortezomib treatment (monotherapy or combination); and had documented progressive disease during or after bortezomib; confirmed diagnosis of MCL and measurable disease; absolute neutrophil count of ≥750/mm^3 and platelet count of ≥50,000/mm^3; no prior ibrutinib or other BTK inhibitor, and; no more than five prior LOTs.

RAY (MCL3001) (CS[1] Table 13 and Dreyling *et al*[15]) included patients who had received at least one prior rituximab-containing chemotherapy regimen and had documented relapse or disease progression

after the last anti-MCL treatment. Confirmed diagnosis of MCL must include morphology and expression of either cyclin D1 in association with one B-cell marker (e.g., CD19, CD20, or PAX5) and CD5 or evidence of t(11;14) as assessed by cytogenetics, fluorescent *in situ* hybridisation, or polymerase chain reaction. Other criteria were: measurable disease by Revised Response Criteria for Malignant Lymphoma;[38] ECOG performance status of 0 or 1; adequate organ function; absolute neutrophil count of at least 1,000/mm^3 independent of growth factor support; platelet count ≥75,000/mm^3 or ≥50,000/mm^3 if marrow involvement independent of transfusion support; haemoglobin ≥ 80 g/l independent of transfusion support; use of contraception for patients of child-bearing age; biochemical values within the following limits: alanine aminotransferase and aspartate aminotransferase ≤3 × ULN, total bilirubin ≤1·5 × ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin); serum creatinine ≤2 × ULN, fasting serum cholesterol level ≤350 mg/dL; fasting serum triglyceride level ≤400 mg/dL. Patients were excluded if they had received prior chemotherapy within 3 weeks, prior anticancer antibodies within 4 weeks, radiotherapy within 3 weeks, radio- or toxin-immunoconjugates within 10 weeks or major surgery within 4 weeks of randomisation; prior treatment with TEM or ibrutinib, or agents from the same class; known central nervous system lymphoma; history of stroke or intracranial haemorrhage within 6 months; requirement for anti-coagulation with warfarin or a strong CYP3A4/5 inhibitor; clinically significant cardiovascular disease; infection with HIV, hepatitis C, hepatitis B or any uncontrolled active systemic infection; pregnancy or breast-feeding.

Baseline characteristics of patients in the three studies are presented in Table 9. Study PCYC1104 enrolled 115 patients, but 4 were not treated due to physician's decision. Characteristics for PCYC1104 are shown for the 111 treated patients. Characteristics for the RAY (MCL3001) and SPARK (MCL2001) studies relate to all enrolled patients.

Table 9: Baseline characteristics of ibrutinib studies

Characteristic	**RAY (MCL3001) Ibrutinib N=139**	**RAY (MCL3001) TEM N=141**	**PCYC1104 N=111 (with data from 115 enrolled)**	**SPARK (MCL2001) N=120**
Median age (range)	67.0 (39-84)	68.0 (34-88)	68 (40-84)	67.5 (35-85)
Age < 65 no. (%)	53 (38.1%)	54 (38.3%)	41 (36.9%)	45 (37.5)
Age ≥ 65	86 (61.9%)	87 (61.7%)	70 (63.1%)	75 (62.5%)
Male sex, no (%)	100 (71.9%)	108 (76.6%)	85 (77%)	104 (86.7%)
Race, no (%)				
White	115 (82.7%)	129 (91.5%)	102 (91.9%)	113 (94.2%)
Asian	16 (11.5%)	5 (3.5%)	1 (0.9%)	0
Other	3 (2.2%)	4 (2.8%)	8 (7.2%)	2 (1.7%)
Unknown/ not reported	5 (3.6%)	3 (2.1%)	0	5 (4.2%)
ECOG PS, no (%)				
0	67 (48.2%)	67 (47.5%)	51 (45.6%)	42 (35.0)
1	71 (51.1%)	72 (51.1%)	48 (43.2%)	67 (55.8)
2	1 (0.7%)	3 (1.4%)	11 (10%)	11 (9.2)
>2	0	0	1 (1%)	0
Median time from initial diagnosis to randomisation (months)	38.90	46.23	42.35 (time to first dose)[37]	43.9 (time to first dose)
Mean time from initial diagnosis to randomisation (months)	49·98 (SD 42·71)[15]	51·17 (SD 33·60)[15]		
Median time from end of last prior therapy to randomisation (months)	8.25	7.03	2.65[37]	[redacted]
Stage of MCL at study entry, no (%)				
I	3 (2.2%)	2 (1.4%)	NR	NR
II	7 (5.0%)	5 (3.5%)	NR	NR
I or II	10 (7.2%)	7 (4.9%)	NR	7 (9.2%)
III	17 (12.2%)	14 (9.9%)	NR	16 (13.3%)
IV	112 (80.6%)	120 (85.1%)	NR	93 (77.5%)
III or IV	129 (92.8%)	134 (95.0%)	80 (72%)	109 (77.3%)
Extent of disease				
Bulky disease: LD ≥ 5cm, n (%)	74 (53.2%)[15]	75 (53.2%)[15]	43 (38.7%)[37]	63 (52.5)
Extranodal disease, no (%)	83 (59.7%)	85 (60.3%)[15]	60 (54.1%)[37]	72 (60.0)
Bone marrow involvement, no (%)	[redacted]	[redacted]	54 (48.6%)	50 (41.7)
Blastoid Histology no (%)	16 (11.51%)	17 (12.06%)[15]	17 (15.32%)	11 (9.17%)
Simplified MIPI, no (%)				
Low risk (1-3)	44 (31.7%)	42 (29.8%)	15 (14%)	28 (23.7)
Intermediate risk (4-5)	65 (46.8%)	69 (48.9%)	42 (38%)	57 (48.3)
High risk (6-11)	30 (21.6%)	30 (21.3%)	54 (49%)	33 (28.0)
Relapsed disease, no (%)	103 (74.1%)	94 (66.7%)	NR	NR
Refractory disease, no	36 (25.9%)	47 (33.3%)	50 (45%)	NR

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Characteristic	RAY (MCL3001) Ibrutinib N=139	RAY (MCL3001) TEM N=141	PCYC1104 N=111 (with data from 115 enrolled)	SPARK (MCL2001) N=120
(%)				
Prior lines of therapy				
Median (range)	2 (1-9)	2 (1-9)	3 (1-5)[37]	2.0 (1.0-8.0)
1, no (%)	57 (41.0%)	[redacted]	22 (19.82%)	20 (16.7)
2, no (%)	38 (27.34%)	[redacted]	28 (25.23%)	43 (35.8)
3, no (%)	28 (20.14%)	[redacted]	24 (21.62%)	29 (24.2%)
4	8 (5.76%)	[redacted]	15 (13.51%)	17 (14.2%)
5	5 (3.6%)	[redacted]	22 (19.82%)	10 (8.3%)
6	0	[redacted]	0	0
7	2 (1.44%)	[redacted]	0	0
8	0	[redacted]	0	1 (0.8%)
9	1 (0.72%)	[redacted]	0	0
3 or more	44 (31.65%)	48 (34.0%)[39]	61 (54.95%)	57 (47.5%)
Prior therapy				
Bortezomib	30 (21.58%)	20 (14.18%)[15]	2 or more cycles 48 (43.24%)	120 (100%)
Stem-cell transplantation	33 (23.74%)	[redacted]	12 (11%)	40 (33.3)
Lenalidomide	8 (5.8%)	[redacted]	27 (24%)	23 (19.17%)
Rituximab or rituximab-containing regimen	[redacted]	[redacted]	99 (89%)	120 (100)

Adapted from CS Tables 17, 31, 35, 39 and Appendix 10, company's clarification response,[21] Dreyling et al,[15] SmPC,[17] SPARK (MCL2001) CSR,[33] Rule et al,[39] and RAY (MCL3001) CSR[26]
ECOG - Eastern Cooperative Oncology Group; MCL – mantel cell lymphoma; MIPI – Mantle Cell Lymphoma International Prognostic Index

The studies were international and so prior treatment pathways may differ from those used in practice in England. There were some UK patients in the studies: in RAY (MCL3001) 27/280 patients were from nine UK centres. Other centres were located within Europe, South America, Canada, Central America and Asia. In PCYC1104, 21/111 patients were from four UK centres, with other centres located within Europe and the US. In SPARK (MCL2001), 6/120 patients were from two UK centres, with other centres located within Europe, Asia and the US.

Population demographics were broadly similar to those likely to be eligible for ibrutinib in clinical practice in England. However, characteristics of the patients in the ibrutinib studies will not be identical to those in UK practice, as stated in the company's clarification response: *"A proportion of patients observed in the HMRN audit would have likely not met the criteria to be enrolled in RAY (MCL3001)"* (Clarification response,[21] question B12). This may mean that patients in real world practice would have lower performance status, more cardiovascular morbidity, requirement of anticoagulation, and/or more significant co-morbidities.

Concomitant therapies were allowed in all three studies (see clarification response,[21] question B3). In the RAY (MCL3001) trial, standard supportive care therapies (e.g. anti-emetics, loperamide) other than anticancer treatment required for the management of symptoms as clinically indicated, were allowed (see CS,[1] page 57). Haematopoietic growth factors were also allowed. Prohibited medications included: any chemotherapy; anticancer immunotherapy; experimental therapy, and; radiotherapy. Systemic use of corticosteroids (i.e. any systemic corticosteroids ≥20mg/day prednisone or its equivalent per day for more than 10 days) was prohibited.

SPARK (MCL2001) allowed standard supportive care therapies required for the management of symptoms, as clinically indicated, other than anticancer treatment and haematopoietic growth factors. Prohibited medications included: any chemotherapy; anticancer immunotherapy; experimental therapy, and; radiotherapy. Systemic use of corticosteroids (i.e. any systemic corticosteroids ≥20mg/day prednisone or its equivalent per day) was prohibited. Patients were excluded if they required concomitant treatment with strong CYP3A4/5 inhibitors or anticoagulation with warfarin or equivalent vitamin K antagonists (see CS,[1] page 94).

In the PCYC1104 study, use of haematopoietic growth factors was permitted after treatment cycle 1 according to the ASCO guidelines,[40] whereas concomitant use of strong CYP3A4/5 or CYP2D6 inhibitors, or strong CYP3A4/5 inducers, was to be avoided, if possible.[37]

At time of primary analysis in the single-arm studies, median time on ibrutinib was 8 months, and for the RAY (MCL3001) trial, median time on ibrutinib was 14.39 months (see Table 10).

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Table 10: Reasons for discontinuation of allocated treatment

	RAY (MCL3001) Ibrutinib N=139	**RAY (MCL3001) TEM N=141**	**PCYC1104 N=111 (at time of primary analysis)**	**SPARK (MCL2001) N=120 (at time of primary analysis)**
Median time on allocated treatment, months	14.39 (range 0.0-28.2)[15]	3.02 (range0.0-27.0)[15]	8.3 (range 0.7, 21.4)[37]	8.0 (range 0.5-20.9) (CS[1] page 95)
Reasons for treatment discontinuation	74 discontinued comprising 55 disease progression 9 AEs 6 deaths 4 refused further treatment	124 discontinued comprising 58 disease progression 36 AEs 16 refused further treatment 6 investigator/ funder decisions 8 deaths	65 discontinued comprising 50 disease progression 7 patient of investigator decision 8 AEs[32]	81 discontinued comprising 53 disease progression 8 AEs (CS[1] page 95) [redacted]

Adapted from CS[1] Sections 4.5.1 and 4.11.2.3, Dreyling et al,[15] Wang et al 2013,[32] CHMP assessment report,[37] SPARK (MCL2001) CSR[33]
TEM – temsirolimus

SUPERSEDED
See erratum

In all three studies, progressed patients could go on to receive subsequent anticancer therapies, including therapies not routinely available in clinical practice in England; these may have affected outcomes collected post-progression.

In the RAY (MCL3001) trial, at time of the primary analysis (20 months median follow-up), there was crossover of 32 (23%) patients in the TEM arm to ibrutinib treatment. Subsequent anti-neoplastic systemic therapy was received by 31.7% (n=44) of patients in the ibrutinib arm, and by 58.2% (n=82) in the TEM arm, including the 32 patients who received ibrutinib (see Table 11).

Table 11: Summary of anti-neoplastic therapy used in at least 2% of patients subsequent to ibrutinib or TEM in PCYC1104, SPARK (MCL2001) and RAY (MCL3001)

Analysis set: intent-to-treat	PCYC1104	SPARK (MCL2001)	RAY (MCL3001)	
	Ibrutinib (n=111)	Ibrutinib (n=120)	Ibrutinib (n=139)	TEM (n=141)
Number of patients receiving subsequent anticancer therapy	[redacted]	[redacted]	44 (32%)	82 (58%)
Most common subsequent anticancer therapies, n	[redacted]	[redacted]	Rituximab: 21 Bendamustine: 15 Cyclophosphamide: 12	Rituximab: 36 Ibrutinib: 32 Bendamustine: 22 Cyclophosphamide: 19
Antineoplastic systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]
Rituximab	[redacted]	[redacted]	[redacted]	[redacted]
Bendamustine	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]	[redacted]	[redacted]
Cytarabine	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]
Prednisolone	[redacted]	[redacted]	[redacted]	[redacted]
Etoposide	[redacted]	[redacted]	[redacted]	[redacted]
Vincristine	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]
TEM	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]
Fludarabine	[redacted]	[redacted]	[redacted]	[redacted]
Mitoxantrone	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]
Investigational drug	[redacted]	[redacted]	[redacted]	[redacted]
Melphalan	[redacted]	[redacted]	[redacted]	[redacted]
Methylprednisolone	[redacted]	[redacted]	[redacted]	[redacted]
Chlorambucil	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]
Ifosfamide	[redacted]	[redacted]	[redacted]	[redacted]
Stem cell transplant	[redacted]	[redacted]	[redacted]	[redacted]
Procarbazine	[redacted]	[redacted]	[redacted]	[redacted]

Adapted from CS[1] Table 20 and clarification response,[21] Table 9

Results from the three ibrutinib studies were pooled, resulting in a combined dataset of 370 patients (RAY [MCL3001] n=139; PCYC1104 n=111; SPARK [MCL2001] n=120). As stated in Section 4.1.5, there are differences in study design and population characteristics between the studies, however, due to the lack of evidence, it was considered acceptable by the ERG and their clinical advisors to combine the available data.

4.2.2 Overall survival

The RAY (MCL3001) study defined OS as the duration from the date of randomisation to the date of the subject's death from any cause. Survival time of living subjects was censored on the last date a subject was known to be alive or lost to follow-up. The estimate of OS included all patients in the ITT population, including patients in the TEM arm who crossed over to ibrutinib as part of the amended protocol. A *post hoc* sensitivity analysis of OS was performed in which data from patients who crossed over from the TEM arm to receive ibrutinib during the study or who had received ibrutinib as subsequent therapy were censored at the date of the first dose of next-line ibrutinib treatment (a "censor at switch" analysis). The result was consistent with that recorded using the ITT analysis set. Median OS was not reached at time at which the CS was submitted (see Table 12).

For Study PCYC1104, at final analysis (26.7 months follow-up), the median OS was 22.5 months (95% confidence interval [CI] 13.7 months, not evaluable [NE]). At the primary analysis, median OS was not evaluable. For the SPARK (MCL2001) study, at a median follow-up of 14.9 month 14.9 months was not reached [redacted]

Table 12: Overall survival

Outcome	**RAY (MCL3001) Ibrutinib N=139 (ITT)**	**RAY (MCL3001) TEM N=141**	**PCYC1104 N=111**	**SPARK (MCL2001) N=120** Primary analysis
OS rate at 12 months, %	68% (95% CI: 59%, 75%)	61% (95% CI: 52%, 69%)	Primary analysis 64.2% (95% CI 54.0, 72.7)	
OS rate at 18 months	[redacted][26]	[redacted][26]	Primary analysis 58.2% (95% CI 47.3, 67.6)	61%
Median (95% CI) OS, months	NE [redacted][26]	21.3 [redacted][26]	Final analysis 22.5 (13.7, NE)	NE [redacted][33]
HR (95% CI) ibrutinib versus TEM	0.76 (95% CI: 0.53; 1.09, *p*=0.1324)		N/A	N/A

Adapted from CS[1] Sections 4.7.2.2 and 4.11, RAY (MCL3001) CSR,[26] and SPARK (MCL2001) CSR[33]
ITT – intention to treat; TEM - temsirolimus OS – overall survival; CI – confidence interval; NE – not evaluable; HR – hazard ratio; N/A – not applicable

The ITT analysis of the RAY (MCL3001) study reported a non-significant effect for OS. The CS suggests that this is due to sample size and the use of subsequent therapy following progression.

The CS suggests that crossover to ibrutinib of 22.3% of patients in the TEM arm may have influenced the OS results. However, according to Dreyling *et al*:[15] *"A post hoc sensitivity analysis of overall survival was done in which data from patients in the temsirolimus group who crossed over to receive ibrutinib during the study or who had received ibrutinib as subsequent therapy were censored at the date of the first dose of next-line ibrutinib treatment. The result was consistent with that recorded using the intention-to-treat analysis set."* The company's clarification response[21] (question B10) states that the TEM OS rate at 12 months in the censor at switch analysis was [redacted]

The TEM arm of the RAY (MCL3001) trial had higher OS than previous studies of TEM, which Dreyling *et al* suggest may be due to improvements in supportive care and the availability of new experimental drugs for salvage therapy.[15]

[redacted]

4.2.3 Progression-free survival

PFS was the primary outcome in the RAY (MCL3001) study. Previous studies have suggested that PFS seems to be an acceptable surrogate endpoint for OS in R/R MCL (estimated at the individual level rather than study level).[41] PFS was defined as the interval between the date of randomisation and the date of disease progression (as assessed by an IRC) or date of death, whichever occurred first, irrespective of the use of subsequent therapy. Progressive disease was determined according to the Revised International Working Group Criteria for NHL.[38] The clinical cut-off for the primary analysis of PFS was defined as the time at which approximately 178 PFS events had been observed. Most patients discontinued treatment because of disease progression or relapse (39.6% ibrutinib versus 41.1% TEM) and AEs (mainly in the TEM arm - 6.5% ibrutinib versus 25.5% TEM). A lower proportion of patients in the ibrutinib arm than the TEM arm (53% versus 79%) had progressed or died at the time of the PFS analysis. The primary analysis of PFS by IRC assessment (ITT analysis) showed a statistically significant advantage for ibrutinib over TEM (HR=0.43, 95% CI 0.32, 0.58; $p<0.0001$), corresponding to a 57% reduction in the risk of disease progression or death with ibrutinib at a median follow-up of 20 months.

Progressive disease in the PYCY1104 study was determined according to the Revised International Working Group Criteria for NHL.[38] At the final analysis of PCYC1104 (26.7 months follow-up),

median PFS was 13.0 months (95% CI 7.0 months, 17.5 months). At the primary analysis, median PFS for the overall population was 13.9 months (95% CI 7.0 months, NE). Median PFS for patients with ≥2 cycles prior bortezomib (n=48) was 16.6 months (95% CI 8.3 months, NE), whilst median PFS for patients with <2 cycles prior bortezomib (n=63) was 7.4 months (95% CI 5.3 months, 19.2 months).

The power calculation for PCYC1104 had expected the bortezomib exposed (≥2 cycles) cohort to have lower response by ORR than the subgroup bortezomib treatment (<2 complete cycles or no treatment). However, the CS uses data from RAY (MCL3001) subgroups to suggest that prior bortezomib was not prognostic (see CS,[1] Appendix 8). It is possible that bortezomib is not the factor explaining the difference in results between the two cohorts of PCYC1104, but instead the difference is due to the prior bortezomib group being more heavily pre-treated, with a median of three, rather than two, prior LOTs. The ERG notes that as the disease progresses it becomes more difficult to treat.

Table 13: Progression-free survival

Outcome	**RAY (MCL3001) Ibrutinib N=139**	**RAY (MCL3001) TEM N=141**	**PCYC1104 N=111 Primary analysis**	**SPARK (MCL2001) N=120 Primary analysis**
PFS rate at 12 months (95% CI)	[redacted][26]	[redacted]	50.6% (40.6, 59.7)[37]	47%
PFS rate at 2 years, %	41%	7%	NR	NR
Median (95% CI) PFS, months	14.6 (10.4; NE)	6.2 (4.2; 7.9)	13.9 (7.0, NE)	10.5 (4.4-15)
HR (95% CI) ibrutinib versus TEM	0.43 (0.32; 0.58), p<0.0001		N/A	N/A
Adjusted* HR (95% CI) ibrutinib versus TEM	0.41 (0.30, 0.57)		N/A	N/A
Subgroup sMIPI low risk HR (95% CI) ibrutinib versus TEM	0.29 (95% CI 0.16, 0.53)		N/A	N/A
Subgroup sMIPI intermediate risk HR (95% CI) ibrutinib versus TEM	0.50 (95% CI 0.32, 0.78)		N/A	N/A
Subgroup sMIPI high risk HR (95% CI) ibrutinib versus TEM	0.44 (95% CI 0.25, 0.78)		N/A	N/A
Subgroup 1 or 2 prior LOTs HR (95% CI) ibrutinib versus TEM	0.39 (95% CI 0.26, 0.59)		N/A	N/A
Subgroup 3 or more prior LOTs HR (95% CI) ibrutinib versus TEM	0.50 (95% CI 0.32, 0.77)		N/A	N/A

Adapted from CS[1] Table 19, SPARK (MCL2001) CSR,[26] EMA CHMP assessment report[37] and Dreyling et al[15]
**adjusted for baseline ECOG performance status, sMIPI, blastoid histology and previous lines of therapy*

TEM – temsirolimus; PFS – progression-free survival; CI – confidence interval; NR – not reported; NE – not evaluable; HR – hazard ratio; N/A – not applicable; sMIPI - Simplified Mantle Cell Lymphoma International Prognostic Index; LOTs – lines of therapy

RAY (MCL3001) also measured PFS2 which was defined as the time interval between the date of randomisation and the date of an event, where events were defined as progressive disease as assessed by the investigator after the next line of therapy, death from any cause, or start of subsequent therapy if no disease progression is noted. Median PFS2 for the ibrutinib group was 19.1 months; this was significantly higher than the 11.3 months observed in the TEM group (HR 0.49, 95% CI 0.36, 0.69; $p<0.0001$).

Subgroup analyses of PFS from RAY (MCL3001) found most subgroups (sex; race; region; age; baseline extranodal disease; baseline ECOG; sMIPI; prior LOTs; stage of disease; tumour bulk; refractory disease) showed a significant advantage for ibrutinib over TEM. The exceptions were patients with blastoid histology (n=33; PFS median 4.1 months) and patients treated with prior bortezomib (n=30; PFS median 7.9 months). The CS suggests that the small sample size means that results for both of these should be interpreted with caution. The CS also points out that the SPARK (MCL2001) study enrolled patients with prior bortezomib and found a median PFS of 10.5 months. [redacted]

Randomisation in RAY (MCL3001) was stratified by number of prior LOTs (1 or 2 versus 3 or more) and Simplified Mantle Cell Lymphoma International Prognostic Index (sMIPI). HRs for PFS for ibrutinib versus TEM according to sMIPI (see Table 13) were: low risk HR=0.29 (95% CI 0.16, 0.53); intermediate risk HR=0.50 (95% CI 0.32, 0.78); high risk HR=0.44 (95% CI 0.25, 0.78). HRs for prior LOTs were: 1 or 2 LOTs HR=0.39 (95% CI 0.26, 0.59); 3 or more LOTs HR=0.50 (95% CI 0.32, 0.77).

A *post hoc* analysis of prior LOTs looked at 1 prior line vs 2 or more prior lines; the ERG notes that this breaks stratified randomisation as stratification was for 1 or 2 versus 3 or more prior LOTs. Section 4.8.2 of the CS presents Kaplan-Meier curves for PFS suggesting an advantage for ibrutinib, although not for TEM, for patients with 1 prior LOT compared with 2 prior LOTs.

The pooled analysis of the ibrutinib arm of RAY (MCL3001) (IRC-assessed PFS), PCYC1104 (investigator-assessed PFS) and SPARK (MCL2001) (IRC-assessed PFS), had a median PFS of 12.81

months (95% CI 8.48 months, 16.56 months). For patients with one prior LOT (n=99), median PFS was [redacted]. For patients with more than one prior LOT (n=271), median PFS was [redacted]

4.2.4 Response outcomes

Response outcomes from the three ibrutinib studies are reported in Table 14. RAY (MCL3001) defined ORR as the proportion of subjects who achieved either CR or PR as their best overall response, as assessed by IRC at or prior to initiation of subsequent antineoplastic therapy. ORR was assessed according to the Revised International Working Group Criteria for NHL:[38] CR - disappearance of all evidence of disease; PR - regression of measurable disease and no new sites; stable disease (SD) - failure to attain CR/PR or PD; relapsed disease or progressive disease (PD) - any new lesion or increase by 50% of previously involved sites from nadir.

Both single-arm studies used ORR defined as either a PR or a CR, according to the Revised International Working Group Criteria for NHL as assessed by the investigator.[38] Additionally, a response evaluation was also carried out by an IRC.

In the final analysis of Study PCYC1104 , the investigator-assessed ORR was 67% (95% CI: 57.1%, 75.3%); CR was 23% (95% CI: 15.1%, 31.4%); PR was 44.1%.[37] For SPARK (MCL2001), the ORR was 62.7% in the response-evaluable population (n=110), and [redacted] in the whole treated population (n=120). The company's clarification response[21] (question B15) states that [redacted]

Table 14: Response rates

Outcome	RAY (MCL3001) Ibrutinib N=139	RAY (MCL3001) TEM N=141	PCYC1104 N=111 Primary analysis	SPARK (MCL2001) N=110 (response evaluable population)
ORR IRC-assessed (CR or PR), n (%)	100 (71.9%)	57 (40.4%)	69%	69 (62.7%, 95% CI: 53.7; 71.8)
Difference in ORR (95% CI), *p*-value	31.5% (20.5, 42.5), *p*<0.0001		N/A	N/A
Odds ratio (95% CI)	3.98 (2.38, 6.65)		N/A	N/A
Best response (assessed by)	IRC	IRC	Investigator assessed	IRC
CR, n (%)	26 (18.7%)	2 (1.4%)	23 (21%)	23 (20.9%, 95% CI: 13.3; 28.5)
PR, n (%)	74 (53.2%)	55 (39.0%)	52 (47%)	46 (41.8%, 95% CI: 32.6; 51.0)
No response, n (%)			35 (32%)	
SD, n (%)	15 (10.8%)	43 (30.5%)	16 (14.4%)[37]	16 (14.5%, 95% CI: 8.0; 21.1)
PD, n (%)	15 (10.8%)	23 (16.3%)	19 (17.1%)[37]	25 (22.7%, 95% CI: 14.9; 30.6)
[redacted]	[redacted]	[redacted]	1 (0.9%)[37]	
[redacted]	[redacted]	[redacted]		

Adapted from CS[1] Tables 22 and 32, company's clarification response[21] and EMA CHMP assessment report[37]
TEM - temsirolimus; ORR - overall response rate; IRC - independent review committee; CR - complete response; PR - partial response; N/A - not applicable; SD - stable disease; PD - progressive disease; NE - not evaluable; NED - no evidence of disease

In RAY (MCL3001), the investigator-assessed ORR (as well as the IRC-assessed ORR) was significantly higher in the ibrutinib arm than the TEM arm (77% versus 46.1%; *p*<0.0001). For the RAY (MCL3001) trial, a *post hoc* analysis by prior LOTs reported that in ibrutinib treated patients there was a similar ORR for 1 prior LOT (71.9%), 2 prior LOTs (68.4%), and 3 or more prior LOTs, but there was a higher CR (and lower PR) for fewer prior LOTs (CR 24.6%, 18.4% and 11.4%, respectively; PR 47.4%, 50.0% and 63.6%, for 1, 2 and 3 prior LOTs respectively). The primary analysis of Study PCYC1104 (median follow-up of 15.3 months) reported an investigator-assessed

ORR of 68% in the total patient cohort (67% in prior bortezomib patients and 68% in bortezomib-naive patients).

[redacted]

DOR results are presented in Table 15. Duration of response (DOR) in RAY (MCL3001) was defined as the duration in days from the date of initial response to the date of first documented evidence of PD (or relapse for subjects who experience CR during the study) or death. Subjects who were progression-free and alive would have been censored at the time of last disease assessment.

Study PCYC1104 measured DOR from the day when criteria for response were met to the first date on which progressive or recurrent disease was documented. At the primary analysis, the median DOR for the subgroup of patients with no prior bortezomib (n=63) was 15.8 months (5.6 months, NE), whereas the median DOR for patients with prior bortezomib (n=48) was not evaluable.

Table 15: Duration of response

Outcome	**RAY (MCL3001) Ibrutinib**	**RAY (MCL3001) TEM**	**PCYC1104 N=111 Primary analysis**	**SPARK (MCL2001) N=120 Primary analysis**
Number of patients with CR or PR	100	57	75	69
Median duration of response, months (95% CI)	Not reached (16.2, not evaluable)	7.0 (4.2, 9.9)	17.5 (15.8, not evaluable) (Final analysis 17.5 (14.9, not evaluable))	14.9 [redacted]
6-month DOR rate (95% CI)	0.83 (0.74, 0.89)	0.60 (0.46, 0.72)	6-month event free rate 0.746 (0.627, 0.832)[37]	NR
12-month DOR rate (95% CI)	0.69 (0.59, 0.77)	0.26 (0.15, 0.38)	12-month event free rate 0.679 (0.554, 0.777)[37]	NR
18-month DOR rate (95% CI)	0.58 (0.46, 0.68)	0.20 (0.09, 0.35)	NR	NR
24-month DOR rate (95% CI)	0.51 (0.35, 0.65)	0.00 (NE, NE)	NR	NR

Time to initial response months median (95% CI)	[redacted]	[redacted]	1.9 (range 1.4, 13.7)[37]	2.1 (1.3-6.3)

Adapted from CS[1] Table 23, SPARK (MCL2001) CSR,[33] RAY (MCL3001) CSR[26]TEM - temsirolimus; CR - complete response; PR - partial response; CI - confidence interval; NE - not evaluable; DOR - duration of response; NR - not reported

In RAY (MCL3001), time-to-next treatment was measured from the date of randomisation to the start date of any anti-lymphoma treatment subsequent to the study treatment. Subjects without subsequent treatment were censored at the date of their last site visit. Median time to next treatment was not reached with ibrutinib, compared with 11.6 months with TEM (p<0.0001). [redacted].

4.2.5 Health related quality of life (HRQoL)

RAY (MCL3001) measured HRQoL using the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) questionnaire. Time to worsening in the FACT-Lym was measured from the date of randomisation to the start date of worsening. Worsening was defined as a 5-point decrease from baseline. FACT-Lym has been validated for use in R/R MCL[42] (see clarification response,[21] question B7). RAY (MCL3001) also measured mean change from baseline in EQ-5D-5L scores for each post-baseline assessment. The SPARK (MCL2001) study also used the FACT-Lym questionnaire (see Table 16).

Table 16: FACT-Lym

Outcome	**RAY (MCL3001) Ibrutinib**	**RAY (MCL3001) TEM**	**SPARK (MCL2001)**
Number of patients completing FACT-Lym at baseline	130	123	
Patients reporting clinically meaningful improvement	61.9% (between groups p<0.0001)	35.5%	[redacted] (CS, page 101)
Median time to improvement	6.3 weeks (between groups p<0.0001)	57.3 weeks	
Patients reporting clinically meaningful worsening	26.6% (between groups p<0.0001)	51.8%	[redacted] (CS, page 101)
Median time to worsening	Not reached (between groups p<0.0001)	9.7 weeks	

Data taken from CS[1] Section 4.7.2.4 and 4.11
TEM - temsirolimus

In the RAY (MCL3001) study, the EQ-5D-5L difference between treatment groups from Week 4 to Week 22 was stable (see Table 17), and the between-group difference remained statistically significant until Week 49, beyond which treatment difference was no longer statistically significant.

SPARK also measured HRQoL using the EQ-5D-5L. The mean visual analogue scale (VAS) score at baseline was

[redacted]

Table 17: EQ-5D-5L - least squares mean (95% CI) change from baseline in EQ-5D-5L utility score over time in RAY (MCL3001) (reproduced from CS Table 24)

	Ibrutinib		**TEM**		**TEM vs ibrutinib**	***p*-value**
Analysis set (ITT)	139		141		-	-
Baseline score, mean (SD)	130	0.73 (0.2)	120	0.73 (0.2)	-	-
	n	**LS mean change from baseline (95% CI)**	**n**	**LS mean change from baseline (95% CI)**		
Week 4	108	0.03 (-0.00, 0.05)	84	-0.07 (-0.10, -0.05)	-0.09 (-0.13, -0.05)	<0.0001
Week 7	101	0.02 (-0.00, 0.05)	71	-0.07 (-0.09, -0.04)	-0.09 (-0.13, -0.05)	<0.0001
Week 10	94	0.02 (-0.00, 0.05)	59	-0.06 (-0.09, -0.03)	-0.09 (-0.12, -0.05)	<0.0001
Week 13	93	0.02 (-0.01, 0.05)	48	-0.06 (-0.09, -0.03)	-0.08 (-0.12, -0.05)	<0.0001
Week 16	88	0.02 (-0.01, 0.05)	41	-0.06 (-0.09, -0.03)	-0.08 (-0.12, -0.04)	<0.0001
Week 19	79	0.02 (-0.01, 0.04)	40	-0.06 (-0.09, -0.03)	-0.08 (-0.11, -0.04)	<0.0001
Week 22	78	0.02 (-0.01, 0.04)	30	-0.06 (-0.09, -0.03)	-0.07 (-0.11, -0.04)	0.0001
Week 31	64	0.01 (-0.01, 0.04)	23	-0.05 (-0.08, -0.02)	-0.06 (-0.10, -0.03)	0.0010
Week 40	53	0.01 (-0.02, 0.04)	21	-0.05 (-0.08, -0.02)	-0.05 (-0.09, -0.01)	0.0073
Week 49	52	0.00 (-0.03, 0.03)	17	-0.04 (-0.08, -0.01)	-0.05 (-0.09, -0.00)	0.0387
Week 58	45	-0.00 (-0.03, 0.03)	13	-0.04 (-0.07, 0.00)	-0.04 (-0.08, 0.01)	0.1327
Week 82	12	-0.01 (-0.05, 0.03)	1	-0.02 (-0.07, 0.03)	-0.01 (-0.07, 0.05)	0.7340
Week 106	3	-0.02 (-0.07, 0.02)	2	-0.01 (-0.07, 0.05)	0.02 (-0.06, 0.09)	0.6857

LS: least squares, CI: confidence interval, TEM: temsirolimus.

4.2.6 Adverse events in ibrutinib-treated patients

The SmPC for ibrutinib presents AEs from clinical studies and post-marketing reports, taken from patients with MCL, CLL or WM (see Table 18).[17] Patients treated for MCL in clinical studies received ibrutinib at a dose of 560mg o.d. whilst patients treated for CLL or WM in clinical studies received ibrutinib at a dose of 420mg o.d. Of the 420 patients treated with ibrutinib for CLL, MCL or

WM, 4% discontinued treatment primarily due to adverse reactions. These included infections and subdural haematoma. Adverse reactions leading to dose reduction occurred in approximately 7% of patients.

Table 18: Ibrutinib adverse reactions (MCL, CLL or WM, reproduced from ibrutinib SmPC)

System organ class	Frequency (All grades)	Adverse reactions
Infections and infestations	Very common	Pneumonia* Upper respiratory tract infection Urinary tract infection Sinusitis* Skin infection*
	Common	Sepsis*
Blood and lymphatic system disorders	Very common	Neutropenia Thrombocytopenia Anaemia
	Common	Febrile neutropenia Leukocytosis Lymphocytosis
	Uncommon	Leukostasis
Metabolism and nutrition disorders	Common	Dehydration Hyperuricaemia
	Uncommon	Tumour lysis syndrome
Nervous system disorders	Very common	Dizziness Headache
Eye disorders	Common	Vision blurred
Cardiac disorders	Common	Atrial fibrillation
Vascular disorders	Very common	Haemorrhage* Epistaxis Bruising* Petechiae
	Common	Subdural haematoma
Gastrointestinal disorders	Very common	Diarrhoea Vomiting Stomatitis* Nausea Constipation
	Common	Dry mouth
Hepatobiliary disorders	Not known	Hepatic failure*†
Skin and subcutaneous tissue disorders	Very common	Rash*
	Uncommon	Angioedema Urticaria
	Not known	Erythema
Musculoskeletal and connective tissue disorders	Very common	Arthralgia Musculoskeletal pain*
General disorders and administration site conditions	Very common	Pyrexia Oedema peripheral

** Includes multiple adverse reaction terms.*
† Spontaneous reports from post-marketing experience

Section 4.13.2 of the CS[1] describes AEs in the RAY (MCL3001) study. Section 4.13.3 of the CS[1] describes AEs in the PCYC1104 and SPARK (MCL2001) studies. RAY (MCL3001) collected data on AEs that occurred between the signing of informed consent through to 30 days following the last dose of the study drug, or until the start of subsequent anti-MCL therapy. Severity of AEs was assessed using the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE)

Version 4.03. AEs led to dose reduction for 3.6% patients in the ibrutinib arm of the RAY (MCL3001) trial. In the RAY (MCL3001) trial, 6.5% of patients treated with ibrutinib discontinued treatment because of AEs. This was similar to the rate of discontinuation due to AEs in the SPARK (MCL2001) study (6.7%). In the PCYC1104 study, 10 patients (9.0%) discontinued ibrutinib treatment due to treatment-emergent AEs at the time of cut off for the primary endpoint.[32] However, 8 patients were classified as discontinuing due to AEs [redacted].[32, 43] In the long-term extension of Study PCYC1104, 11.7% total discontinued due to AEs (see CS,[1] Table 43).

Table 19: Adverse events reported in the ibrutinib studies

Adverse event	**RAY (MCL3001) Ibrutinib N=139***	**PCYC1104 primary analysis n=111 and n=9 from Phase I study of ibrutinib in MCL[37] (total n=120)†**	**SPARK (MCL2001) Ibrutinib N=120‡**
Any AE	138 (99.3%)	119 (99.2%)	[redacted][36]
Grade ≥3	94 (67.6%)	92 (76.7%)	[redacted]
Drug related (any grade)	[redacted]	108 (90.0%)	[redacted]
Any SAE	[redacted]	71 (59.2%)	[redacted]
Grade ≥3	[redacted]	62 (51.7%)	[redacted]
Drug related SAE	[redacted]	29 (24.2%)	[redacted]
AEs leading to treatment discontinuation	9 (6.5%)	14 (11.7%)	20 (6.7%)
AEs with outcome death	[redacted]	Death during or with 30 days of treatment 17 (14.2%)	[redacted]

Adapted from CS Table 44 and ibrutinib CHMP assessment report[37] and SPARK (MCL2001) CSR[33]
** RAY (MCL3001) median treatment duration 14.1 months.*
† PCYC1104 and ibrutinib Phase I study median treatment duration 8.3 months.
‡ SPARK (MCL2001) median treatment duration 8 months.
AE – adverse event; SAE – serious adverse event

In the ibrutinib arm of the RAY (MCL3001) trial, the most common AEs (≥20% of patients) were: diarrhoea (29%); cough (22%), and; fatigue (22%). Grade 3 or higher AEs were reported in 67.6% of ibrutinib patients. The most frequently occurring Grade 3 or higher AE (≥ 10% of patients) in the ibrutinib arm was neutropenia (12.9%). [redacted]

The PCYC1104 study had long-term follow-up (median 26.7 months). The most common AEs (≥20% of patients) were: diarrhoea (54.1%); fatigue (49.5%); nausea (33.3%); dyspnoea (32.4%); [redacted] and;

thrombocytopenia (21.6%). The prevalence of Grade 3 or higher infections was 27%. The incidence of additional malignancies was 4%.[37]

In the SPARK (MCL2001) study, the most common AEs (≥20% of patients) were: fatigue (43.3%); diarrhoea (42.5%); cough (25.0%); thrombocytopenia (24.2%); neutropenia (23.3%); peripheral oedema (23.3%); nausea (21.7%); muscle spasms (20.8%); and pyrexia (20.8%). Infection, diarrhoea and bleeding were reported more commonly in the first 6 months of therapy than later in treatment for the single-arm studies.

Section 4.13.4 of the CS[1] presents Grade 3 or higher AEs from the pooled analysis of the ibrutinib studies (see Table 20), based on updated the datacut of PCYC1104 and SPARK (MCL2001).

Table 20: Grade 3 or higher AEs (reproduced from CS Table 49)

Adverse event	**RAY (MCL3001) Ibrutinib (N=139)**	**SPARK (MCL2001) (N=120)**	**PCYC1104 (N=111)**	**Pooled (N=370)**
Neutropenia	18 (12.9%)	25 (20.8%)	19 (17.1%)	62 (16.8%)
Thrombocytopenia	13 (9.4%)	17 (14.2%)	14 (12.6%)	44 (11.9%)
Anaemia	11 (7.9%)	10 (8.3%)	12 (10.8%)	33 (8.9%)
Pneumonia	11 (7.9%)	11 (9.2%)	8 (7.2%)	30 (8.1%)
Hypokalaemia	8 (5.8%)	5 (4.2%)	2 (1.8%)	15 (4.1%)
Hyperglycaemia	1 (0.7%)	1 (0.8%)	1 (0.9%)	3 (0.8%)
Sepsis	2 (1.4%)	3 (2.5%)	1 (0.9%)	6 (1.6%)
Neutrophil count decreased	7 (5.0%)	2 (1.7%)	0 (0.0%)	9 (2.4%)
Platelet count decreased	2 (1.4%)	0 (0.0%)	0 (0.0%)	2 (0.5%)
Fatigue	6 (4.3%)	4 (3.3%)	5 (4.5%)	15 (4.1%)
Abdominal pain	5 (3.6%)	3 (2.5%)	6 (5.4%)	14 (3.8%)
Atrial fibrillation	5 (3.6%)	7 (5.8%)	7 (6.3%)	19 (5.1%)
Diarrhoea	4 (2.9%)	3 (2.5%)	6 (5.4%)	13 (3.5%)
Hypertension	4 (2.9%)	5 (4.2%)	5 (4.5%)	14 (3.8%)
Major Bleeding	10 (7.2%)	1 (0.8%)	5 (4.5%)	16 (4.3%)
Tumour lysis syndrome	1 (0.7%)	0 (0.0%)	1 (0.9%)	2 (0.5%)
Leukostasis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lymphocytosis	2 (1.4%)	0 (0.0%)	1 (0.9%)	3 (0.8%)
Renal failure	2 (1.4%)	0 (0.0%)	2 (1.8%)	4 (1.1%)
Cytomegalovirus (CMV) reactivation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Abnormal liver function test	0 (0.0%)	1 (0.8%)	1 (0.9%)	2 (0.5%)

The CS also presents AE data from the TEM arm of RAY (MCL3001). This is used to illustrate that there were fewer serious adverse events (SAEs) with ibrutinib compared with TEM (see Table 21). The most common AEs in the TEM arm (≥20% of patients) were reported in the CS as: thrombocytopenia (56%); anaemia (43%); diarrhoea (31%); fatigue (29%); neutropenia (26%); epistaxis (24%); cough (22%); peripheral oedema (22%); nausea (22%); pyrexia (21%), and; stomatitis (21%). However, as noted previously, TEM is not used in clinical practice in the UK. The

CS reports that in the CUP, low rates of treatment discontinuation due to AEs were reported (1.3%) and no new safety signals were identified. The CS also reports that in an Early Access Programme (EAP) in the United States, 4/149 (2.7%) patients discontinued treatment due to AEs. Other results from the EAP (detailed on page 116 of the CS[1]) reported were: Grade 3 and above AEs - 59 patients (39.6%); any SAEs - 46 patients (30.9%); serious non-fatal AEs of atrial fibrillation - 3 patients (2.0%), and; serious non-fatal AE of atrial flutter - 1 patient (0.7%). Two cases of major haemorrhage without precedent trauma or anticoagulation exposure were reported.

Table 21: Summary of AEs in both treatment arms in RAY (MCL3001) (reproduced from CS Table 44)

Adverse event	**Ibrutinib (n=139)**	**TEM (n=139)**
Any AE	138 (99.3%)	138 (99.3%)
Grade ≥3	94 (67.6%)	121 (87.1%)
Drug related	[redacted]	[redacted]
Any SAE	[redacted]	[redacted]
Grade ≥3	[redacted]	[redacted]
Drug related	[redacted]	[redacted]
AEs leading to treatment discontinuation	9 (6.5%)	36 (25.5%)
Dose reduction due to AEs	5 (3.6%)	60 (43.2%)
AEs with outcome death	[redacted]	[redacted]

Data taken from Dreyling et al and RAY (MCL3001) CSR[26]
TEM – temsirolimus; AE – adverse event

4.2.7 Compassionate use programme

Alongside the RAY (MCL3001), SPARK (MCL2001) and PCYC1104 studies, Section 4.11.3 of the CS presents details of a CUP. This CUP, an international, multicentre open-label programme, reported data from 175 patients; 154 patients were from the UK. From the clarification response[21] (question A3), 61.5% had 3 or more prior LOTs. The mean age was 69 years, 77.1% patients were male, and 43.1% were diagnosed within last two years. The primary endpoint was time on treatment. At 12 months, 52.3% (95% CI 43.5%, 60.4%) of the global CUP population were still on treatment. Multivariate analysis found that timing of MCL diagnosis was the only independently significant variable, with time on treatment being longer in patients diagnosed with MCL in the previous two years. Age, refractory disease, advanced disease, relapsed disease, and prior response with previous therapy were not found to be prognostic for a significant difference in time on treatment. 168 patients (23.5%) discontinued treatment during the observation period (12 months) with the most common reasons for treatment discontinuation being death (10.8%), disease progression (7.3%), or AEs (1.3%).

4.3 Trial identified and included in the indirect comparison

No head-to-head trials comparing ibrutinib against comparators listed in the final NICE scope[11] were identified. Section 4.10 of the CS describes attempts to identify evidence comparing ibrutinib to

treatments currently used in practice in the UK. However, no such trials were identified within the CS. Clinical advisors to the ERG were not aware of any such comparative studies. Consequently, the company undertook indirect comparisons to estimate the relative benefit of ibrutinib compared with chemotherapy and rituximab plus chemotherapy. The clinical section of the CS includes an indirect comparison to estimate relative treatment effects for ibrutinib versus chemotherapy. The cost-effectiveness section of the CS includes a further adjustment to account for the additional benefit of rituximab (thus comparing ibrutinib versus R-chemo).

With respect to the first indirect comparison, only one additional study was included: the OPTIMAL trial (Hess *et al*,[8] see Table 22). This study compared TEM with physician's choice of single-agent chemotherapy. The ERG notes that many of the regimens included in the control arm of the OPTIMAL study are not commonly used in clinical practice in England.

Patients were eligible for OPTIMAL if they were aged 18 years or over and had MCL confirmed by histology, immunophenotype, and cyclin D1 analysis, relapsed or refractory after two to seven prior lines of therapy.[8] All reasonable alternatives with combination therapy should have been exhausted and prior treatment must have included an alkylating agent, an anthracycline, and rituximab, and could have included haematopoietic stem cell transplantation.[8] Other eligibility criteria were: life expectancy of three months or more; a Karnofsky performance score of 60 or higher; measurable disease, and; adequate bone marrow and organ functions.[8] Patients were excluded if they had active central nervous system lymphoma, HIV or hepatitis B or C virus infections, and anticancer treatment or major surgery within 3 weeks prior to the study.[8] Baseline characteristics for the RAY (MCL3001) and OPTIMAL trials are shown in Table 23.

Table 22: OPTIMAL study characteristics

Trial	Trial design	Sample size	Dates of enrolment	Population	Intervention	Comparator	Outcomes
OPTIMAL[8] (NCT00117598)	Phase III Multicentre open-label RCT	162 TEM n=108 Treatment of physician's choice n=53	June 2005 – July 2007	R/R MCL 2-7 prior therapies	TEM monotherapy (i.v.) 175mg per week for 3 weeks followed by weekly doses of either 75mg (175/75mg arm, n=54) or 25mg (175/25mg arm, n=54)	Treatment of physician's choice single-agent chemotherapy Gemcitabine i.v. (42%), fludarabine i.v. (23%), fludarabine oral (4%), chlorambucil oral (6%), cladribine i.v. (6%), etoposide i.v. (6%), cyclophosphamide oral (4%), thalidomide oral (4%), vinblastine i.v. (4%), alemtuzumab i.v. (2%), and lenalidomide oral (2%)	Primary PFS IRC-assessed Secondary OS ORR DOR AEs

Data taken from CS[1] Section 4.10.2 and Hess et al 2009[8]

RCT - randomised controlled trial; TEM - temsirolimus; R/R MCL - relapsed/refractory mantle cell lymphoma; i.v. - intravenous; PFS - progression-free survival; IRC - independent review committee; OS - overall survival; ORR - overall response rate; DOR - duration of response; AE - adverse event

The OPTIMAL trial included two TEM treated arms. Only the 175/75mg was used in the company's indirect comparison as this was consistent with the dose used in the RAY (MCL3001) trial. The OPTIMAL trial included centres in Canada, France, Germany, Sweden and the US.

Baseline characteristics in the trial were reported to be *"Median age: 67 years (range 39-88 years), time from diagnosis to randomisation: 48.5 months (range 5-216 months), Stage III-IV disease at baseline: 97%"* (CS,[1] Table 26). The median number of prior therapies was 3 in the TEM arms and 4 in the single-agent chemotherapy arm. The median number of prior rituximab and other anti-CD20 immunotherapy regimens was two in both arms, and prior haematopoietic stem cell transplantation was approximately 32% in each arm.

The TEM 175/75mg arm had 46 patients with confirmed MCL, and 8 unconfirmed MCL patients (sample insufficient or too poor quality for independent assessment). The single-agent chemotherapy arm had 45 patients with confirmed MCL patients, 8 unconfirmed MCL patients, and 1 NHL patient.

Table 23: Characteristics of baseline populations of RAY (MCL3001) and OPTIMAL trials

Characteristic	**RAY (MCL3001) Ibrutinib N=139**	**RAY (MCL3001) TEM N=141**	**OPTIMAL TEM 175/75mg N=54**	**OPTIMAL Single-agent chemo N=53**
Median age (range)	67.0 (39-84)	68.0 (34-88)	68 (43, 85)	64.5 (39, 88)
Male sex, no (%)	100 (71.9%)	108 (76.6%)	46 (85%)	46 (85%)
Bone marrow involvement	[redacted][26]	[redacted][26]	24 (44%)	21 (39%)
Blastoid	16 (11.51%)	17 (12.06%)[15]	0	4 (7%)
Mean time from initial diagnosis to randomisation (months)	49.98 (SD42.71)[15]	51.17 (SD33.60)[15]	Mean 49.6 (range 10, 151)	Mean 48.3 (range 5, 159)
Stage of MCL at study entry, no (%)				
I	3 (2.2%)	2 (1.4%)	0	0
II	7 (5.0%)	5 (3.5%)	0	3 (6%)
III, IV	129 (92.8%)	134 (95.0%)	54 (100%)	51 (94%)
Prior LOTs				
Median (range)	2 (1-9)	2 (1-9)	3 (NR)	4 (NR)
1 prior regimen	57 (41.0%)	[redacted]	0	0
2-3 prior regimens	66 (47.5%)		28 (52%)	21 (39%)
4-7 prior	15 (10.8%)	[redacted]	26 (48%)	33 (61%)

Characteristic	RAY (MCL3001) Ibrutinib N=139	RAY (MCL3001) TEM N=141	OPTIMAL TEM 175/75mg N=54	OPTIMAL Single-agent chemo N=53
regimens				
8 or more prior regimens	1 (0.7%)	[redacted]	0	0
Prior haematopoietic stem cell transplantation	33 (23.74%)	[redacted]	17 (32%)	20 (37%)
Prior bortezomib	30 (21.6%)	20 (14.18%)[15]	10 (19%)	17 (31%)

Data taken from CS[1] Table 39, company's clarification response,[21] Dreyling et al,[15] RAY (MCL3001) CSR,[26] and Hess et al[8]
TEM - temsirolimus; MCL - mantle cell lymphoma; LOT - line of therapy

The baseline characteristics of the TEM 175/75mg and single-agent chemotherapy arms of the OPTIMAL trial were similar, except that no patients in the TEM arm had blastoid histology compared with 7% of the single-agent chemotherapy arm, fewer patients in the TEM arm had received prior bortezomib, and the median number of prior LOTs was lower in the TEM arm (median LOTs=3) compared with the single-agent chemotherapy arm (median LOTs=4). The difference in number of prior LOTs may have biased results in favour of TEM. An analysis excluding patients with blastoid histology did not change results of the statistical analyses.[8]

Outcomes for the OPTIMAL trial are shown in Table 24. There was no significant treatment group difference for OS (p=0.3053 at July 2007 datacut; p=0.3519 at February 2008 datacut), however the study was not adequately powered to detect a difference in this endpoint. There was a non-significant trend for improved PFS for TEM 175/75mg versus single-agent chemotherapy (p=0.0618). Patients in the TEM 175/75mg arm had a significantly better ORR than those in the single-agent chemotherapy arm (p=0.0019).[8]

Table 24: Outcomes of the OPTIMAL trial

Outcome	OPTIMAL TEM 175/75mg N=54	OPTIMAL Single-agent chemo N=53	Between group comparison
OS datacut July 19th 2007 (95% CI) months	11.1 months (8.2, 18.0)	9.5 months (5.3, 15.1)	HR 0.77 (0.46, 1.28)
OS datacut February 1st 2008 (95% CI) months	12.8 months (8.6, 19.3)	9.7 months (7.2, 14.6)	HR 0.80 (0.50, 1.28)
PFS IRC-assessed (97.5% CI) months	4.8 months (3.1, 8.1)	1.9 months (1.6, 2.5)	HR 0.44 (97.5% CI 0.25, 0.78)
ORR IRC-assessed (95% CI) months	22% (11, 33)	2% (0, 5)	OR 15.14 (1.89, 121.19)

Data taken from CS[1] Section 4.10 and Hess et al[8]

TEM - temsirolimus; OS - overall survival; CI - confidence interval; HR - hazard ratio; PFS – progression-free survival; IRC - independent review committee; ORR - overall response rate; OR - odds ratio

Table 25 reports outcomes from RAY (MCL3001) at a median duration of treatment 14.4 months for ibrutinib and 3.0 months for TEM.[15] Median duration of treatment in OPTIMAL was 12 weeks (range 1 to 97 weeks) in the TEM 175/75mg arms and 5 weeks (range 1 to 35 weeks) in the single-agent chemotherapy arm. Outcomes for the TEM arm of RAY (MCL3001) were better than for the TEM 175/75mg arm of OPTIMAL. Tumour response in OPTIMAL was assessed using the Modified Criteria for NHL published in 1999.[44] RAY (MCL3001) used modified criteria published in 2007.[38]

Table 25: Outcomes of RAY (MCL3001) and OPTIMAL trials

Outcome	**RAY (MCL3001) Ibrutinib N=139**	**RAY (MCL3001) TEM N=141**	**OPTIMAL TEM 175/75mg N=54**	**OPTIMAL Single-agent chemo N=53**
Median OS months	Not reached	21.3	12.8	9.7
Median PFS months	14.6	6.3	4.8	1.9
ORR	71.9%	40.4%	22%	2%

Data taken from CS[1] Sections 4.7 and 4.10 and Hess et al[8]
TEM – temsirolimus; TPC – physician's choice of chemotherapy; OS – overall survival; PFS – progression free survival; ORR – overall response rate

There were some differences in the baseline characteristics of patients in the TEM arms of the OPTIMAL and RAY (MCL3001) trials (see Table 23). In the OPTIMAL study, there were no patients in the TEM arm with Stage I and II cancer, whilst in the RAY (MCL3001) study, a small percentage (5.0%) of patients had Stages I and II cancer in the TEM arm. Patients in OPTIMAL were more heavily pre-treated than patients in RAY (MCL3001). Patients in the TEM arm of the OPTIMAL study had more prior LOTs than patients in the TEM arm of the RAY (MCL3001) study (median 3 and 2 respectively).

An analysis of patients with fewer than three prior LOTs (number of patients not reported) in the TEM 175/75mg arm of the OPTIMAL study reported a median PFS of 7.4 months.[8] The outcome for this subgroup was more similar to that of the RAY (MCL3001) TEM treated patients. For patients with three or more prior LOTs in the TEM 175/75mg arm of OPTIMAL, median PFS was 4.5 months.

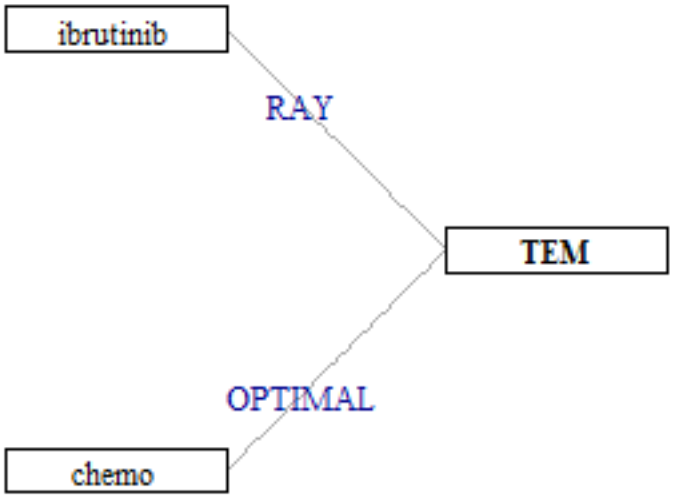
4.4 Summary and critique of the indirect comparison

4.4.1 Summary of analyses undertaken

The indirect comparison reported in the company's clinical section compares the treatment effects of ibrutinib versus single-agent chemotherapy for three outcomes: (i) PFS; (ii) OS and (iii) ORR. The indirect comparisons were undertaken for each outcome separately. The indirect comparison was

conducted using the RAY (MCL3001) and OPTIMAL trials using TEM as a common comparator (see Figure 4). As noted in Section 4.3, the indirect comparison of PFS used in the company's health economic analysis includes an additional adjustment using the HMRN audit[7] to account for the benefits of adding rituximab to chemotherapy; this is not described in the clinical section of the CS.

Figure 4: Diagram of the indirect comparison between ibrutinib (RAY [MCL3001]) and chemotherapy (OPTIMAL) via TEM



TEM - temsirolimus

Methods for the indirect comparison

The company conducted the indirect comparison of ibrutinib versus single-agent chemotherapy using the approach reported by Bucher *et al*.[45] This is a simple indirect comparison method that produces results equivalent to performing a fixed effects NMA.

Results of the company's indirect comparison

Input data used in the company's indirect comparison of ibrutinib versus single-agent chemotherapy are provided in Table 26. A summary of results is provided in Table 27. The company's indirect comparison suggests that ibrutinib is associated with a slower rate of disease progression compared with single-agent chemotherapy (HR=0.19, 95% CI 0.10, 0.36) and a survival benefit (HR=0.61, 95% CI 0.34, 1.10), although the result for OS is inconclusive as it did not reach statistical significance at the 95% level.

Table 26: Data for indirect comparison of ibrutinib versus single-agent chemotherapy (adapted from CS Table 27)

Study	Treatment	Comparator	Outcomes		
			OS	**PFS**	**ORR**
			HR (95% CI)	**HR (95% CI)**	**OR (95% CI)**
RAY (MCL3001)	Ibrutinib	TEM 175/75 mg	0.76 (0.53, 1.09)*	0.43 (0.32, 0.58)	3.98 (2.38, 6.65)
OPTIMAL	TEM 175/75mg	Single-agent chemo	0.80 (0.50, 1.28)†	0.44 (0.25, 0.78)	15.14 (1.89,121.19)‡

** Cox regression model with MIPI and prior lines of therapy from IWRS as stratification factors. ITT population censored at initiation of subsequent ibrutinib therapy*
†Two estimates for median OS are available for the Hess 2009 study. Only the later datacut (February 1st 2008) is presented here.
‡ The OR is calculated with # of patients per arm and % of patients achieved ORR: TEM 175/75 mg 22% ORR; Single-agent chemo: 2% ORR from Table 3 in the Hess 2009 publication.
OS - overall survival; PFS – progression-free survival; ORR - overall response rate; HR - hazard ratio; CI - confidence interval; OR – odds ratio; TEM – temsirolimus

Table 27: Results of indirect comparison of ibrutinib versus single-agent chemotherapy (adapted from CS Table 28)

Outcome	Bucher indirect comparison	
	TE*	**95% CI**
OS (2008 data)	0.61	(0.34, 1.10)
PFS	0.19	(0.10, 0.36)
ORR	60.26	(7.07, 513.4)

TE - treatment effect; CI - confidence interval; OS - overall survival; PFS – progression-free survival; ORR - overall response rate

The treatments within the comparator arm of the OPTIMAL study included only single-agent chemotherapy regimens, whereas rituximab is used in routine clinical practice in England. To account for the differential effectiveness of using rituximab alongside chemotherapy, the company performed an additional adjustment to the HR for PFS reported in Table 27. This adjustment involved multiplying the treatment effect for ibrutinib versus single-agent chemotherapy (HR=0.19, 95% CI 0.10 to 0.36) by an HR for the addition of rituximab to chemotherapy reported in the HMRN audit[7] (HR [adjusted by age and sex] =0.69, 95% CI 0.42 to 1.13). The population in which this HR was estimated relates to MCL patients included in the audit dataset who achieved response to first-line therapy. The adjusted HR for PFS for ibrutinib versus R-chemo was estimated to be 0.28.

Critique of company's indirect comparison

The ERG has concerns regarding: (i) the methods for estimating treatment effects (and uncertainty around these), and; (ii) the evidence used to inform the indirect comparisons.

(i) Concerns regarding indirect comparison methods

The approach adopted by the company to estimate treatment effects for ibrutinib versus R-chemo involves two stages. Given that the relevant comparator is R-chemo, the indirect comparisons against single-agent chemotherapy are not relevant to the decision problem. The ERG considers that it would have been better to adopt a single stage approach from the outset. The ERG asked the company to provide an estimate for the treatment effect of ibrutinib compared to R-chemo in a one-step approach using a random effects NMA, however the company did not undertake this analysis (see clarification response,[21] question C11). Whilst the ERG acknowledges that there may be reservations over combining these studies in an NMA, a random effects NMA would give a better representation of uncertainty than the informal adjustment presented by the company.

In response to a request for clarification from the ERG[21] (question C9), the company provided results from a Bayesian random effects NMA comparing ibrutinib versus single-agent chemotherapy for PFS. Despite conducting the analysis, the company stated that they "*strongly argue against the use of a random effects model for this network as there is not enough information to properly estimate between study variability given that only 2 studies are available to inform comparison*" (clarification response,[21] question C9). When there are too few studies to estimate the between-study standard deviation from the sample data alone and a fixed effect model is used, this can be viewed as asserting that the between-study standard deviation is zero. The ERG considers that it is counterintuitive to imply that because there is limited evidence with which to estimate the between-study standard deviation, it will be assumed to be zero, but if we have more information then we will allow it to be non-zero; less data should lead to an increase in uncertainty rather than a decrease. Therefore, the ERG considers that the results of a random effects NMA provide a more accurate representation of the uncertainty surrounding estimated treatment effects. However, the results provided by the company were based on uninformative priors, despite the ERG's suggestion to use weakly informative priors. Due to the small number of studies in the network, and lack of replication within pairs of treatments, a weakly informative prior for the between-study heterogeneity was required in this analysis (as used in the ERG NMA analyses detailed in Section 4.5). For this reason, the results of the company's random effects NMA are therefore not presented here.

(ii) Concerns regarding evidence used to inform the company's indirect comparison

The ERG notes the following concerns regarding the evidence used to inform the company's indirect comparison.

- Patients in the OPTIMAL study were more heavily pre-treated than patients in the RAY (MCL3001) study. Patients in the TEM arm of the OPTIMAL study had more prior LOTs than patients in the TEM arm of the RAY (MCL3001) study (median 3 and 2 LOTs, respectively).

- The OPTIMAL study involved only single-agent chemotherapy; all options defined in the final NICE scope[11] (except cytarabine) relate to combination chemotherapy regimens.
- The adjusted HR for PFS which is used to reflect the "rituximab effect" was drawn from the HMRN audit.[7] This analysis does not specifically relate to patients with relapsed/refractory disease, does not differentiate between chemotherapy regimens, and has been estimated only in those patients achieving response (n=108). It is also noteworthy that since this is not a trial, differences in outcomes between patients receiving R-chemo and those receiving chemotherapy alone may be subject to confounding. The HR reported in the audit includes adjustments only for age and sex.
- The CS[1] (page 130) states that R-CHOP is perceived to be the most effective chemotherapy option available in the UK. However, the indirect comparison assumes that all R-chemo options are equivalent in terms of efficacy. One clinical advisor to the ERG suggested that R-bendamustine would be the treatment of choice rather than R-CHOP.
- The indirect comparison used in the health economic model is restricted to PFS. The company's clarification response[21] (question C11) states that *"there is no evidence to prove that the use of rituximab has an effect on survival beyond extension of PFS."* However, this is not true. Forstpointner *et al*[14] compared rituximab plus FCM versus FCM alone in the R/R MCL population. This study reported a statistically significant improvement in OS for patients in the rituximab plus FCM group (p=0.0042). The ERG notes that it would have been possible to compare ibrutinib versus R-chemo in terms of OS within an NMA (see Section 4.5). It should be noted however that only 52 patients in this trial had R/R MCL.

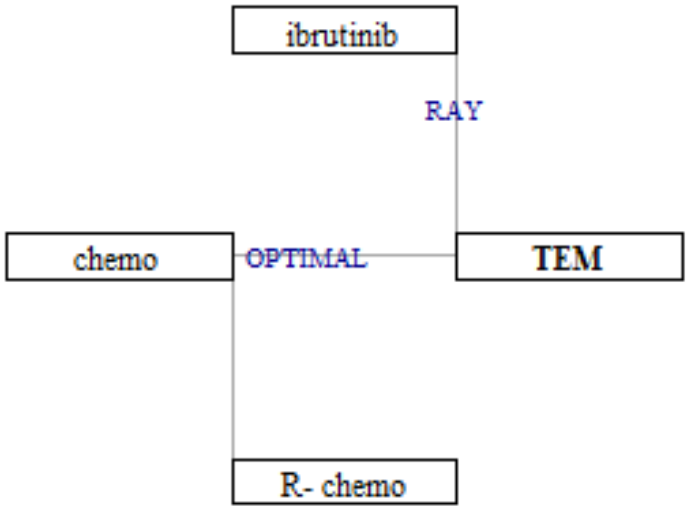
It should be noted that these issues relate to the evidence rather than the analytic method hence these concerns apply equally to the ERG's additional analyses. However, the ERG's analyses better represent the uncertainty surrounding the estimated treatment effect.

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG undertook an NMA comparing ibrutinib to R-chemo for both PFS and OS using random effects models based on the network shown in Figure 5. Since there were too few studies to estimate the between-study standard deviation from the sample data alone, and in the absence of further information on which to base the choice of prior, a weakly informative half-normal prior with variance 0.32^2 was used. The choice of this prior is discussed in more detail in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 3.[46] For all outcomes, a burn-in of 50,000 iterations of the Markov chain was used with a further 20,000 iterations retained to estimate parameters. Results of the Bayesian NMA were summarised using posterior medians, 95% credible intervals (CrIs) and 95% predictive intervals (PrIs). In the presence of heterogeneity it is recommend

that the predictive distribution, rather than the distribution of the mean treatment effect, better represents uncertainty about comparative effectiveness for a future rollout of a particular intervention.[47]

Figure 5: Diagram of the indirect comparison between ibrutinib and R-chemo



TEM - temsirolimus; R-chemo - rituximab and chemotherapy

The additional data used for the extended network is provided in Table 28. For PFS, data from the HMRN audit[7] are used, as described by the company (see CS,[1] page 139). For OS, the ERG presents alternative scenarios, using the HMRN audit,[48] Forstpointner *et al*,[14] or both.

The results of the random effects NMA are presented in Table 29 for the extended network comparing ibrutinib to R-chemo.

Ibrutinib is associated with a slower rate of disease progression, compared to R-chemo (random effects HR=0.27, 95% CrI 0.06, 1.26), although based on the random effects model the result is inconclusive as it did not reach statistical significance at the 95% level. The estimated HRs for OS for ibrutinib versus R-chemo range from 0.98 to 1.96. The results for OS illustrate the high level of uncertainty for this comparison with large differences in the median HR depending on the data source used for the rituximab arm of the network.

Table 28: Additional data for indirect comparison of ibrutinib versus R-chemo

Study	Treatment	Comparator	Outcomes	
			OS	PFS
			HR (95% CI)	HR (95% CI)
HMRN audit[7]	R-chemo	Chemo	0.62 (0.43, 0.89)	0.69 (0.42, 1.13)
Forstpointner *et al*[14]	R-chemo	Chemo	0.31 (0.14, 0.72)	-

OS - overall survival; PFS – progression-free survival; HR - hazard ratio; CI - confidence interval; HMRN - Haematological Malignancy Research Network

Table 29: Results of indirect comparison of ibrutinib versus R-chemo

Outcome		Method					
		Company's approach	FE NMA		RE NMA		
		HR	TE*	95% CrI	TE*	95% CrI	95% PrI
PFS		0.28	0.27	(0.12, 0.62)	0.27	(0.06, 1.23)	(0.05, 1.64)
OS	Forstpointner *et al*[14] only	N/A	1.96	(0.71, 5.40)	1.98	(0.45, 8.74)	(0.35, 11.74)
	HMRN[7] only	N/A	0.98	(0.49, 1.97)	1.00	(0.26, 3.82)	(0.19, 5.34)
	Forstpointner *et al*[14] and HMRN[7]	N/A	1.1	(0.56, 2.17)	1.15	(0.35, 4.53)	(0.26, 6.28)

FE - fixed effects; RE - random effects; NMA - network meta-analysis; TE - treatment effect; CrI - credible interval; PrI - predictive interval; PFS – progression-free survival; OS - overall survival; N/A - not applicable; HMRN - Haematological Malignancy Research Network

The ERG notes that the results of the indirect comparison between ibrutinib and R-chemo for OS are heavily influenced by the large HR associated with adding rituximab to chemotherapy. This is particularly true when this treatment effect is based on the Forstpointner trial. The ERG suggests that the results of the analysis should be interpreted with caution.

4.6 Conclusions of the clinical effectiveness section

The CS did not identify any RCTs meeting the criteria of the final NICE scope.[11] The ERG does not believe that any relevant studies of ibrutinib have been omitted from the company's review of clinical effectiveness evidence. Studies presented were relevant to the population, intervention and outcomes of the decision problem. However, no studies providing comparator data reflecting UK clinical practice were identified.

Three studies of ibrutinib in R/R MCL were included in the CS. These comprised the RAY (MCL3001) RCT and two single-arm studies (PCYC1104 and SPARK [MCL2001]). All three studies administered ibrutinib in line with its marketing authorisation. All three studies enrolled patients with R/R MCL, reflecting the population that would be eligible for ibrutinib treatment. The RAY (MCL3001) RCT compared ibrutinib against TEM; the ERG notes that TEM is not used in clinical practice in England.

Only one RCT of ibrutinib was included in the company's review of clinical effectiveness. Given the scarcity of evidence, it was deemed acceptable to include lower quality study designs, in this case single-arm studies which are subject to selection bias. All trials were adequately powered for the primary endpoint of PFS (RAY [MCL3001]) or ORR (PCYC1104, SPARK [MCL2001]). All studies were open-label, and therefore prone to performance bias and measurement bias. HRQoL measures were prone to bias due to the study design. However, all studies addressed the issue of measurement bias for the primary outcome through the use of IRC assessment for the primary outcome.

At the time of the company's submission, median OS had not been reached in the ibrutinib arm of the RAY (MCL3001) study (n=139) or in the SPARK (MCL2001) study (n=120). In Study PCYC1104 (n=111), median OS was 22.5 months. The OS rate at 18 months for ibrutinib-treated patients was similar across studies (RAY - [redacted]; PCYC1104 - 58.2%; SPARK - 61%). In the RAY (MCL3001) study, TEM-treated patients (n=141) had a median OS of 21.3 months, but this did not differ significantly from the ibrutinib-treated patients (HR=0.76, 95% CI 0.53, 1.09; p=0.1324). The CS highlights that the RAY (MCL3001) study was not adequately powered to detect a treatment difference for OS. A "censor at switch" analysis reported by Dreyling *et al*[15] reported an HR for OS which was consistent with the ITT analysis. However, the use of subsequent anticancer therapies in both treatment arms may have affected OS.

Median PFS of ibrutinib-treated patients was 14.6 months in the RAY (MCL3001) trial, 13.0 months in the final analysis of PCYC1104, and 10.5 months in the SPARK (MCL2001) study. In the RAY (MCL3001) study, median PFS within the TEM arm was 6.2 months, which was significantly worse than the ibrutinib arm (HR=0.43, 95% CI 0.32; 0.58, p<0.0001).

ORR assessed by IRC was similar for ibrutinib-treated patients across studies (71.9% in RAY [MCL3001], 69% in PCYC1104, and 69% in SPARK [MCL2001]). In RAY (MCL3001), there was a significant advantage for ibrutinib over TEM (ORR 40.4%), odds ratio=3.98 (95% CI 2.38, 6.65).

HRQoL was measured by FACT-Lym in the RAY and SPARK studies, a measure validated for use in MCL. The percentage of patients reporting a clinically meaningful improvement was 61.9% in ibrutinib-treated patients in the RAY (MCL3001) study, and [redacted] in the SPARK (MCL2001) study. Within RAY (MCL3001), significantly fewer TEM-treated patients (35.5%, p<0.0001) reported a clinically meaningful improvement. A significant benefit for ibrutinib versus TEM was found in the percentage of patients reporting clinically meaningful worsening (26.6% versus 51.8%, p<0.0001). For SPARK (MCL2001), [redacted] of patients reported clinically meaningful worsening. EQ-5D-5L was also assessed in RAY (MCL3001) and SPARK (MCL2001). In RAY (MCL3001), there was a significant treatment group difference favouring ibrutinib over TEM, starting in Week 4 of treatment

and continuing until Week 49. [redacted]

A pooled analysis of ibrutinib-treated patients for the three included studies was conducted. Pooling RCTs is generally not recommended as this breaks randomisation. However, due to of the paucity of evidence for the use of ibrutinib for the treatment of R/R MCL, it was considered acceptable by the ERG to combine the studies. Within the pooled analysis (n=370), median OS was 25.00 months, median PFS was 12.21 months, and ORR was 66.22%.

In the RAY (MCL3001) trial, 6.5% of patients treated with ibrutinib discontinued treatment because of AEs. This was similar to the rate of discontinuation due to AEs in the SPARK (MCL2001) study (6.7%). In the PCYC1104 study, at median follow-up of 26.7 months, a total of 11% of patients had discontinued due to AEs. Across studies, the most common AEs (≥ 20% of patients) were: diarrhoea; cough; fatigue; thrombocytopenia; neutropenia; peripheral oedema; nausea; muscle spasms, and; pyrexia. Serious AEs were experienced by [redacted] ibrutinib-treated patients in RAY (MCL3001), 55.9% at the time of PCYC1104 primary analysis and [redacted] in SPARK (MCL2001).

The clinical section of the CS includes indirect comparisons of ibrutinib versus single-agent chemotherapy for the outcomes of PFS, OS and ORR, based on the RAY (MCL3001) study which compared ibrutinib versus TEM and the OPTIMAL study which compared TEM versus physician's choice of single-agent chemotherapy. The TEM arm in the RAY (MCL3001) study had better outcomes than the TEM arm in the OPTIMAL study. The TEM arm of the RAY (MCL3001) study had higher OS than earlier studies of TEM, which Dreyling *et al*[15] suggest may be due to advancements in treatment. The TEM arm of RAY (MCL3001) also had higher OS than that reported within the HMRN audit;[7] it is unclear how much of the difference is due to TEM treatment, differences in populations between the studies and routine practice, and the use of other therapies. The results of a Bucher indirect comparison with the OPTIMAL study provided HRs for PFS and OS for ibrutinib versus single-agent chemotherapy of 0.19 (95% CI 0.10, 0.36) and 0.61 (95% CI 0.34, 1.1), respectively.

The approach adopted by the company to estimate treatment effects for ibrutinib versus R-chemo involves two stages. The ERG considers that a single stage approach using a random effects NMA would provide a better representation of the uncertainty in the resulting treatment comparisons. Based on the ERG's additional analyses, ibrutinib is associated with a slower rate of disease progression, compared to R-chemo (random effects HR=0.27, 95% CrI 0.06, 1.26). The estimated HRs for OS for ibrutinib versus R-chemo range from 0.98 to 1.96. This illustrates the high level of uncertainty for this

comparison with large differences in the median HR depending on the data source used for the rituximab arm of the network. Due to concerns regarding the evidence used to inform the indirect comparisons, the ERG considers that the results of the indirect comparison should be interpreted with caution.

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 combined review to identify cost-effectiveness or cost and resource use studies relevant to the decision problem (CS,[1] Section 5.1). The company's review of HRQoL evidence was undertaken separately (CS,[1] Section 5.4.3). The aim of the company's review was to obtain any economic evidence (cost-effectiveness analyses, cost studies and HRQoL data in the form of utilities) available in the published literature. According to the CS, the searches for these two reviews were undertaken before the final scope of the appraisal was determined; consequently, the company's review includes a number of interventions which are not included in the final NICE scope.[11] The company's inclusion and exclusion criteria for both reviews are summarised in Table 30. The searches followed the same format as those described in the clinical effectiveness chapter, and the same selection of databases and congresses was searched, albeit with the addition of EconLit and the NHS Economic Evaluation Database (NHS EED) for the economic review. Study selection was undertaken using the same process as that described for the clinical review (see Section 4.1).

Table 30: Company's inclusion/exclusion criteria for review of economic and HRQoL studies (adapted from CS Table 52)

Inclusion criteria	
Population	R/R MCL patients
Interventions and comparators (applied at full text screening)	• Interventions - ibrutinib monotherapy/combination therapy • Comparators - bendamustine and rituximab (BR); rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP); fludarabine, cyclophosphamide and mitoxantrone (FC ± M); fludarabine + (bendamustine or cisplatin or chlorambucil or rituximab or cyclophosphamide); chlorambucil + rituximab; bortezomib monotherapy ± rituximab; bleomycin monotherapy; vinblastine monotherapy; dacarbazine monotherapy; TEM monotherapy; doxorubicin monotherapy; rituximab monotherapy; rituximab, dexamethasone, cytarabine and cisplatin (R-DHAP) ± low-dose aracytine; lenalidomide monotherapy; rituximab and cytarabine (RC); rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CVP).
Outcomes	• Value or change in value of PRO/HRQoL scores • Economic-related outcomes (QALYs, ICER) o Medical resource use and related costs o Intervention-related costs o Disease progression/end-of-life-related costs o Baseline utility o Utility increment due to response o Post-progression utility decrement o Utility increment due to PFS in subsequent line of treatment o Disutility of AEs o Conclusions • PROs or HRQoL outcomes • PRO or QoL elicitation • Mapping • Valuation • Description of health states and/or AEs • QoL score or change in score with CIs or variance estimates • Patient preference score or change in score with CIs or variance estimates • Uncertainty around values • Consistency with Reference Case • Appropriateness of health states given condition and treatment pathway • Appropriateness of the study for cost-effectiveness analysis • Trend-related to PROs over time • Impact of pharmacological treatments on PROs from real-world studies • Factors associated with impaired PROs
Study design	• Prospective interventional trials • Observational studies • Retrospective analyses, health technology assessments (HTAs), economic or modelling studies
Other	English language
Exclusion criteria	
• Patients without at least 85% R/R MCL, i.e. studies involving treatment-naïve MCL patients, other lymphoma subtypes, or patients receiving first/front-line therapies • Publications that do not report economic outcomes, PROs, or HRQoL outcomes for R/R MCL specifically • Narrative publications, non-systematic reviews, case studies, case reports, and editorials • Non-English, full-text articles or articles without an abstract published in English	

Following de-duplication, the company's searches identified a total of 306 citations. Following a sift at the abstract level, 239 of these potentially relevant studies were excluded from the review. A further 62 studies were excluded following a sift at the full text level. Of the five studies which met inclusion criteria for the company's review, two were full economic evaluations of treatments for MCL,[49, 50] and three studies were cost/resource use studies.[51-53]

Both of the economic evaluations[49, 50] included in the company's review were available only in abstract form. Lachaine *et al*[49] evaluated the cost-effectiveness of R-bendamustine versus fludarabine plus rituximab (FR) for the treatment of relapsed indolent NHL and MCL in Canada. This economic analysis was based on a three state Markov model including states for progression-free, post-progression and dead. Yoong *et al*[50] evaluated the cost-effectiveness of bortezomib versus FCM in patients with relapsed MCL in Canada. No information is provided in the abstract with respect to the methodology used to undertake the economic evaluation by Yoong *et al.*[50]

The CS states that neither study was deemed relevant to the final NICE scope,[11] hence a *de novo* health economic analysis was undertaken to inform the appraisal.

5.1.2 ERG critique of company's systematic review of cost-effectiveness evidence

The company's searches included the application of filters in order to identify evidence of interest (economic evaluations and cost/resource use studies, and utility data respectively), however no sources are acknowledged.

The ERG identified a minor typographical error in Table 128 (DARE/ NHS EED/ HTA search from 2015), line 13 "QUALY" which is presumed to mean "QALY." Since this term has been spelled correctly in all other searches, it is not expected to have resulted in any relevant studies being missed.

Broadly speaking, the ERG is confident that these searches would have found all published evidence indexed in the databases at the time they were conducted, however, during the course of the appraisal, the ERG identified one further study which was not identified by the company's searches.[22] Peng *et al*[22] reports the results of a simulation model comparing health outcomes for ibrutinib, R-bendamustine, fludarabine, mitoxantrone, and cyclophosphamide (FMC), TEM, and other comparators (undefined) for the treatment of R/R MCL. The analysis adopted a partitioned survival modelling approach in order to estimate life years gained (LYGs) and QALYs gained for each option. Clinical inputs for the ibrutinib group were informed by the PCYC-1104 study[43] and included extrapolation of survival outcomes. Clinical inputs for the comparator groups were informed by published sources identified through a systematic review. Health utilities were informed by published studies. Health outcomes were discounted at a rate of 3.5% per annum. The model analysis suggested

that ibrutinib produces an additional 0.86 to 0.92 LYGs and an additional 0.70 to 0.72 QALYs compared with R-bendamustine, FMC and TEM.[22]

The ERG notes that the Peng *et al* study[22] was published only in abstract form, hence insufficient information was available to provide a detailed critique of the methods used in this study. The study is not a full economic evaluation as the resources required to generate the estimated health gains have not been included in the model. Furthermore, the methods used to inform the indirect comparisons between treatments are unclear from the abstract, and the study only uses data for ibrutinib from the PCYC1104 study; outcomes data from the RAY (MCL3001) and SPARK (MCL2001) studies were not included. The ERG does however note that the partitioned survival methodology adopted within this study differs from the Markov approach used in the *de novo* health economic analysis presented in the CS[1] (see Section 5.2).

It is unclear why this study has not been included in the company's review. As a conference abstract from November 2014, it would have been published too late to be retrieved by the initial searches of May 2014, and may not have appeared in the full versions of Medline/EMBASE even by June 2015 when the final set of database searches was conducted. The ERG notes that the company's searches did include PubMed-In-Process, however content is added to this some months behind the "ePub ahead of print" section of Medline (which the ERG recommends as the most up-to-date source for finding recent studies). The company's best chance of finding this study, therefore, would have been through the congress searches, which are reported to have included ISPOR 2013-2015. However, these searches are not reproduced in the CS, hence it was not possible for the ERG to deduce why this study was missed.

The ERG agrees with the CS that the studies reported by Lachaine et al[49] and Yoong et al[50] are not directly relevant to the decision problem set out in the final NICE scope.[11] The ERG also considers that the analysis reported by Peng et al[22] is insufficient to address the decision problem. However, ERG notes that given that Peng et al[22] appears to have been funded by the company, this model could have been further developed for use in this appraisal. The ERG also notes that the partitioned survival approach was also adopted in a previous unpublished economic evaluation undertaken in the Swedish setting[54] referred to elsewhere in the CS.

5.2 Description of the company's model

5.2.1 Health economic evaluation scope

As part of their submission to NICE,[1] 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 ibrutinib versus R-chemo for the

treatment of patients with R/R MCL. 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. 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 relapsed/refractory MCL
Intervention	Ibrutinib 4 x 140mg capsules (560mg) o.d.
Comparator	The base case assumes patients receive R-CHOP according to the regimen: • Rituximab - 375mg/m^2 i.v. on day 1, every 21 days for 6 cycles • Cyclophosphamide - 750mg/m^2 i.v. on day 1, every 21 days for 6 cycles; • Doxorubicin - 50mg/m^2 i.v. on day 1, every 21 days for 6 cycles; • Vincristine - 1.4mg/m^2 i.v. on day 1, every 21 days for 6 cycles; • Prednisolone - 100mg p.o. on days 1-5, every 21 days for 6 cycles Other R-chemo options are considered in the company's scenario analyses
Primary health economic outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Time horizon	Lifetime
Discount rate	3.5% per year
Price year	2014/2015

MCL - mantle cell lymphoma; R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; QALY – quality-adjusted life year; PSS - Personal Social Services

Population

The population considered within the company's model reflects those patients with R/R MCL who were enrolled into the RAY (MCL3001), SPARK (MCL2001) and PCYC1104 ibrutinib studies. Within the modelled ibrutinib group, data for patients receiving ibrutinib in these studies were pooled into a single dataset (see CS,[1] Section 4.12). At model entry, the population is assumed to be 68 years of age and 78.11% of patients are assumed to be male. The mean body mass of the population is assumed to be 77.39kg.

The CS also includes subgroup analyses based on the pooled ibrutinib dataset for patients who have received 1 prior LOT or >1 LOT. Within this subgroup analysis, event probabilities are altered to reflect outcomes observed within the subgroup, however the structure of the model remains unchanged (see Section 5.2.2).

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 560mg daily (four capsules). The SmPC for ibrutinib states that treatment with ibrutinib should continue until disease progression or no

longer tolerated by the patient.[17] The company's model assumes that treatment duration will reflect that observed within the pooled ibrutinib studies (RAY [MCL3001], SPARK [MCL2001] and PCYC1104) and is estimated using a parametric model fitted to the observed Kaplan-Meier data for time to treatment discontinuation or death (TTD/D). The ERG notes that in the deterministic version of the company's base case analysis, treatment discontinuation consistently occurs before progression (with one minor exception during the first cycle). The deterministic version of the company's model therefore reflects the marketing authorisation for ibrutinib. The same is not however true in the probabilistic version of the company's model, whereby the sampled cumulative probabilities for TTD/D are frequently greater those for PFS; this contravenes the marketing authorisation for ibrutinib. This issue is discussed further in Section 5.3.

Comparators

Within the company's base case analysis, the comparator is assumed to be R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone). Within the company's scenario analyses, ibrutinib is compared separately against three R-chemo options: R-CVP (rituximab, cyclophosphamide, vincristine and prednisolone); FCR (fludarabine, cyclophosphamide and rituximab), and; RC (rituximab and cytarabine). Owing to the paucity of evidence concerning the relative efficacy of R-CHOP and other R-chemo regimens, the company's economic analysis assumes that the clinical efficacy of all R-chemo options is the same. The assumed R-chemo treatment regimens are summarised in Table 32.

Table 32: R-chemo comparators evaluated in the company's base case and scenario analyses (adapted from CS Table 55)

R-chemo option	Assumed dosing and frequency
R-CHOP (base case analysis)	• Rituximab - 375mg/m^2 i.v. on day 1, every 21 days for 6 cycles; • Cyclophosphamide - 750mg/m^2 i.v. on day 1, every 21 days for 6 cycles; • Doxorubicin - 50mg/m^2 i.v. on day 1, every 21 days for 6 cycles; • Vincristine - 1.4mg/m^2 i.v. on day 1, every 21 days for 6 cycles; • Prednisolone - 100mg p.o. on days 1-5, every 21 days for 6 cycles. Treatment continued until disease progression or maximum treatment duration
R-CVP (scenario analysis)	• Rituximab - 375mg/m^2 i.v. on day 1, every 21 days for 6 cycles; • Cyclophosphamide - 750mg/m^2 i.v. on day 1, every 21 days for 6 cycles; • Doxorubicin - 50mg/m^2 i.v. on day 1, every 21 days for 6 cycles; • Prednisolone - 100mg p.o. on days 1-5, every 21 days for 6 cycles. Treatment continued until disease progression or maximum treatment duration
FCR (scenario analysis)	• Fludarabine - 30mg/m^2 i.v. on days 1-3, every 28 days for 6 cycles; • Rituximab - 375mg/m^2 i.v. on day 1, every 28 days for 6 cycles; • Cyclophosphamide - 250mg/m^2 i.v. on days 1-3, every 28 days for 6 cycles. Treatment continued until disease progression or maximum treatment duration
RC (scenario analysis)	• Rituximab - 375mg/m^2 i.v. on day 1, every 28 days for 6 cycles; • Cytarabine - 500mg/m^2 i.v. on days 2-4, every 28 days for 6 cycles. Treatment continued until disease progression or maximum treatment duration

R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-CVP - rituximab, cyclophosphamide, vincristine and prednisolone; FCR - fludarabine, cyclophosphamide and rituximab; RC - rituximab, cytarabine

In addition, the CS presents a further scenario analysis based on a blended comparison of ibrutinib versus R-CHOP, R-CVP and FCR. The use of RC is assumed to be zero. Within the blended comparison, the costs associated with each R-chemo regimen are weighted according to their expected usage (R-CHOP – 85%, R-CVP – 10%, FCR – 5%), however the health outcomes for each regimen are assumed to be the same. The ERG's concerns regarding the interpretation of this blended comparison are discussed in Section 5.3.

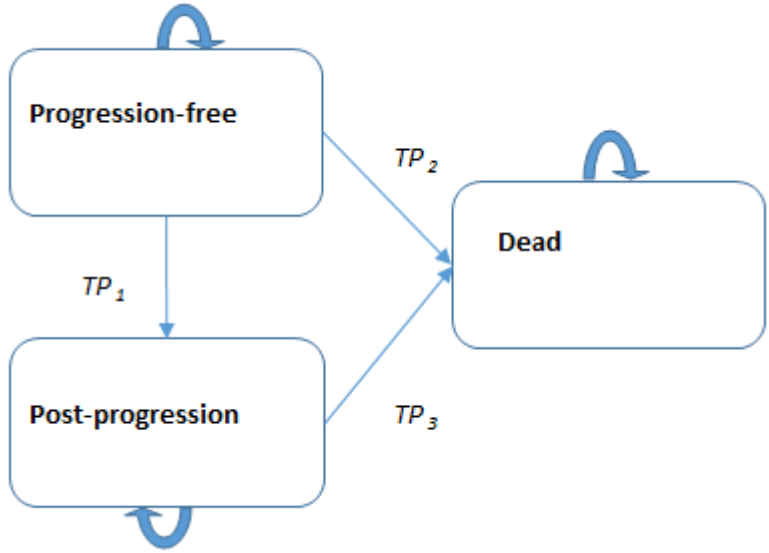
The base case analysis compares ibrutinib versus R-CHOP followed on progression by no further lines of therapy in either group. A secondary analysis is also presented in the CS in which ibrutinib followed on progression by R-CHOP is compared with R-CHOP (referred to in the CS as the "sequential" model).

An alternative scenario analysis is also presented in which both ibrutinib and R-CHOP are assumed to be followed on progression by FCR. In this analysis, only the costs for each group are affected; health outcomes in each group are assumed to be the same as those estimated within the base case analysis.

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 6. The model adopts a simple Markov approach based on three health states: (1) Progression-free; (2) Post-progression, and; (3) Dead. PFS is intended to reflect the interval between commencing ibrutinib/R-chemo and either disease progression or death. With one minor exception in both groups, patients are assumed to discontinue ibrutinib/R-chemo prior to disease progression. Post-progression survival (PPS) is intended to reflect the interval between the point at which the patient's disease has progressed and death. The model adopts a 28-day cycle duration. Costs and health outcomes for competing treatment options are evaluated over a total of 195 cycles (until the patient is approximately 83 years of age); at this point more than 99.9% of patients in both groups have died. A half-cycle correction is applied to account for the timing of events.

Figure 6: Company's model structure (re-drawn by the ERG)



TP – transition probability

Model logic – ibrutinib group

Patients enter the model in the progression-free state and receive treatment with ibrutinib. The probability of being on treatment at any time *t* is modelled based on a parametric (Weibull) survivor function fitted to the empirical time-to-event data for time to treatment discontinuation or death (TTD/D) from the pooled data from the RAY (MCL3001), SPARK (MCL2001) and PCYC1104 studies. The probability of being progression-free (on treatment or discontinued) at any time *t* is modelled using a parametric (Weibull) survivor function fitted to the empirical time-to-event data for PFS. Whilst not directly calculated within the company's model, the probability of being progression-free following discontinuation of ibrutinib at any time *t* is estimated as the difference between the PFS cumulative survival probability and the TTD/D cumulative survival probability at time *t*. The probability that a patient who has not yet progressed dies during the interval *t*-1 and *t* is modelled

using a time-independent probability (exponential distribution), based on data from the pooled ibrutinib studies.

Patients who do not die prior to progression are assumed to transit to the post-progression health state. The probability of transiting from the post-progression state to the dead state is modelled using a time-independent probability, based on an exponential parametric model fitted to the PPS Kaplan-Meier data from the pooled ibrutinib studies. For any time *t*, the probability of remaining in the post-progression state is calculated as the surviving post-progression population at time *t*-1 plus new progressors at time *t* less any patients dying after progression during the interval *t*-1 and *t*.

Model logic – R-chemo group

The model logic for the R-chemo group is generally the same as that for the ibrutinib group, and is based on the same definition of health states (progression-free, post-progression and dead). There are three differences compared with the ibrutinib model. Firstly, the probability of pre-progression mortality is higher for the R-chemo group compared with the ibrutinib group. Secondly, an HR is applied to the ibrutinib PFS curve to estimate the PFS trajectory for the R-chemo group. Thirdly, the HR for PFS for ibrutinib versus R-chemo is also applied to the R-chemo TTD/D curve; it should be noted that all R-chemo regimens included in the company's model are discontinued after a maximum of six cycles (see Table 32). The PPS curve is assumed to be the same for both the ibrutinib and R-chemo groups.

Model logic – modelling health gains, costs and cost-effectiveness

Health utility is differentiated according to the presence/absence of disease progression, with higher baseline values applied to the progression-free state compared with the post-progression state. Within the R-chemo group, a QALY loss of 0.015 (equating to an absolute disutility of 0.20) is applied to all patients during every cycle based on the cumulative survival probabilities calculated from the entire projected TTD/D curve for R-chemo. Separate disutilities associated with AEs are not included in the model.

The company's model includes costs associated with drug acquisition, drug administration (applied to the R-chemo group only), treatment-specific follow-up costs modelled according to the patients' best overall response, treatment-specific costs associated with managing AEs, best supportive care (BSC) costs (applied in the PPS state), and a cost associated with death. The base case version of the company's model assumes that vial sharing is not permitted for R-chemo options. Treatment costs in each group are adjusted according to relative dose intensity (RDI).

The application of different time-to-event curves for PFS and TTD/D and different probabilities of pre-progression mortality for ibrutinib and R-chemo lead to different trajectories of patients through the model's health states, which together with assumptions of health losses for patients receiving R-chemo and different costs between the groups, 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 R-chemo.

Key structural assumptions employed within the company's model

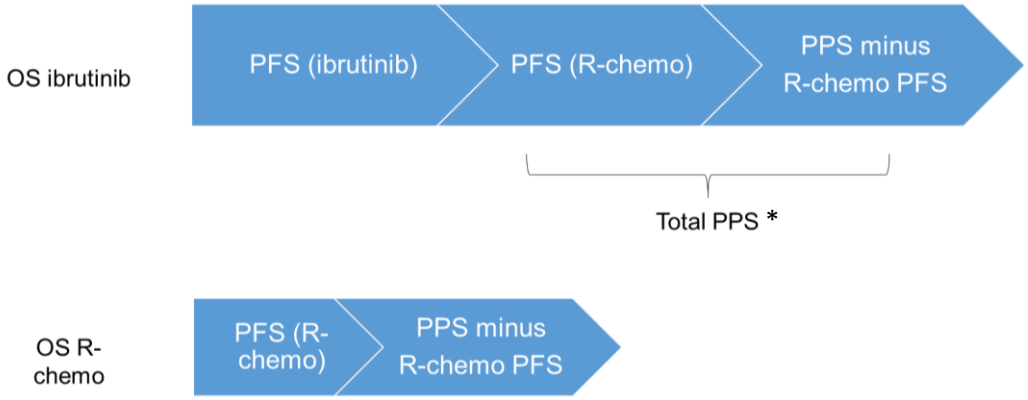
The company's model makes the following structural assumptions:

- All patients enter the model in the progression-free health state
- Health utility is determined by the presence/absence of disease progression and treatment received. A utility decrement is applied according to the HR-adjusted TTD/D curve for the R-chemo group for the entire duration of the curve (that is, during R-chemo treatment and beyond discontinuation). Utilities are age-adjusted.
- In the deterministic version of the model, ibrutinib is assumed to be discontinued upon or prior to disease progression; the same is not true within the probabilistic version of the company's model (see Section 5.3). R-chemo is assumed to be continued for a maximum of six 28-day cycles.
- The hazards of TTD/D and PFS are assumed to follow a Weibull distribution in both groups. The model assumes proportional hazards between the ibrutinib and R-chemo groups for both TTD/D and PFS.
- The probability of pre-progression mortality is assumed to be time-independent; an exponential model is assumed whereby the hazard of pre-progression mortality is constant with respect to time.
- The PPS survivor function is assumed to be identical between the two groups. An exponential model is assumed whereby the hazard of post-progression mortality is constant with respect to time.
- The HR for PFS for R-chemo versus ibrutinib derived from the company's indirect comparison is applied to both PFS and TTD/D.
- Per-cycle follow-up costs are assumed to differ according to the patients' best overall response.
- The costs associated with managing AEs are assumed to be incurred once during the first model cycle only.

Scenario analysis methods – "sequential" model

The sequential model operates differently to the base case model. A schematic of the company's sequential model approach is shown in Figure 7.

Figure 7: Company's sequential model approach – ibrutinib followed on progression by R-chemo versus R-chemo (adapted from CS Figure 34)



** Total PPS in sequential model (PFS2+PPS) equal to PPS in base case model*
OS - overall survival; PFS – progression-free survival; R-chemo - rituximab and chemotherapy; PPS - post-progression survival

The application of the sequential approach within the company's model impacts upon the costs and QALY gains in both the ibrutinib and R-chemo groups. In the ibrutinib group, PFS and PPS for patients receiving ibrutinib are calculated using the same method as that for the base case. However, under the sequential approach, the PPS period is partitioned into two discrete segments: the first segment is intended to reflect an additional period in which patients are alive and progression-free whilst receiving subsequent-line R-chemo (after discontinuing ibrutinib, hereafter denoted "PFS2"), whilst the second segment reflects the interval between the second progression event and post-progression death. PFS2 for subsequent-line R-chemo after ibrutinib is modelled by applying the HR for PFS derived from the indirect comparison of ibrutinib versus R-chemo to an exponential model fitted to the ibrutinib PFS Kaplan-Meier curve from the pooled ibrutinib dataset.[19] The probability of transiting to death from the second progression-free state was estimated to be 1.44% per 4-week cycle (again based on the pooled ibrutinib dataset). In the subsequent-line R-chemo progression-free state, the RDI-adjusted total cost of 6 cycles of R-chemo is applied to all patients entering the state without adjustment for TTD/D. HRQoL for patients in the second progression-free health state is modelled based on the health state utility for the progression-free state together with the QALY loss associated with R-chemo (the ERG notes that this calculation is subject to programming errors, see Section 5.3). Whilst the PFS curves used in the model for the first and second progression periods are different (PFS1 adopts a Weibull model whilst PFS2 adopts an exponential function), they have been derived from the same observed Kaplan-Meier data, hence there is an implicit assumption that the PFS

trajectory for patients receiving R-chemo is the same irrespective of whether patients have previously received ibrutinib or not (i.e. PFS1=PFS2); the ERG notes that this assumption favours ibrutinib.

Within the R-chemo group, the progression-free period is modelled using the same approach applied in the base case. However, following progression, PPS is modelled instead based on the average post-progression mortality rate estimated for the ibrutinib group in the sequential model analysis. This post-progression mortality probability is estimated to be 0.16 per 4-week cycle. This subsequently leads to a worse PPS trajectory for R-chemo compared with the base case.

5.2.3 Evidence used to inform the company's model parameters

Table 33 summaries the evidence sources used to inform the company's model parameters. These are discussed in more detail in the following sections.

Table 33: Summary of evidence sources used to inform the company's model parameters

Parameter/group	Source(s)
Patient characteristics	
Patient start age at model entry	Pooled ibrutinib dataset (RAY [MCL3001], SPARK [MCL2001] and PCYC1104).[19]
Proportion of patients who are male	
Body surface area (BSA)	Pooled ibrutinib dataset (RAY [MCL3001], SPARK [MCL2001] and PCYC1104).[19]
Clinical outcomes	
PFS - ibrutinib	Parametric survivor function fitted to observed Kaplan-Meier curve from pooled ibrutinib dataset.[19]
PFS HR for ibrutinib versus R-chemo (also applied to TTD/D)	Indirect comparison using pooled ibrutinib dataset[19] and OPTIMAL,[8] with further adjustment for the "rituximab effect" using the HMRN audit.[7] HR applied to both PFS and TTD/D.
Pre-progression mortality - ibrutinib	Calculated based on number of events observed and mean PFS follow-up time within pooled ibrutinib dataset.[19]
Pre-progression mortality – R-chemo	Calculated based on number of events observed and mean PFS follow-up time within the TEM arm of the RAY (MCL3001) trial.[15]
Time to treatment discontinuation or death (TTD/D) - ibrutinib	Parametric survivor function fitted to observed Kaplan-Meier curve from pooled ibrutinib dataset.[19]
Post progression survival – both groups	Exponential survivor function fitted to ibrutinib Kaplan-Meier post-progression curves observed within the pooled ibrutinib dataset.[19]
Health-related quality of life	
Heath state utility values	Utilities for progression-free and post-progression states derived from EQ-5D data collected in RAY (MCL3001),[15] SPARK (MCL2001)[33]
Utility age adjustment	Ara and Brazier[55]
Utility decrement for R-chemo	Clinical opinion[1]
Resource use and unit costs	
Cost of ibrutinib	Monthly Index of Monthly Index of Medical Specialities (MIMs, Jan 2016).[56] RDI based on pooled ibrutinib dataset.[19]

Parameter/group	Source(s)
Cost of R-chemo	MIMs (Jan 2016),[56] Commercial Medicines Unit (CMU) Electronic Market Information Tool (eMit, Nov 2015),[57] NHS Reference Costs 2014/15.[58] RDI assumed to be the same as for ibrutinib.
Health state related resource use	Resource use estimated using company's clinical survey.[1] Costs valued using NHS Reference Costs 2014/15.[58]
AE rates	AE rates estimated from pooled ibrutinib dataset,[19] Kluin-Nelemans *et al*,[59] and Flinn *et al*.[60] Valued using NHS Reference Costs 2014/15.[58]
Cost of death	Georghiou and Bardsley[61]

5.2.3.1 Patient characteristics

The model includes three patient characteristics: (i) patient age at model entry; (ii) gender, and (iii) body surface area (BSA). Patients are assumed to enter the model aged 68 years; this is broadly in line with the mean age of patients receiving ibrutinib in the pooled ibrutinib dataset (mean 66.84 years, standard deviation [s.d.] 9.07 years).[19] More than seventy eight percent of patients in the model are assumed to be male; this estimate was again calculated directly using the pooled ibrutinib dataset. BSA was calculated for males and females separately based on the characteristics of all patients in the pooled dataset; this was used to estimate the average number of vials required to complete one administration of the each i.v. drug (see Section 5.2.3.2).

5.2.3.2 Clinical effectiveness parameters

Progression-free survival for patients receiving ibrutinib

Kaplan-Meier curves for PFS for patients receiving ibrutinib were derived from the pooled ibrutinib dataset.[19] Disease progression was determined using the Revised International Working Group Criteria for NHL.[38] PFS was defined as the interval from the date of randomisation to the date of disease progression (as assessed by IRC) or date of death.[1] Exponential, Weibull, log logistic and log normal survivor functions were fitted to the observed Kaplan-Meier curves for PFS. Other potentially plausible survivor functions (generalised gamma, gamma, generalised F and Gompertz models) were not considered. According to the CS, the log cumulative hazard plot for PFS [(log(-log(S(t)) versus log(t)] suggests an approximately straight line hence the use of a standard parametric model was considered to be appropriate (see CS,[1] page 137). Model discrimination was undertaken through examination of the statistical goodness-of-fit of the alternative candidate survivor functions based on the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC), together with consideration of the clinical plausibility of each model. Figure 8 presents a comparison of the fitted parametric models and the observed Kaplan-Meier PFS curves. The AIC and BIC statistics for each candidate survivor function are summarised in Table 34; the lowest AIC and BIC values are highlighted in bold.

Figure 8: Progression-free survival – base case, comparison of company's fitted parametric survivor functions (drawn by the ERG)

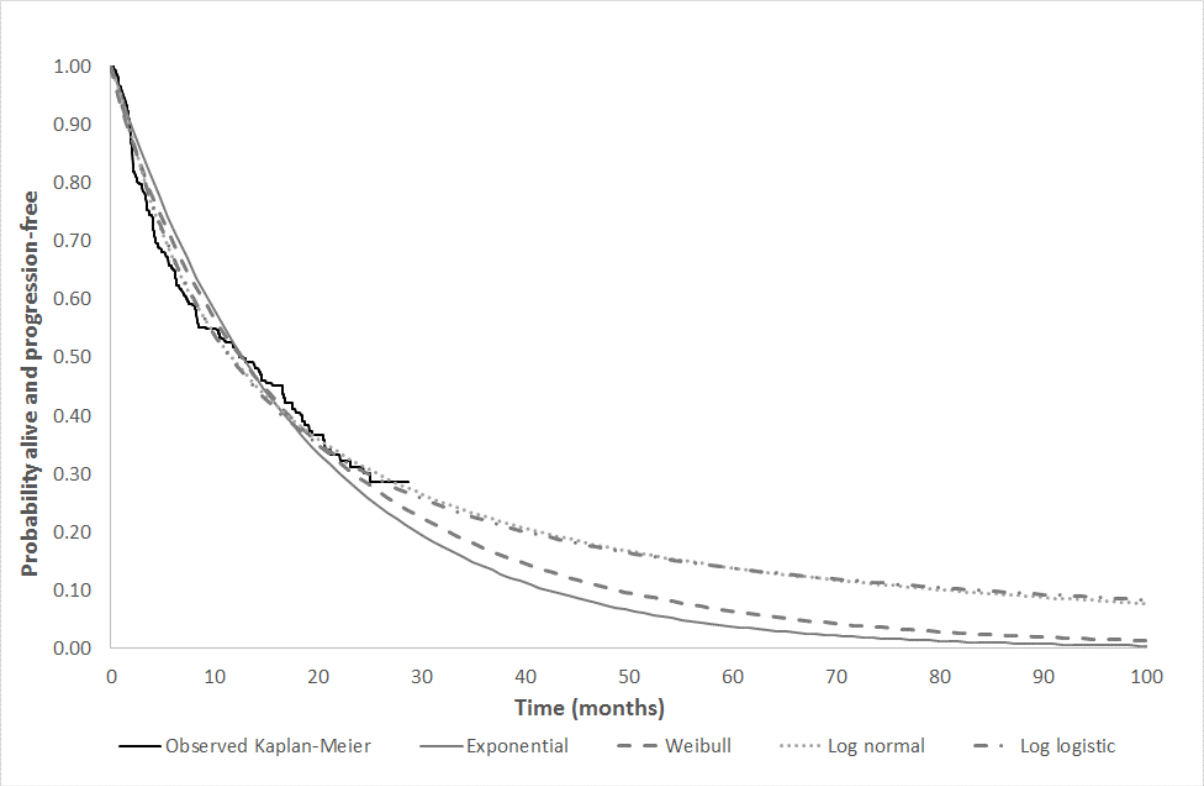


Table 34: Progression-free survival – base case, goodness-of-fit statistics (AIC and BIC)

Parametric function	AIC	BIC
Exponential	1061.22	1065.13
Weibull	1058.36	1066.18
Log logistic	1044.98	1052.81
Log normal	**1033.88**	**1041.71**

AIC – Akaike information criterion, BIC – Bayesian information criterion

The log logistic and log normal curves were not deemed to be plausible as *"both these curves project that a 3-4% of patients remain alive and progression-free for up to 20 years"* (CS,[1] page 137). Scrutiny of the cumulative survival probabilities by the ERG indicates that these are actually slightly lower than reported in the CS (log logistic=3.3%; log normal=2.2%). The CS also states that the log cumulative hazard plot indicates that the event hazard rate is not constant, thereby suggesting that the exponential model is inappropriate. Consequently, the Weibull survivor function was selected for inclusion in the company's base case analysis.

Progression-free survival for individuals receiving R-chemo

PFS for individuals receiving R-chemo was estimated by applying an HR to the parametric PFS curve for ibrutinib (detailed in the previous section). This HR was calculated through the estimation of two separate HRs: the first relates to the relative HR for PFS for ibrutinib versus single-agent

chemotherapy without rituximab; the second HR is intended to reflect the relative HR for PFS associated with R-chemo versus chemotherapy alone (referred to in the CS[1] as the "rituximab effect").

The HR for ibrutinib versus single-agent chemotherapy was estimated by performing an indirect comparison of data from the RAY (MCL3001) study[15] and the OPTIMAL study[8] using the methods reported by Bucher *et al*[45] (previously discussed in Section 4.4). Within the RAY (MCL3001) trial, ibrutinib was compared against TEM. The OPTIMAL trial[8] compared TEM versus investigator's choice of single-agent chemotherapy. The agents considered in the comparator arm of the OPTIMAL trial are detailed in Table 35. Within both studies, HRs were estimated for PFS in the ITT population.

Table 35: Treatments used in the comparator arm in the OPTIMAL trial

Therapy	**Regimen**	**Number patients (%)**
Gemcitabine i.v.	1g/m^2 as 30 minute infusion on days 1,8 and 15 every 28 days Or 1g/m^2 as 30 minute infusion on days 1 and 8 every 21 days	22 (42%)
Fludarabine i.v.	25mg/m^2 as a minute infusions daily for 5 consecutive days every 28 days	12 (23%)
Fludarabine oral	40mg/m^2 daily for 5 consecutive days every 28 days	2 (4%)
Chlorambucil oral	0.1 to 0.2mg/kg daily for 3 to 6 weeks	3 (6%)
Cladribine i.v.	5 mg/m^2 daily for 5 consecutive days every 28 days (1 cycle) for 2 to 6 cycles	3 (6%)
Etoposide i.v.	50 to 150mg/m^2 for 3 to 5 days every 21 to 28 days	3 (6%)
Cyclophosphamide oral	200 to 450mg/m^2 daily for 5 consecutive days every 21 to 28 days	2 (4%)
Thalidomide oral	200mg daily	2 (4%)
Vinblastine i.v.	10mg weekly	2 (4%)
Alemtuzumab i.v.	30mg/d for 3 times a week on alternate days for 12 weeks	1 (2%)
Lenalidomide oral	25mg daily for 28 days	1 (2%)

i.v. - intravenous

The HR for R-chemo versus chemotherapy was derived from the HMRN audit[7] (HR=0.69, adjusted by age and sex). The population in which this HR was estimated relates to MCL patients included in the dataset who achieved response to first-line therapy.

The two HRs obtained from the indirect comparisons are summarised in Table 36. The HR for ibrutinib versus R-chemo was estimated using the following formula:

HR R-chemo compared to ibrutinib = [1/HR for PFS for ibrutinib versus single-agent chemotherapy] x HR for the addition of rituximab to chemotherapy [i]

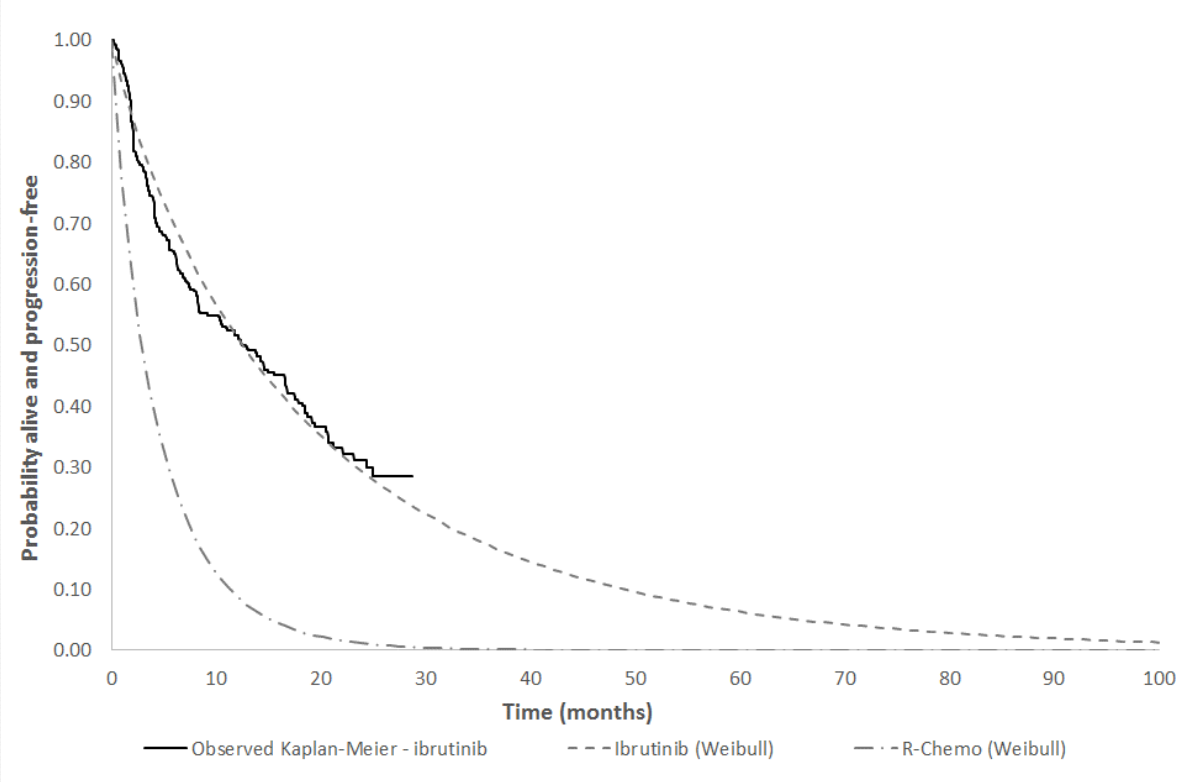
Table 36: Hazard ratio for progression-free survival estimate for ibrutinib versus R-chemo

Parameter	Value	Source
HR for PFS for ibrutinib compared with single-agent chemotherapy	0.19	Indirect comparison of the pooled ibrutinib dataset[19] and OPTIMAL study[8]
HR for the addition of rituximab to chemotherapy	0.69	HMRN audit[7]
HR for PFS of R-chemo versus ibrutinib	3.63	Calculation given in equation [i]

HR - hazard ratio; PFS – progression-free survival; HMRN - Haematological Malignancy Research Network

The survivor function for R-chemo was calculated by applying the estimated PFS HR for R-chemo versus ibrutinib to the baseline Weibull PFS curve for ibrutinib (see Figure 9). It should be noted that this approach assumes proportional hazards.

Figure 9: Progression-free survival – base case, modelled Weibull curves for ibrutinib and R-chemo (drawn by the ERG)



Time to treatment discontinuation or death in patients receiving ibrutinib

TTD/D was used to estimate the mean time on treatment in the ibrutinib group. It should also be noted that this curve indirectly informs mean time on treatment as well as the duration of time that the treatment-related disutility is applied in the R-chemo group. Parametric survivor functions (exponential, Weibull, log logistic and log normal models) were fitted to the observed Kaplan-Meier curves for TTD/D within the pooled ibrutinib dataset.[19] According to the CS, the log cumulative hazard plot for TTD/D [(log(-log(S(t)) versus log(t)] suggests an approximately straight line hence the

use of a standard parametric model was considered to be appropriate (see CS,[1] page 155). As with PFS, model discrimination was undertaken through examination of visual fit and statistical goodness-of-fit (AIC and BIC) of the alternative candidate survivor functions. It is unclear from the CS whether the plausibility of the extrapolation was considered. Figure 10 presents a comparison of the fitted parametric models and the observed Kaplan-Meier TTD/D curves. The AIC and BIC statistics for each candidate survivor function are summarised in Table 37; the lowest AIC and BIC values are highlighted in bold.

Figure 10: Time to treatment discontinuation or death – base case, comparison of company's fitted parametric survivor functions (drawn by the ERG)

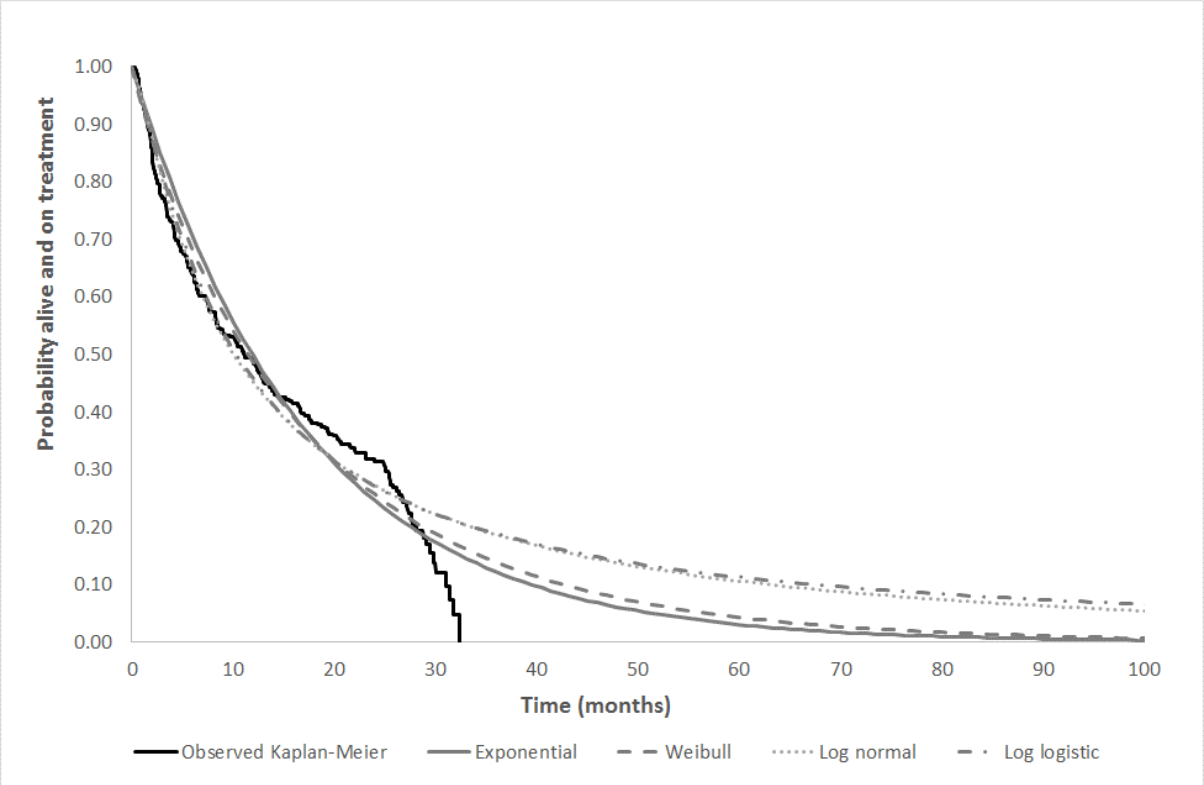


Table 37: Time to treatment discontinuation or death – base case, goodness-of-fit statistics (AIC and BIC)

Parametric function	AIC	BIC
Exponential	1166.46	1170.40
Weibull	1165.33	1173.16
Log logistic	1167.09	1174.92
Log normal	**1156.51**	**1164.34**

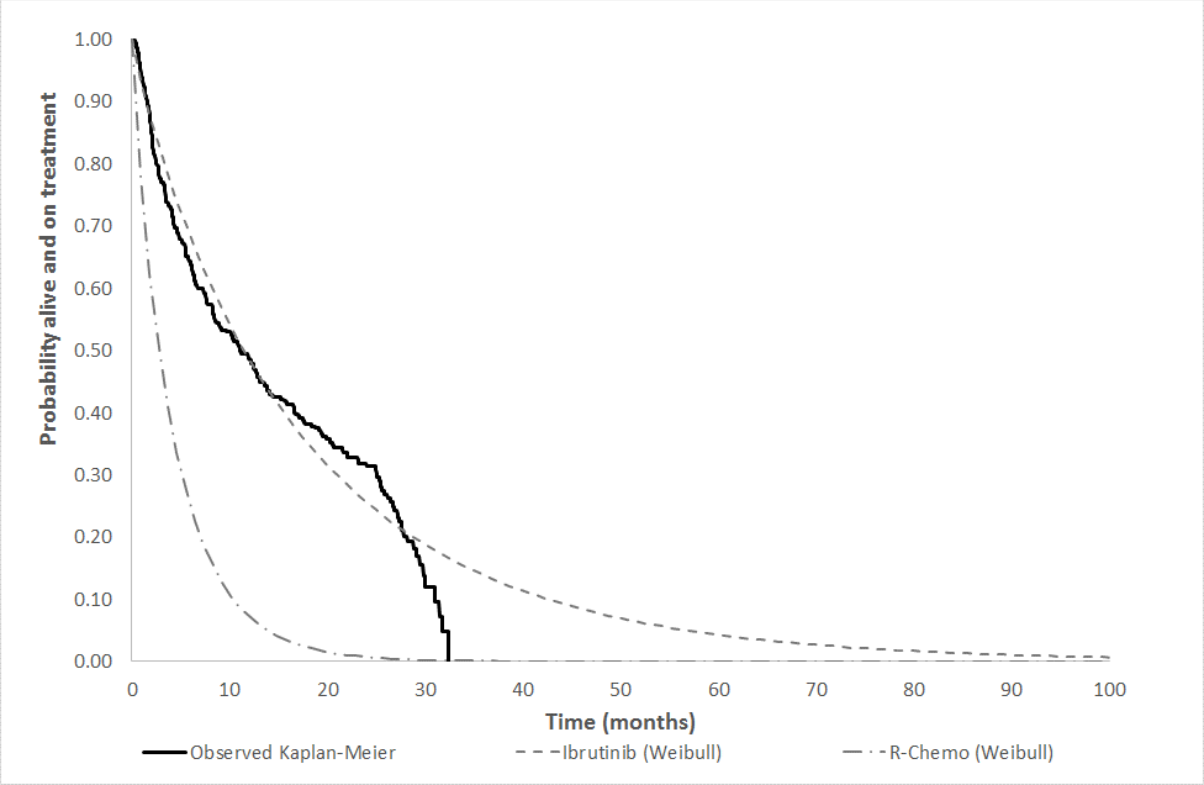
AIC - Akaike information criterion; BIC - Bayesian information criterion

According to the CS,[1] (page 155), all four curves provide a good fit to the data available; the opinion of the ERG differs on this matter (see Section 5.3). The CS states that TTD/D is heavily dependent upon the progression status of the patient and that the Weibull model was selected for use in the company's base case model in order to retain consistency with the approach used to model PFS.

Time to treatment discontinuation or death for patients receiving R-chemo

TTD/D for patients receiving R-chemo was estimated by applying the HR for PFS for ibrutinib versus R-chemo to the TTD/D curve for the ibrutinib group (detailed in the previous section). The probability that a patient in the R-chemo group is receiving treatment is assumed to be zero after 6 cycles (to reflect the regimens detailed in Table 32). The disutility associated with the toxicity of R-chemo is assumed to apply for the entire duration of the R-chemo TTD/D curve (prior to and post-discontinuation). The modelled TTD/D curve for the R-chemo group is shown in Figure 11.

Figure 11: Time to treatment discontinuation or death – base case, modelled Weibull curves for ibrutinib and R-chemo (drawn by the ERG)



Pre-progression mortality

A time-invariant risk of death in the progression-free state was applied to both groups in the model. In the base case, the probability of pre-progression mortality was estimated using data from the pooled ibrutinib dataset[19] for the ibrutinib group and from the TEM arm of the RAY (MCL3001) trial[15] for the R-chemo group. The CS[1] (page 141) notes that whilst TEM is not used in current practice, it was assumed that the risk of death for R-chemo would be similar due to the similar HRs predicted for PFS. In both treatment groups, the probability of pre-progression mortality during each cycle was calculated as:

Probability of pre-progression death per cycle = (*Number pre-progression deaths /Number patients / Mean PFS follow-up time [in weeks]*) *x 4* [ii]

Deaths were assumed to occur uniformly over the mean PFS follow-up time. Based on this calculation, the company estimated the probabilities of pre-progression mortality per 4-week cycle to be 0.71% and 1.44% in the ibrutinib and TEM groups, respectively (see Table 38).

Table 38: Probability of pre-progression mortality for ibrutinib and TEM

	Number deaths prior to disease progression	N	Mean PFS follow-up time (weeks)	Probability of death per 4 week period	Source
Ibrutinib	38	370	58.2	0.71%	Pooled dataset[19]
TEM	19	141	37.5	1.44%	RAY (MCL3001)[15]

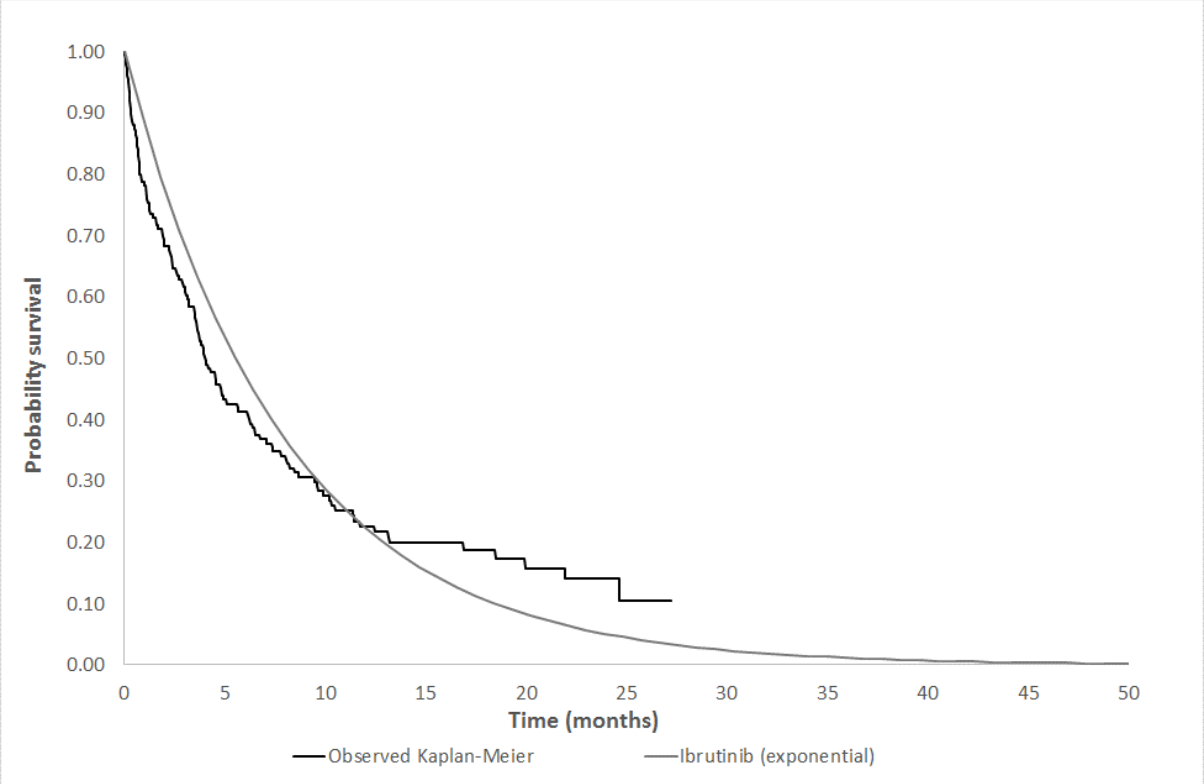
PFS – progression-free survival; TEM - temsirolimus

The observed Kaplan-Meier survivor functions for pre-progression mortality (censoring for disease progression) are not presented within the CS.

Post-progression survival

In the base case, the company applied a fixed PPS approach. This assumes that following disease progression, the probability of death for all surviving progressed patients is the same for both the ibrutinib and R-chemo groups. The 4-week probability of PPS was estimated using the ibrutinib pooled dataset.[19] An exponential curve was fitted to the available PPS data; other parametric functions were not reported in the CS. The CS[1] (page 142) states that the exponential model was selected in order to avoid the need to include tunnel states to account for time-variant transition probabilities. A constant probability of death of 10.83% is applied to patients in the post-progression state during every cycle (see Figure 12).

Figure 12: Post-progression survival – base case, modelled exponential curve for ibrutinib (drawn by the ERG)



Health-related quality of life

Health state utilities (progression-free / post-progression)

As discussed in Section 4.2, HRQoL was measured in the RAY (MCL3001)[15] and SPARK (MCL2001)[33] studies using the EQ-5D-5L; Study PCYC1104 did not include the use of the EQ-5D. The company conducted a mixed model analysis of mean HRQoL in a pooled dataset of patients in the ibrutinib arms of the RAY (MCL3001) and SPARK (MCL2001) studies to estimate utility values for the progression-free and post-progression health states. The utility values applied in the company's model are summarised in Table 39.

Table 39: Progression-free and post-progression utility values used in the company's model

Model health state	Mean utility	s.e.	N
Progression-free	0.78	0.01	234
Post-progression	0.68	0.02	36

With the exception of a disutility associated with toxicity and fatigue for patients receiving R-chemo, the model does not include additional disutilities associated with AEs.

Age adjustment of utility values

The health utilities used in the model were adjusted to account for the increasing age of the modelled cohort over time. This was done using the following regression equation, as reported by Ara and Brazier:[55]

General population EQ-5D = 0.9508 + 0.0212126(1=male, 0=female) - 0.00025877*age – 0.0000332*age^2* [iii]

General population health utility was estimated every year for a hypothetical cohort of people aged 68 to 100 assuming that a constant proportion (78%) of the population are male (based on the proportion of patients in the pooled dataset who were male). Age-specific utilities for each population age were then converted into a fraction of a 68 year old's utility, thereby giving a multiplier for each individual population age relative to that of the 68 year old cohort. Health utilities were then weighted by this multiplier as the age of the modelled cohort increases.

QALY decrement for individuals receiving R-chemo

The company's model includes a QALY loss for all patients receiving R-chemo over the entire duration of the TTD/D curve (generated using the ibrutinib TTD/D curve and the HR for PFS derived from the indirect comparison). This QALY loss was included *"to reflect the toxic effect of receiving chemotherapy and the impact on patients' QoL and functioning"* (CS,[1] page 149). Based on clinical opinion, the company's model assumes a utility decrement of -0.20 (corresponding to a 4-week QALY loss of 0.015). This QALY loss is applied beyond the period during which patients are receiving R-chemo. With respect to this assumption, the CS[1] states *"the impact of treatment with R-chemo often persists even after treatment is stopped"* (CS,[1] page 149). It should be noted that the level of HRQoL assumed for patients who are receiving R-chemo prior to progression is estimated to be lower than that for patients who have experienced disease progression and have discontinued active treatment (R-chemo pre-progression utility=0.48; post-progression utility=0.68).

Resource use

The company's model includes the following resource costs: drug acquisition costs; drug administration costs (R-chemo group only); follow-up costs; costs associated with managing AEs; BSC costs, and; a cost associated with death.

Drug acquisition and administration costs

The drug acquisition costs used in the company's model are summarised in Table 40. The acquisition cost for ibrutinib was taken from MIMS[56] (£51.10 per capsule); the base case analysis includes a simple PAS which involves a [redacted] reduction in the price of the drug (thus equating to [redacted] per

capsule). Acquisition costs associated with the R-chemo regimens were obtained from MIMS and eMit.[57] As the price for prednisone was not available via eMit, this was assumed to have the same unit cost as prednisolone. As the R-chemo regimens are delivered in an inpatient setting, an administration cost of £329.32 was assumed based on NHS Reference Costs 2014/15 (day case visit, code SB13Z - deliver more complex parenteral chemotherapy at first attendance).[58]

Table 40: Drug acquisition and administration costs used in the company's model (adapted from CS Table 66)

Treatment	Unit size	Tablet/vial size	Unit cost	Source
Ibrutinib (list price)	140mg	1	£51.10	CS[1]
Cyclophosphamide	500mg	1	£9.00	CMU[57]
Doxorubicin	2mg/ml	25ml	£4.16	CMU[57]
Fludarabine	50mg/ml	1ml	£149.92	MIMS[56]
Prednisone*	5mg	1ml	£0.02	CMU[57]
Rituximab	10mg/ml	50ml	£873.13	MIMS[56]
Vincristine	1mg/ml	1.0ml	£13.47	MIMS[56]
Cytarabine	20mg/ml	5.0ml	£4.33	MIMS[56]

CMU - Commercial Medicines Unit; MIMS - Monthly Index of Medical Specialties

For the R-chemo options, the average number of vials required to complete one administration of each i.v. drug was calculated using methods reported by Hatswell *et al.*[62] The mean number of vials per dose was estimated separately for males and females, and the weighted average was calculated using the ratio of males to females in the model. This was combined with unit cost estimates to calculate the total cost of drugs used in each model cycle.

Drug acquisition and administration costs in both groups are adjusted according to RDI. In the ibrutinib group, the RDI was estimated to be 94.21%, based on an analysis of the pooled dataset.[19] Owing to the absence of equivalent information on RDI for R-chemo regimens, the company's model assumes that the RDI for R-chemo is the same as that for ibrutinib.

Health state related resource use

Health state related resource use was based on a survey undertaken by the company[1] conducted in 2014. The survey involved the elicitation of information on the types and frequencies of medical resource use for an average individual with R/R MCL prior to and following disease progression. One hundred actively practicing NHS haematologists and oncologists were invited to participate. Of these, 52 individuals provided a complete or partial response to the survey. The survey recorded estimated resource use for four groups of patients according to their treatment response: (i) CR; (ii) PR; (iii) stable disease, and; (iv) post-progression. In order to obtain estimates of mean resource use for the progression-free health state, the response rates for ibrutinib and R-chemo were weighted according to the distribution of best overall response. Within the ibrutinib group, this distribution was derived from

the pooled ibrutinib dataset[19] (CR [redacted]; PR [redacted], and; stable disease [redacted]). The response rate for R-chemo was obtained from the HMRN audit. Two steps were applied to obtain the response rate for R-chemo. Firstly the response rate to first-line R-CHOP was taken from the HMRN audit (response rate = 75.86%). Secondly the relative risk of response at second-line therapy (response rate = 32.97%) given the response rate at first-line chemotherapy (response rate = 41.87%) was used to calculate the relative risk of response of second-line chemotherapy compared to first-line chemotherapy (relative risk = 0.79). Based on these data, overall response to second-line R-CHOP treatment was calculated to be 59.73%;[7] the remainder (40.27% patients) were assumed to have stable disease. The proportionate split of the 58.13% R-chemo patients between CR and PR was based on the relative proportions of patients achieving CR and PR in the pooled ibrutinib dataset.[19] This resulted in an estimated [redacted] patients with CR and [redacted] with PR. Unit costs for each resource item were valued using NHS Reference Costs 2014/15.[58] Annual resource use for each response outcome, unit costs associated with each resource component and the total per cycle costs by response outcome are presented in Table 41.

Table 41: Total annual resource and health state costs used in the company's model

Annual resource use					
Resource use component	**Progression-free (ibrutinib)**	**Progression-free (R-chemo)**	**Post-progression**	**Cost per event**	**NHS Reference Cost code**
Full blood count	4.68	4.81	9.33	3.01	DAPS05: Haematology
X-Ray	0.75	0.75	0.75	£30.23	DAPF: Direct Access Plain Film
Blood glucose	0.22	0.20	0	£1.19	DAPS04: Clinical Biochemistry
Lactate dehydrogenase	3.12	3.20	5.33	£1.19	DAPS04: Clinical Biochemistry
Lymphocyte counts	4.68	4.81	9.33	£3.01	DAPS05: Haematology
Bone marrow exam	0.75	0.74	0	£288.45	Outpatient - Clinical Haematology - SA33Z
Consultation with a haematologist	4.68	4.81	9.33	£150.38	WF01A Consultant Led, Non-admitted face to face follow-up Service code: 303
Inpatient visit	0.34	0.40	2	£2,922.50	Weighted average of CLL, including Related Disorders, with CC Score 0-7+ Elective and Non-elective inpatient stays. (SA32A – SA32D)
Biopsy	0.53	0.54	0	£4,212.69	Weighted average Major General Abdominal Procedures, all ages, with CC Score 0 - 10+,(FZ12L-FZ12U).Complex General Abdominal Procedures with CC Score 0- 6+ (FZ79C-FZ79E) and Procedures on the Lymphatic System with CC Score 0- 1+ (WH54A-B).†
Blood transfusion	0.79	0.81	4	£288.23	Outpatient Procedures, Clinical haematology, SA13A, Single Plasma Exchange, Leucophoresis or Red Cell Exchange, 19 years and over
Platelet infusion	0.00	0.00	2	£288.23	Outpatient Procedures, Clinical haematology, SA13A, Single Plasma Exchange, Leucophoresis or Red Cell Exchange, 19 years and over
Health state costs used in the model					
Cost per model cycle (4 weeks)*	£338	£359	£695	N/A	Calculation

*R-chemo - rituximab and chemotherapy; N/A, not applicable, * the values given in Table 72 of the company's submission differ from these values, values reported in table are used in the company's model; †All relate to elective inpatient stays*

Adverse events

Within the ibrutinib group, the model includes all Grade 3 or higher AEs which occurred in more than 5% of individuals in the pooled ibrutinib dataset,[19] *"unless regarded clinically irrelevant by the clinicians consulted"* (CS,[1] page 147). In addition to the AEs identified by this method, clinicians recommended the inclusion of bleeding, atrial fibrillation, tumour lysis syndrome, leukostasis, lymphcytosis, renal failure, cytomegalovirus (CMV) reactivation and abnormal liver function testing as these events were different between ibrutinib and R-chemo; these events were also included in the company's model. AE rates in the R-chemo group were obtained from studies of treatments for first-line MCL identified from the company's clinical effectiveness review[1] and the literature review included in the draft NICE guideline for NHL.[10] In instances whereby multiple data sources were available for the incidence of a particular AE, the study with the longest follow-up was selected. The costs associated with managing AEs were derived from NHS Reference Costs 2014/15.[58]

The CS states that the use of AE rates from the trials reported by Kluin-Neumans *et al*[59] and Flinn *et al*[60] will lead to an underestimation of the adverse impact of R-chemo on patients because: (i) relapsed/refractory patients are on average substantially less fit and are therefore more likely to experience treatment-related toxicity than patients at first-line, and; (ii) there are several AEs for which information was available for ibrutinib but not for R-chemo; the frequency of these AEs for comparators was assumed to be 0%.

The incidence of the AEs, the unit cost of managing each event and the total cost of AEs in each treatment group is summarised in Table 42.

Table 42: Adverse event rates and unit costs

Adverse event	Ibrutinib pooled data[19]	R-CHOP rate[59]	FCR rate[59]	R-CVP[60]	Unit cost	NHS Reference Cost
Neutropenia	16.8%	60.0%	69.0%	56.0%	£162	Outpatient visit. Costed as weighted average of non-admitted, consultant led, clinical haematology visit codes: WF01A, WF01B, WF01C, WF01D, WF02A, WF02B, WF02C, WF02D
Anaemia	8.9%	12.0%	20.0%	5.0%	£162	
Leukopenia		59.0%	18.0%	38.0%	£162	
Atrial fibrillation	5.1%	5.5%†	5.5%†	5.5%†	£162	
Tumour lysis syndrome	0.5%	0.1%	0.1%	0.1%	£162	
Leukostasis	0.0%	-	-	-	£162	
Lymphocytosis	0.8%	-	-	-	£162	
Abnormal liver function	0.5%	1.0%	1.0%	1.0%	£162	
Pneumonia	8.1%			1.0%	£2720	Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 0-7 (DZ11Q). Costed as weighted average of: elective Inpatient; non-elective inpatient (long and short stay); and day case
Febrile neutropenia	-	17.0%	11.0%	-	£633	Other Haematological or Splenic Disorders, with CC Score 0-2 (SA08J). Costed as weighted average of: elective Inpatient; non-elective inpatient (long and short stay); and day case
Infection	-	14.0%	17.0%	7.0%	£563	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 short stay); and day case
CMV reactivation	0.0%	2.0%‡	2.0%‡	2.0%‡	£563	
Major bleeding	4.3%	0.6%*	0.6%*	0.6%*	£738	Gastrointestinal Bleed without Interventions, with CC Score 0-4 (FZ38P). Costed as weighted average of: elective Inpatient; non-elective inpatient (long and short stay); and day case
Renal failure	1.1%	0.0%	0.0%	0.0%	£3,055	General Renal Disorders with Interventions, with CC Score 0-2 (LA09L). Costed as weighted average of: elective Inpatient; non-elective inpatient (long and short stay); and day case
Total cost of adverse events in the model						
	Ibrutinib	**R-CHOP**	**FCR**	**R-CVP**		**Source**
Total cost of modelled AEs	£ 338.45	£ 424.74	£ 364.73	£ 252.98	-	Calculation

** sourced from doxorubicin summary of product characteristics; † sourced from Mabthera SmPC; ‡ sourced from Kelesidis et al. 2011; § Long stay non-elective inpatients visits were not used to calculate the cost of an infection of CMV reactivation*

R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-CVP - rituximab, cyclophosphamide, vincristine and prednisolone; FCR - fludarabine, cyclophosphamide and rituximab; RC - rituximab, cytarabine

Cost of death

The company's model includes a cost associated with death. This was included to reflect the resource use associated with terminal care in the last four weeks of an individual's life. According to the CS,[1] a report by the Nuffield Trust (Georghiou and Bardsley[61]) estimated the cost of terminal care to be £7,287 per cancer related death in 2014. The company uplifted this cost to 2015 prices using the hospital and community health service pay and prices inflation index; the cost of death included in the model is assumed to be £7,352.

Subgroup analyses according to number of previous LOTs

The company's subgroup analysis applies different values to a number of model parameters, based on a re-analysis of the pooled ibrutinib dataset according to number of prior LOTs (prior LOT=1 or prior LOT>1). The following parameters are re-estimated within the subgroup analysis:

- The modelled TTD/D curves for both treatment groups
- The modelled PFS curves for both treatment groups
- The distribution of patients across the response categories for ibrutinib and R-chemo (note that the distribution for R-chemo is affected because it is partly estimated using data from the pooled ibrutinib dataset[19]).
- The follow-up costs applied in the progression-free state for both groups (calculated according to the distribution of response outcomes)
- The probability of pre-progression mortality for both treatment groups
- The modelled PPS curves for both treatment groups.

Within the LOT subgroup analysis, PFS was re-estimated for each subgroup by adding a subgroup-specific covariate to the parametric survival models. For each subgroup, parametric survival curves (exponential, Weibull, log logistic and log normal models) were fitted to the observed PFS Kaplan-Meier curves. In order to maintain consistency with the base case analysis, the Weibull survivor function was selected to model PFS. Figures 13 and 14 present a comparison of the fitted parametric models and the observed Kaplan-Meier PFS curves for the LOT=1 and LOT≥2 subgroups, respectively. The AIC and BIC statistics for each candidate survivor function are summarised in Table 43; the lowest AIC and BIC values are highlighted in bold.

Figure 13: Progression-free survival – LOT=1 subgroup, comparison of company's fitted parametric survivor functions (adapted from company's model by the ERG)

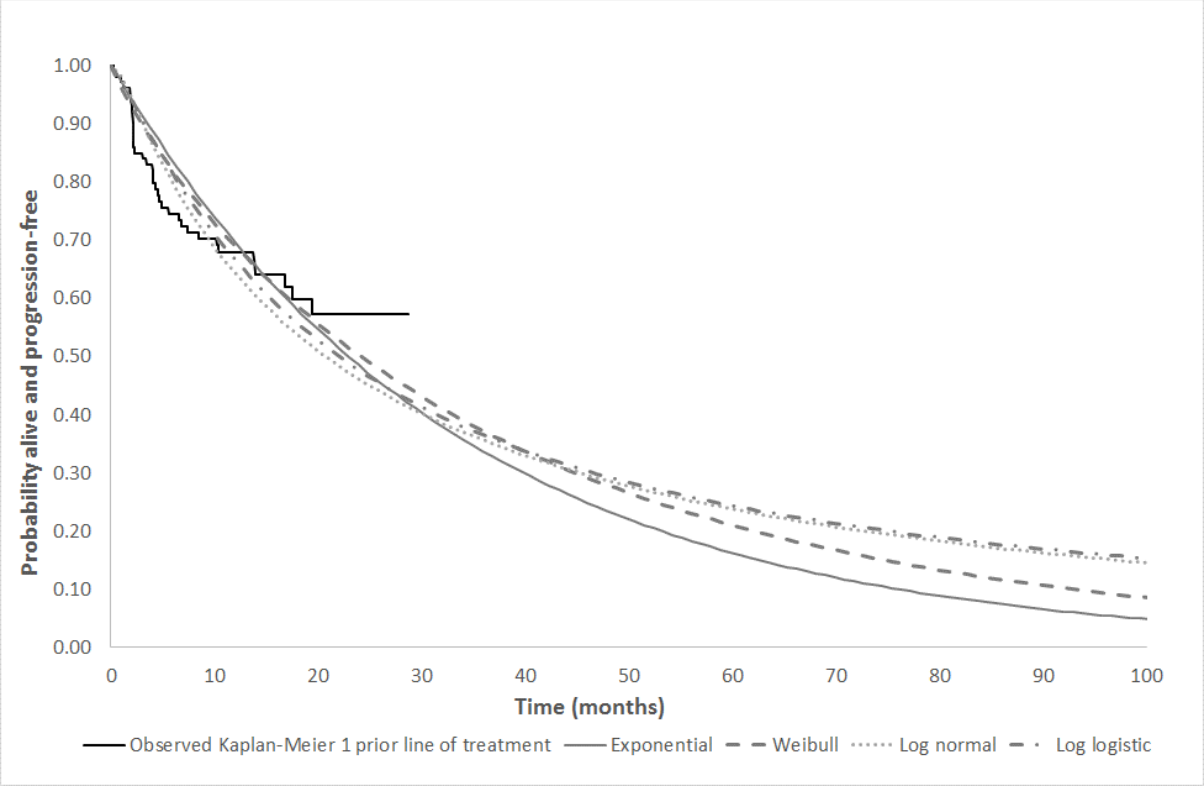


Figure 14: Progression-free survival – LOT≥2 subgroup, comparison of company's fitted parametric survivor functions (adapted from company's model by the ERG)

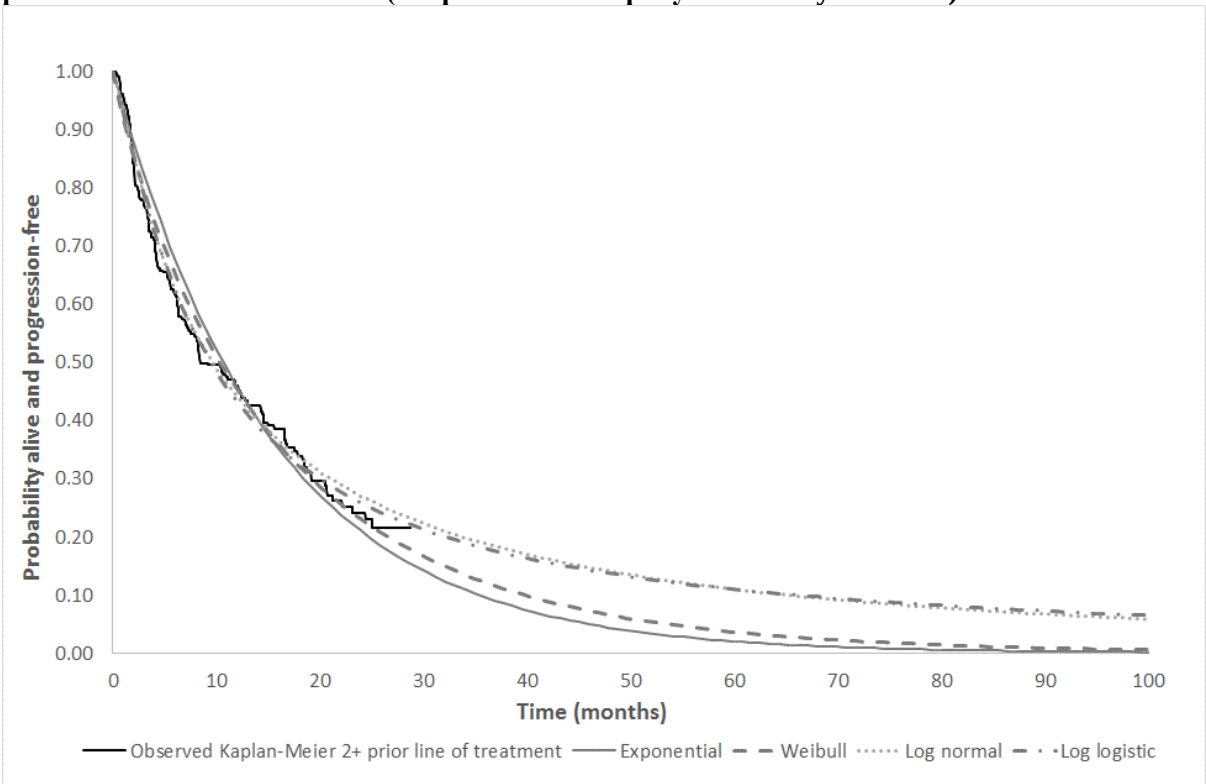


Table 43: Progression-free survival – LOT subgroup analysis, goodness-of-fit statistics (AIC and BIC)

Parametric function	AIC	BIC
Exponential	1041.99	1049.81
Weibull	1039.81	1051.55
Log logistic	1029.52	1041.26
Log normal	**1020.80**	**1032.54**

AIC - Akaike information criterion, BIC - Bayesian information criterion

TTD/D was also re-estimated for each LOT subgroup by adding a subgroup-specific covariate to the parametric survival models. For each subgroup, parametric survival curves (exponential, Weibull, log logistic and lognormal models) were fitted to the observed PFS Kaplan-Meier curves. In order to maintain consistency with the base case analysis, the Weibull survivor function was selected to model TTD/D. Figures 15 and 16 present a comparison of the fitted parametric models and the observed Kaplan-Meier TTD/D curves for the LOT=1 and LOT≥2 subgroups, respectively. The AIC and BIC statistics for each candidate survivor function are summarised in Table 44; the lowest AIC and BIC values are highlighted in bold.

Figure 15: Time to treatment discontinuation or death – LOT=1 subgroup, comparison of company's fitted parametric survivor functions (adapted from company's model by the ERG)

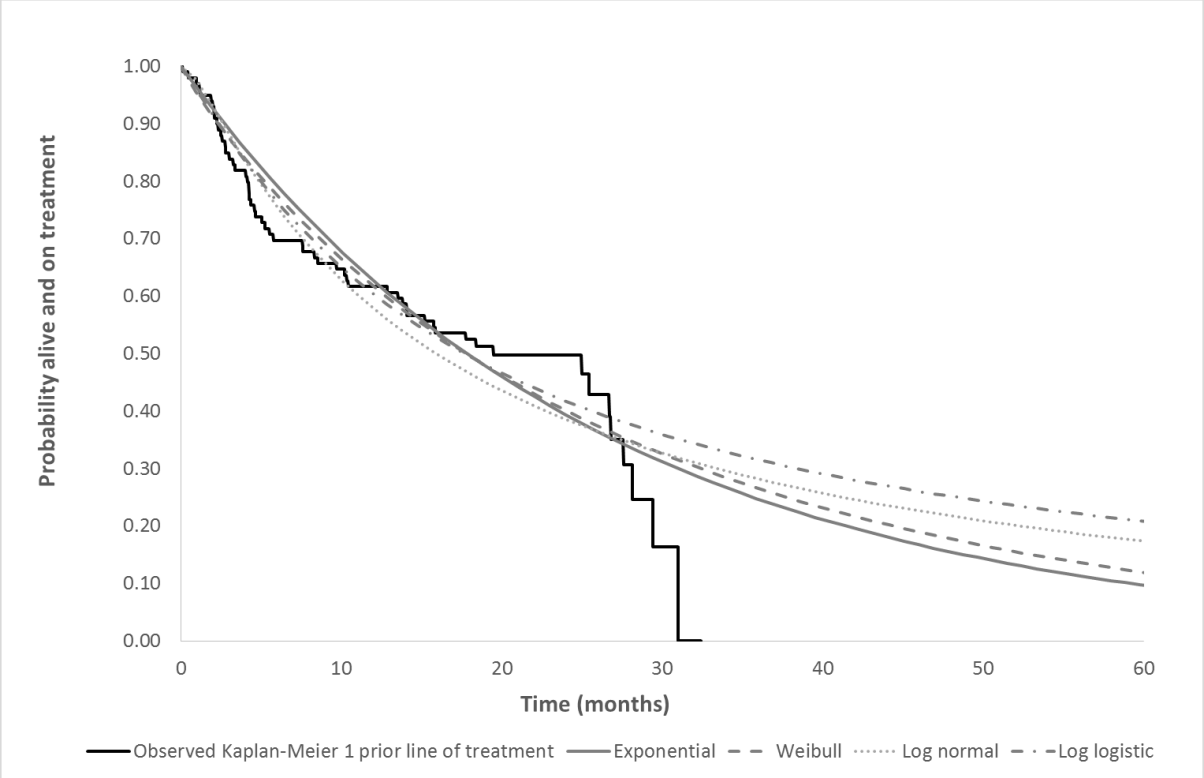


Figure 16: Time to treatment discontinuation or death – LOT≥2 subgroup, comparison of company's fitted parametric survivor functions (adapted from company's model by the ERG)

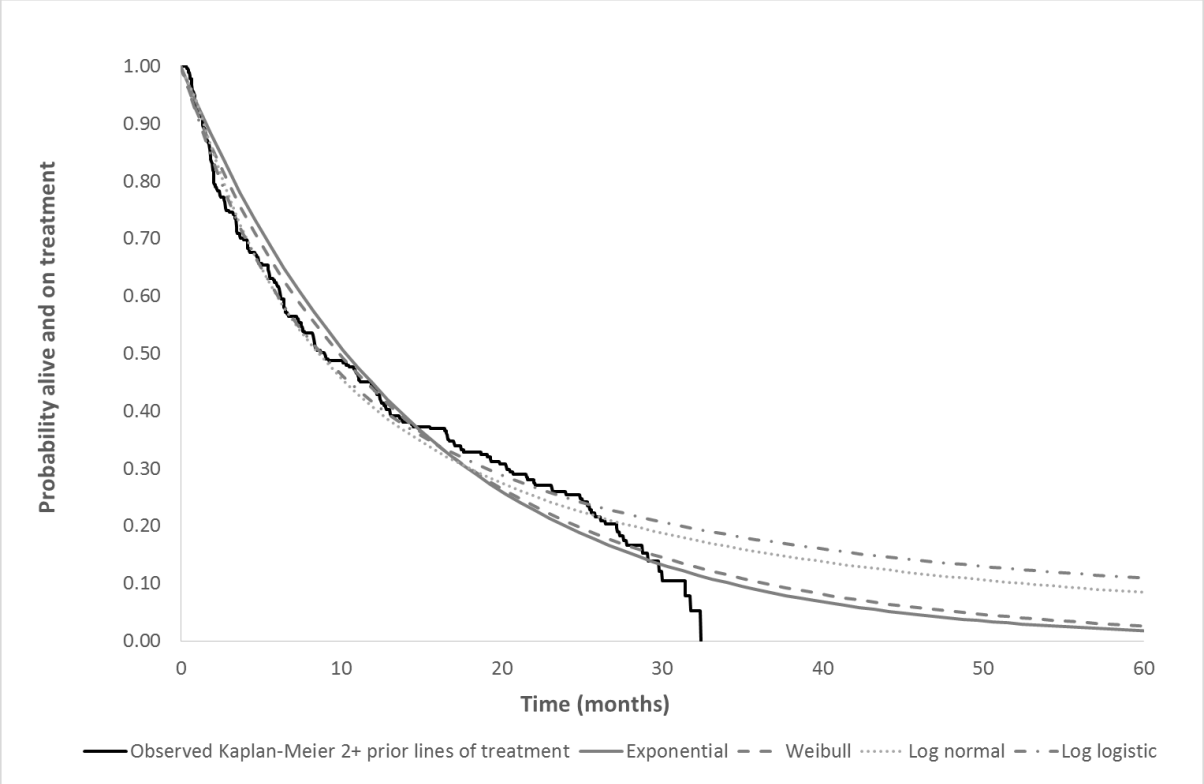


Table 44: Progression-free survival – LOT subgroup analysis, goodness-of-fit statistics (AIC and BIC)

Parametric function	AIC	BIC
Exponential	1153.44	1161.26
Weibull	1152.75	1164.49
Log logistic	1156.05	1167.79
Log normal	**1146.21**	**1157.95**

AIC - Akaike information criterion, BIC - Bayesian information criterion

The values of other parameters amended in the company's subgroup analyses are summarised in Table 45.

Table 45: Updated parameters in the company's LOT subgroup analyses

Parameter	Base case	LOT =1	LOTs ≥2
Proportion complete responders - ibrutinib	[redacted]	[redacted]	[redacted]
Proportion partial responders - ibrutinib	[redacted]	[redacted]	[redacted]
Proportion non-responders - ibrutinib	[redacted]	[redacted]	[redacted]
Estimated follow-up cost for progression-free state - ibrutinib	£338.33	£306.25	£350.05
Estimated follow-up cost for progression-free state - R-chemo	£359.09	£347.03	£364.01
Probability of pre-progression death - ibrutinib	0.71%	0.40%	1.42%
Probability of pre-progression death - R-chemo*	1.44%	1.02%	1.76%
Probability of post-progression death	10.83%	12.20%	10.57%
Utility – progression-free (excluding R-chemo utility decrement)	0.780 (0.010)	0.794 (0.017)	0.774 (0.011)

** In the base case (and the scenario analyses) it was assumed that the death rate in PFS for patients receiving R-chemo was the same as the death rate in PFS for patients receiving temsirolimus in the RAY (MCL3001) trial*
LOT - line of therapy; PFS - progression-free survival

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 ibrutinib versus R-CHOP. 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), scenario analyses, subgroup analyses according to number of prior LOTS, and a threshold analysis to determine the necessary PFS HR in order for the ICER for ibrutinib versus R-chemo to be below various willingness-to-pay (WTP) thresholds. 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 DSA are presented in the form of a tornado diagram based on incremental net monetary benefit, assuming a WTP threshold of £50,000 per QALY gained. The distributions applied in the company's PSA are summarised in Table 46.

Table 46: Summary of distributions used in company's PSA

Parameter/Parameter group	Distribution	ERG notes
Patient characteristics	Fixed	-
Drug costs		
Unit costs of drugs	Fixed	
Cost of drug administration	Gamma	SE assumed to be 20% of mean - this could have been estimated using the inter-quartile range (IQR) from the NHS Reference Costs.
Dose intensity	Beta	Method used to calculate SE unclear
Health state related costs		
Health state related resource use	Fixed	-
Unit costs for health state related resource use (except biopsy and inpatient stays)	Normal	SE assumed to be 20% of mean – this could have been estimated using inter-quartile range (IQR) using NHS Reference Costs.
Unit costs of a biopsy or an inpatient stay	Fixed	No uncertainty considered
Complete and partial responders to ibrutinib in the pooled dataset	Beta	-
Proportion of R-chemo patients who respond to treatment	Beta	Unclear why SE assumed to be 20% of mean – this could have been based on numbers of responders and non-responders
Adverse event costs		
AE rates	Beta	All AEs that occur at 0% probability have been implicitly fixed in the PSA. These should include a continuity correction.
AE costs	Normal	SE assumed to be 20% of mean – this could have been estimated using the IQR from the NHS Reference Costs.
Terminal care costs		
Cost of terminal care	Gamma	-
Progression Free Survival		
The shape and scale parameters of the parametric survival curves	Multivariate normal	-
PFS HR obtained from the indirect comparison of ibrutinib compared to single line chemotherapy	Log normal	-
PFS HR for the rituximab effect	Log normal	-
Time to treatment discontinuation or death		
The shape and scale parameters of the parametric survival curves	Multivariate normal	-
Risk of death		
Risk of death during PFS for ibrutinib	Beta	Alpha and beta parameters not calculated consistently with other binomial parameters in model
Risk of death during PFS for R-chemo	Beta	-
Risk of death during PPS	Normal	Based on normal distribution fitted to the hazard rate

SE - standard error; IQR - inter-quartile range; AE - adverse event; PSA - probabilistic sensitivity analysis; PFS - progression-free survival; PPS - post-progression survival

5.2.5 Cost-effectiveness results presented within the CS

5.2.5.1 Base case cost-effectiveness results

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. During the appraisal process, the company identified a programming error in their submitted model which was corrected within the company's clarification response[21] (question C2); the results presented in this section include the correction of this error. All probabilistic results also include uncertainty around the ibrutinib RDI parameter; this was added to the model following the clarification process (see clarification response,[21] question C32).

Table 47 presents the company's base case cost-effectiveness results for ibrutinib versus R-CHOP. 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 0.94 QALYs at an additional cost of [redacted] compared with R-CHOP; the ICER for ibrutinib versus R-CHOP is expected to be £76,014 per QALY gained. The results of the deterministic model are similar, with ibrutinib yielding an ICER of £75,317 per QALY gained compared with R-CHOP.

Table 47: Company's central estimates of cost-effectiveness – ibrutinib versus R-CHOP

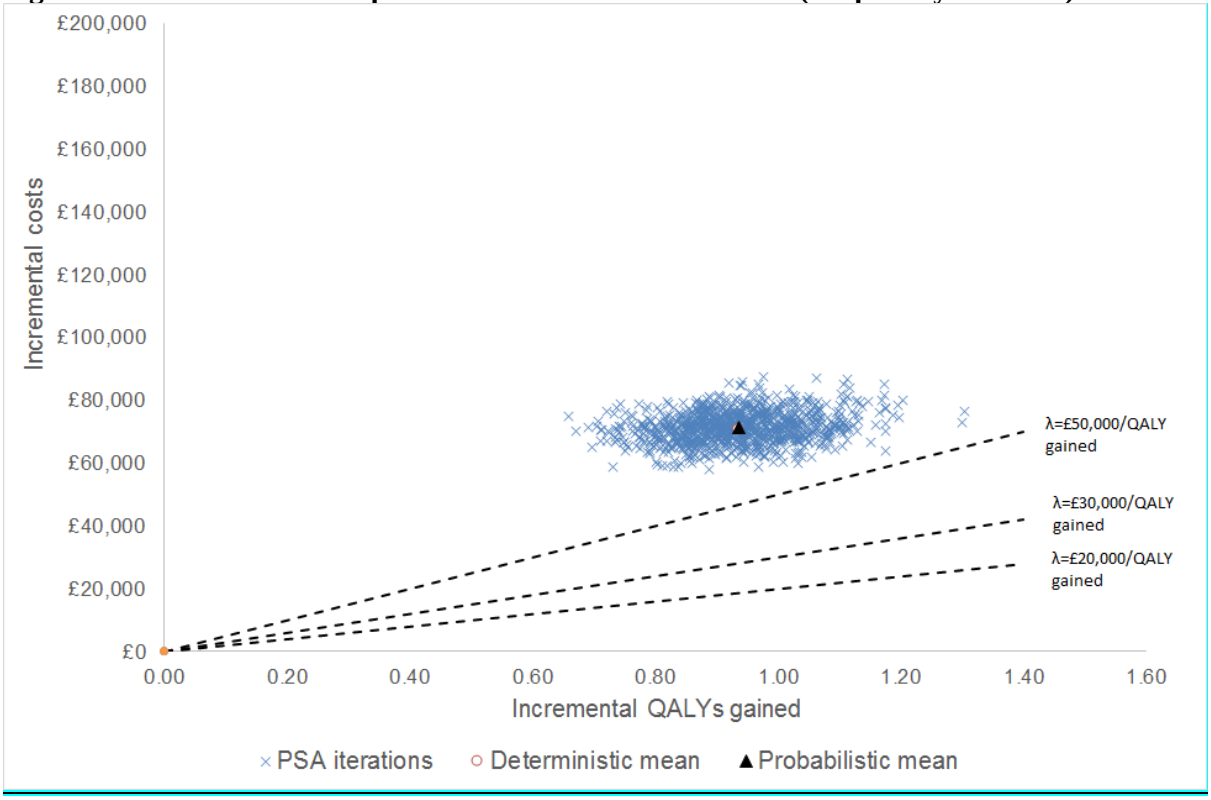
Probabilistic model*					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	0.94	£71,249	**£76,014**
R-CHOP	[redacted]	[redacted]	-	-	-
Deterministic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	0.94	£70,522	**£75,317**
R-CHOP	[redacted]	[redacted]	-	-	-

** obtained by reprogramming the PSA subroutine to record absolute costs and QALYs*
QALY – quality adjusted life year; R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

5.2.5.2 Probabilistic sensitivity analysis results

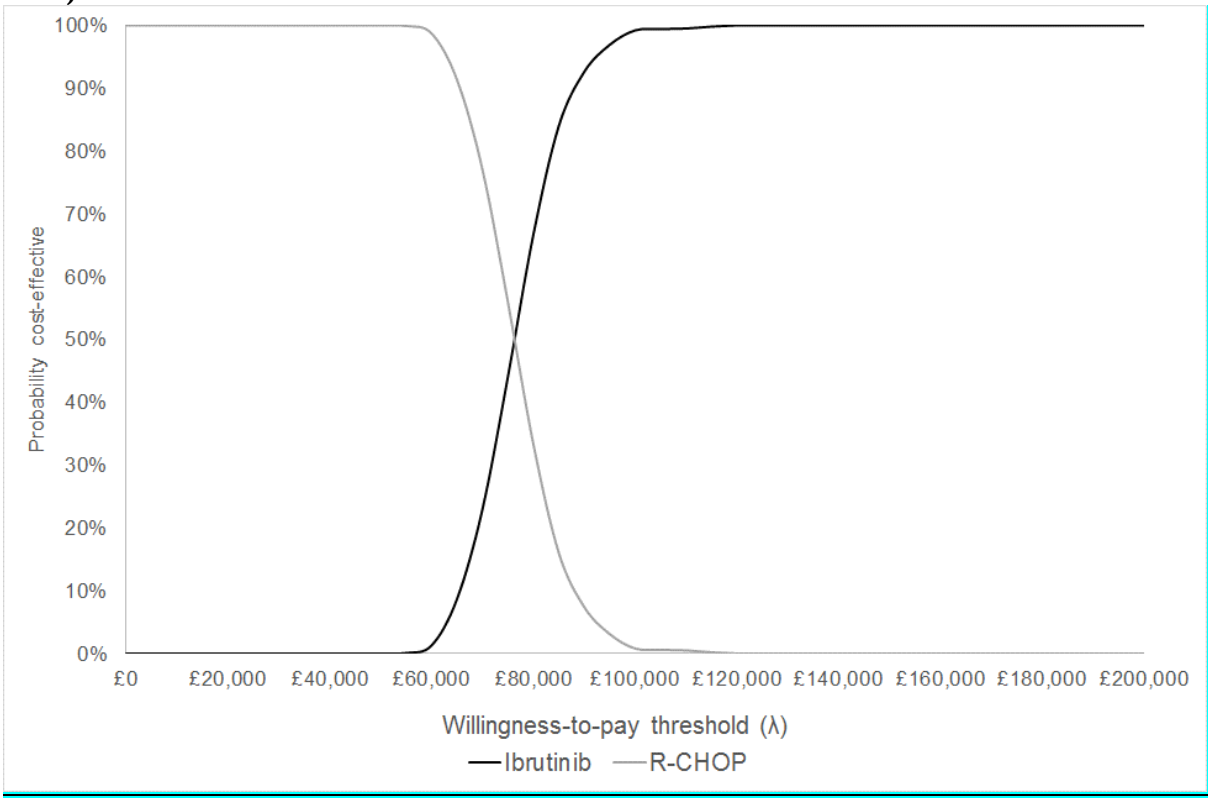
Figures 17 and 18 present the cost-effectiveness plane and CEACs for ibrutinib versus R-CHOP, respectively; each figure is based on a re-run of the company's PSA. Assuming a WTP threshold of £50,000 per QALY gained, the company's base case model suggests that the probability that ibrutinib produces more net benefit than R-CHOP is approximately zero.

Figure 17: Cost-effectiveness plane – ibrutinib versus R-CHOP (adapted by the ERG)



QALY – quality-adjusted life year

Figure 18: Cost-effectiveness acceptability curves – ibrutinib versus R-CHOP (adapted by the ERG)

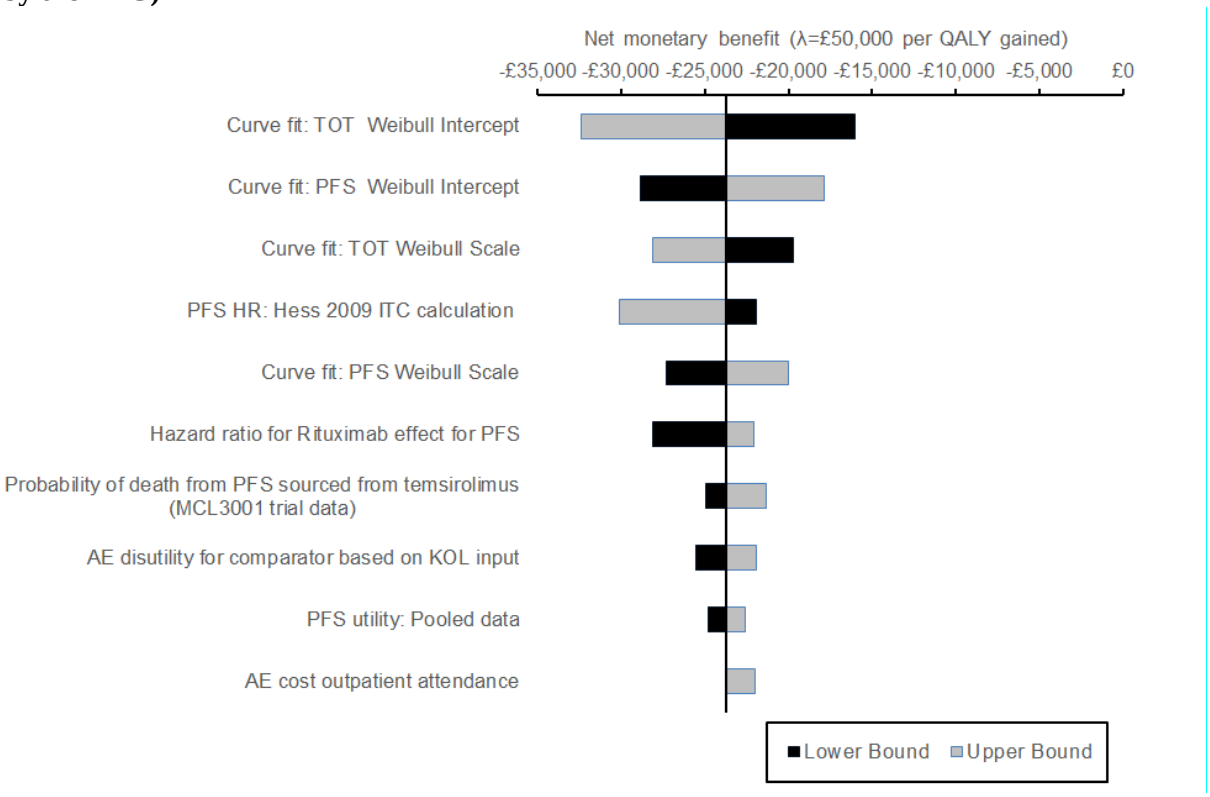


R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

5.2.5.3 Deterministic sensitivity analysis results

Figure 19 presents the results of the company's one-way DSA (ranges defined according to upper and lower 95% CIs for parameters), based on net monetary benefit assuming a WTP of £50,000 per QALY gained. Results are presented only for the ten most influential parameters. The results of the DSA suggest that the parameters of the survivor functions for PFS and time on treatment (TTD/D), the individual elements of the composite HR for PFS, the pre-progression mortality probability for R-chemo, the disutility associated with R-chemo, the PFS utility value and the cost of outpatient appointments for the management of AEs are the most influential parameters. The ERG notes that the net monetary benefit remains negative across all DSAs, hence the ICER for ibrutinib versus R-CHOP would be greater than £50,000 per QALY gained.

Figure 19: One-way sensitivity analysis tornado diagram (λ=£50,000 per QALY gained, adapted by the ERG)



QALY – quality-adjusted life year; TOT - time on treatment; PFS – progression-free survival; HR - hazard ratio; ITC – indirect treatment comparison; AE - adverse event

5.2.5.4 Scenario analysis results

Table 48 presents the results of the company's scenario analyses. Across almost all scenario analyses, the ICER remains in excess of £70,000 per QALY gained. The only exception to this relates the analysis in which the modelled OS for R-CHOP is "calibrated" against the HMRN OS estimate of 8.4 months by adjusting the post-progression mortality rate in this group only. Within this analysis, the HR for PPS for R-chemo versus ibrutinib (after discontinuation of both therapies) is assumed to be 2.40; the ICER for this scenario is estimated to be £59,345 per QALY gained. Whilst unclear from the

CS, it is important to note that this is actually an analysis in the 1 prior LOT subgroup rather than the overall population considered in the base case.

Table 48: Summary of company's scenario analyses – ibrutinib versus R-chemo (adapted from clarification response Table 17)

Scenario	Incremental (ibrutinib vs R-chemo)		
	QALYs	Costs	ICER
1. Base case*	0.94	£70,522	£75,317
2. Comparator efficacy HR for PFS using TEM data†	0.82	£68,255	£83,685
3. Time horizon = 10 years‡	0.93	£70,253	£75,681
4. Time horizon = 20 years‡	0.94	£70,541	£75,279
5. Comparator - R-CVP‡	0.94	£71,847	£76,732
6. Comparator - FCR‡	0.94	£68,354	£73,002
7. Comparator - RC‡	0.94	£69,580	£74,312
8. Blended comparison‡	0.94	£70,546	£75,343
9. No wastage included‡	0.94	£70,948	£75,773
10. R-chemo disutility based on Schenkel *et al.*[63]	0.93	£70,522	£76,194
11. Utilities not age-adjusted	0.95	£70,522	£74,336
12. Sequential approach§	1.08	£82,751	£76,671
13. Including FCR as subsequent treatment	0.94	£68,940	£73,628
14. PFS exponential model	0.83	£66,914	£80,296
15. PFS log normal model	1.30	£93,071	£71,636
16. PFS log logistic model	1.32	£97,926	£74,194
17. Pre-progression mortality for R-chemo equal to ibrutinib	0.92	£70,275	£76,605
18. Response rates of R-chemo equal to TEM response	0.94	£70,068	£74,833
19. Response rates of R-chemo equal to response in OPTIMAL[8]	0.94	£69,607	£74,341
20. Response rates of R-chemo equal to ibrutinib	0.94	£70,626	£75,429
21. Rituximab PFS HR=1	1.00	£72,309	£72,311
22. Rituximab PFS HR applied to OPTIMAL[8] ITC = 0.75	0.95	£70,933	£74,429
23. Rituximab PFS HR applied to OPTIMAL[8] ITC = 0.89	0.98	£71,760	£73,019
24. Rituximab PFS HR applied to OPTIMAL[8] ITC = 1.6	1.05	£74,321	£70,779
25. Assuming R-chemo post-progression mortality probability = 0.27 (to reflect HMRN median OS of 8.4 months) using the 1 prior LOT subgroup	1.87	£110,949	£59,345

** Generated using the company's model due to minor typographical error identified in clarification response; † analysis not presented in clarification response; ‡ values presented in clarification response correspond to analysis presented on previous row of Table 17; § subject to programming errors - see Section 5.3*

R-chemo - rituximab and chemotherapy; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; HR - hazard ratio; PFS – progression-free survival; TEM - temsirolimus; R-CVP - rituximab, cyclophosphamide, vincristine and prednisolone; FCR - fludarabine, cyclophosphamide and rituximab; RC – rituximab and cytarabine; ITC - indirect treatment comparison; LOT - line of therapy; HMRN - Haematological Malignancy Research Network

5.2.5.5 Subgroup analysis results

Table 49 presents the results of the company's subgroup analysis based on the number of prior LOTs received by the modelled population (LOT=1 or LOT≥2). The probabilistic results are based on a re-run of the PSA subroutine by the ERG. Within the subgroup of patients who have received only one prior LOT, the probabilistic version of the company's model suggests that ibrutinib is expected to generate an additional 1.67 QALYs at an additional cost of [redacted] per patient; this results in an ICER of £65,977 per QALY gained for ibrutinib versus R-CHOP. This is lower than the company's

probabilistic base case estimate for all patients (ICER=£76,014 per QALY gained). Within the subgroup of patients who have received two or more prior LOTs, ibrutinib is expected to produce and additional 0.71 QALYs at an additional cost of [redacted] per patient; the corresponding ICER is £84,263 per QALY gained. This is less favourable than the ICERs for the company's base case and the 1 prior LOT subgroup.

Table 49: Summary of company's subgroup analyses

1 prior LOT - probabilistic model*					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	1.67	£110,151	**£65,977**
R-CHOP	[redacted]	[redacted]	-	-	-
1 prior LOT - deterministic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	1.67	£108,398	**£64,755**
R-CHOP	[redacted]	[redacted]	-	-	-
≥2 prior LOTs - probabilistic model*					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	0.71	£60,142	**£84,263**
R-CHOP	[redacted]	[redacted]	-	-	-
≥2 prior LOTs - deterministic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	0.72	£59,685	**£83,256**
R-CHOP	[redacted]	[redacted]	-	-	-

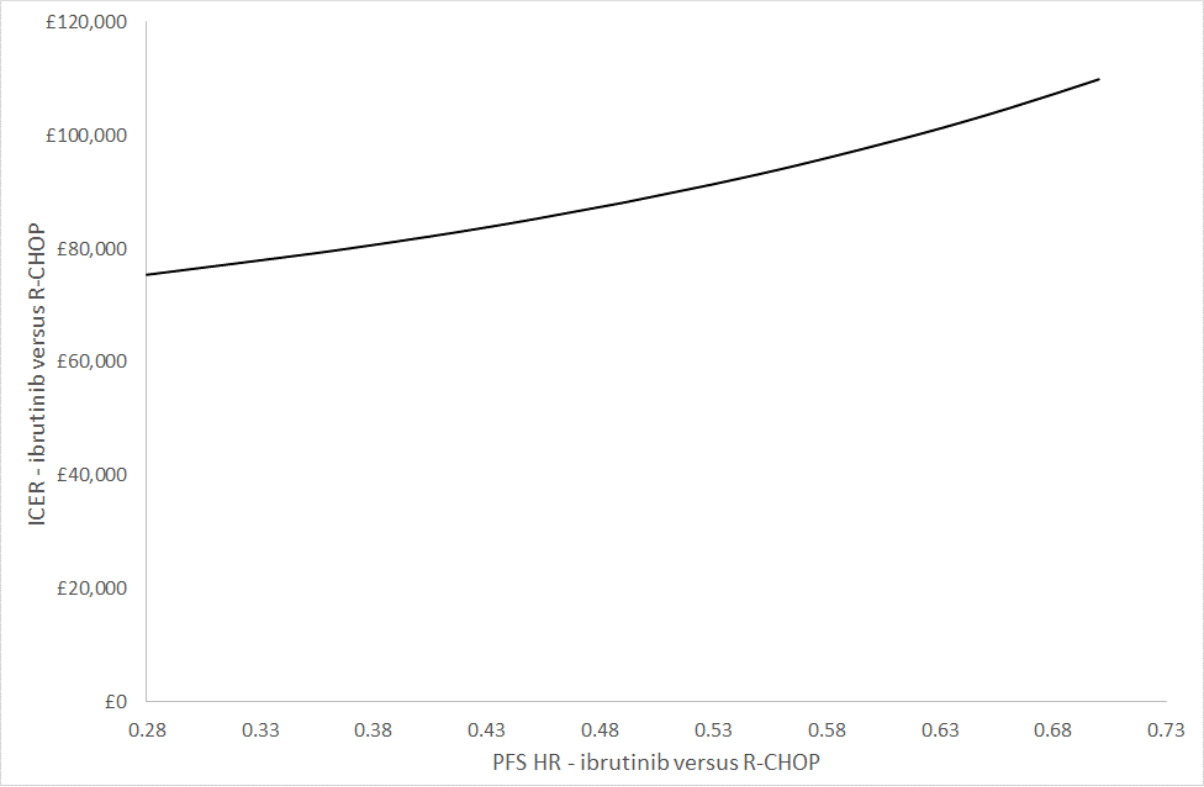
** Results generated by re-programming the PSA subroutine*
LOT - line of therapy; QALY – quality-adjusted life year; R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone

The ERG has some concerns regarding the *post hoc* nature of the subgroup analyses and poor fit of the PFS survivor function to the 1 prior LOT subgroup (see Section 5.3).

5.2.5.6 Threshold analysis

Figure 20 presents the results of the company's threshold analysis. Whilst this analysis is referred to in the CS as a threshold analysis, this is somewhat inaccurate since the "threshold" ICER of £50,000 per QALY gained is never met for the range of values presented. As shown in Figure 20, as the HR for PFS for ibrutinib versus R-CHOP increases (thereby lessening the distance between the PFS and TTD/D curves), so too does the ICER for ibrutinib. It is unclear from the CS why more favourable HRs (that would produce more favourable ICERs for ibrutinib) were not considered within the analysis.

Figure 20: Threshold analysis around PFS HR for ibrutinib versus R-CHOP



R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; PFS – progression-free survival; HR - hazard ratio

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.[20] Section 5.3.3 summarises the ERG's verification of the company's implemented model and inconsistencies between the model, the CS,[1] and the sources used to inform the model parameter values. Section 5.3.4 presents a detailed critique of the main issues and concerns underlying the company's analysis.

5.3.1 Methods for reviewing the company's economic evaluation and health economic model

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic evaluation and the underlying health economic model upon which this was based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists[64, 65] 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.

- Double-programming of the deterministic version of the company's model to fully 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, scenario analysis, subgroup analysis and threshold 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 economic evaluation and the assumptions underpinning the model.

5.3.2 Adherence of the company's model to the NICE Reference Case

In general, the company's economic evaluation is in line with the NICE Reference Case[20] (see Table 50). The ERG has some specific concerns relating to the blended comparison (presented as a scenario analysis), the use of non-preference based disutilities and the approach used to model the incremental health gains associated with ibrutinib versus R-chemo. These deviations from the Reference Case are discussed in detail in Section 5.3.4.

Table 50: Adherence of the company's model to the NICE Reference Case

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The company's economic analysis is generally in line with the final NICE scope.[11]
Comparator(s)	As listed in the scope developed by NICE	The base case analysis is presented as a comparison of ibrutinib versus R-CHOP. The other R-chemo regimens listed in the final NICE scope[11] (R-CVP, FCR and RC) are considered in the company's scenario analyses and as part of a blended comparison. Owing to a lack of comparative evidence, the effectiveness of all R-chemo options is assumed to be equivalent. The ERG notes that the use of a blended comparison is problematic.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Health gains for patients are modelled in terms of QALYs gained.
Perspective on costs	NHS and PSS	The company's economic analysis adopts an NHS and PSS perspective.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The company's economic evaluation takes the form of a cost-utility analysis. The results of the analysis are presented in terms of the incremental cost per QALY gained for ibrutinib versus R-chemo.

Element	Reference case	ERG comments
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a 15-year (lifetime horizon). Scenario analyses are also presented for alternative time horizons of 10 years and 20 years.
Synthesis of evidence on health effects	Based on systematic review	Treatment effects for PFS are modelled using an indirect comparison based on the pooled ibrutinib dataset, OPTIMAL[8] and HMRN audit data.[7] The HMRN audit did not form part of the systematic review. Pre-progression mortality for R-chemo is assumed to reflect that in the TEM arm of the RAY (MCL3001) trial.[15]
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health utility values for the progression-free and post-progression states were derived from EQ-5D-5L assessments within the RAY (MCL3001) and SPARK (MCL2001) studies.[15, 33] The disutility for patients receiving R-chemo was derived from expert opinion and is not a preference-based valuation.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gains.
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 and PSS. Unit costs were valued at 2014/15 prices.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	All costs and QALYs are discounted at a rate of 3.5%

R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; R-chemo - rituximab and chemotherapy; R-CVP - rituximab, cyclophosphamide, vincristine and prednisolone; FCR - fludarabine, cyclophosphamide and rituximab; RC - rituximab and cytarabine; QALY - quality-adjusted life year; PSS - Personal Social Services; PFS - progression-free survival; HMRN - Haematological Malignancy Research Network; TEM – temsirolimus

5.3.3 Model verification and correspondence between the model, the CS and parameter sources

The ERG rebuilt the deterministic version of the company's base case model in order to verify its implementation. Table 51 presents a comparison of total QALYs and costs for ibrutinib and R-CHOP,

as estimated using the company's model and the ERG's rebuilt model. As shown in Table 51, the ERG was able to produce very similar estimates of health gains, costs and cost-effectiveness to those estimated using the company's model. The ERG is satisfied that following the correction of the error identified during clarification, the company's base case model has been implemented as intended and without major programming errors. As noted in Section 5.3.4, programming and formulae errors were however identified in the QALY calculations within the company's sequential model (this scenario analysis was not subjected to a full model re-build by the ERG).

Table 51: Comparison of company's base case model and ERG's rebuilt model

Option	Company's model			ERG's rebuilt model		
	QALYs	Costs	ICER	QALYs	Costs	ICER
Ibrutinib	[redacted]	[redacted]	£75,317	[redacted]	[redacted]	£75,323
R-CHOP	[redacted]	[redacted]	-	[redacted]	[redacted]	-

QALY – quality-adjusted life year; ICER - incremental cost-effectiveness ratio; R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

Correspondence of written submission and model

The ERG identified two discrepancies between the company's written submission and the implemented model. Firstly, the costs of PFS for ibrutinib (£258 per cycle) and PFS for R-chemo (£301) were incorrectly reported as a consequence of the error identified by the company during clarification (see clarification response,[21] question C2). The corrected values used in the base case model are reported in Table 41. It was noted that the cost of an infection or CMV reactivation was stated to be the cost of: *"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 short stay); and day cases."* The ERG notes that the NHS Reference Costs associated with non-elective inpatient long stays were not included in the estimated cost. The company's stated cost (used in the model) is £563 per infection or CMV reactivation. However, if non-elective inpatient long stays were also included, the estimated cost rises to £1,106 per infection or CMV reactivation. The cost of AEs and the two costs of an infection or CMV reactivation are given in Table 52.

Table 52: Total cost of infections and CMV reactivation

Cost of an infection and CMV reactivation	Ibrutinib	R-CHOP	FCR	R-CVP
£536	£338.45	£424.74	£364.73	£257.98
£1,106	£338.45	£511.29	£467.56	£301.55
Difference	£0	+£86.55	+£102.83	+£43.57

R-CHOP - cyclophosphamide, doxorubicin, vincristine and prednisolone; FCR – fludarabine, cyclophosphamide and rituximab; R-CVP - rituximab, cyclophosphamide, vincristine and prednisolone

The ERG notes that this correspondence issue is unfavourable to ibrutinib, as the costs in the R-chemo arms have been underestimated. Compared with the incremental costs in the company's base case, the cost differences due to different weighted average costs of infection and CMV reactivation are

relatively small and only have a minor impact upon the cost-effectiveness of ibrutinib versus R-CHOP.

As noted in the footnotes to Table 48, several of the company's scenario analyses reported in the clarification response[21] were subject to reporting errors whereby the results did not correspond to the scenario evaluated.

Correspondence of model inputs and original sources of parameter values

The ERG was unable to locate the company's estimated cost of death within Georghiou and Bardsley.[61] Since all modelled patients in both groups die, albeit at different times, this is unlikely to have a material impact on the ICER for ibrutinib versus R-chemo.

The ERG was unable to identify the precise source used to estimate the cost of prednisone (assumed to be the same as prednisolone) within eMit.[57] However, since this cost is very low, this should not be considered a matter of concern. In addition, since MIMS is updated regularly, the ERG was unable to locate the costs of fludarabine and cytarabine reported in the CS;[1] however, the differences between the values reported in the CS and those contained in the June 2016 edition of MIMS are negligible.

All other parameters appear to correspond with their original sources.

5.3.2 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 economic analysis. These issues are discussed in further detail in the subsequent sections.

Box 1: Main issues identified within the critical appraisal of the company's model

(1) Concerns regarding company's model structure and use of evidence
(2) Issues surrounding use of parametric survival modelling
(3) Methods for modelling time to treatment discontinuation (or death)
(4) Uncertainty surrounding relative effectiveness of ibrutinib versus treatments currently used in clinical practice in England
(5) Exclusion of costs of subsequent therapies beyond progression
(6) Concerns regarding the company's implementation of the "sequential" model
(7) Inappropriate use of blended comparison of R-chemo options
(8) Questionable approach to modelling HRQoL
(9) Ibrutinib treatment not constrained to progression-free period within the PSA
(10) Discrepancy between observed and predicted OS
(11) Uncertainty surrounding company's subgroup analyses and risk of confounding

(1) Concerns regarding company's model structure and use of evidence

The company's base case model adopts a Markov approach based on three health states: progression-free, post-progression and dead. This requires three sets of transition probabilities: (i) transitions from the progression-free state to the dead state (pre-progression mortality); transitions from the progression-free state to the post-progression state (calculated using PFS adjusted for pre-progression mortality), and; transitions from the post-progression state to the dead state (post-progression mortality). The data used to parameterise these transitions in each group are summarised in Table 53.

Table 53: Evidence used to inform company's transition probabilities

Transition	Approach used to derive transition probabilities	
	Ibrutinib	**R-chemo**
Progression-free to dead	4-week pre-progression mortality rate from pooled ibrutinib dataset.[19] (assuming exponential distribution)	4-week pre-progression mortality rate from TEM group in RAY (MCL3001)[15] (assuming exponential distribution)
Progression-free to post-progression	Weibull survivor function fitted to PFS curve from pooled ibrutinib dataset[19]	Modelled using ibrutinib Weibull survivor function and indirect comparison including "rituximab effect"[1] (assuming proportional hazards)
Post-progression to dead	Exponential survivor function fitted to PPS curve from pooled ibrutinib dataset[19]	Assumed to be the same as that for the ibrutinib group

R-chemo - rituximab and chemotherapy; TEM - temsirolimus; PFS - progression-free survival; PPS - post-progression survival

Markov models are in common use in many areas of evaluation, including the economic analysis of oncology products. However, given the nature of evidence reported in clinical trials of oncology treatments (PFS and OS from the point of randomisation), the ERG notes that use of a Markov design imposes several structural constraints which in some instances can preclude the model from making the best use of available evidence. The ERG has three main concerns with respect to the company's model structure: (a) the hazard of pre-progression mortality is assumed to be constant; (b) the use of PPS may introduce a selection bias, and; (c) the Markov approach imposes structural constraints which may produce bias. These issues are discussed below.

(a) The hazard of pre-progression mortality is assumed to be constant

Pre-progression mortality is modelled assuming an exponential distribution; this assumes that the hazard rate for patients dying prior to progression is constant. The CS does not report any evidence to support this assumption. In response to a request for clarification from the ERG (see clarification response,[21] question C22), the company provided a log-cumulative hazard plot and Kaplan-Meier survival curve for pre-progression mortality (see Figures 21 and 22). The company's clarification response suggests that the log cumulative hazard shows an approximately straight line with a gradient of 1 (45 degrees), which supports the use of an exponential distribution. The company's clarification

response also suggests that due to the small numbers of patients experiencing pre-progression death, *"using [a] more complicated methodology would not be supported by the available evidence."*[21] Given the company's choice of model structure and the evidence available, the ERG considers this to be broadly reasonable, although it would have been preferable to consider the use of sensitivity analysis to explore alternative survivor functions.

Figure 21: Log-cumulative hazard plot - pre-progression mortality (reproduced from clarification response Figure 12)

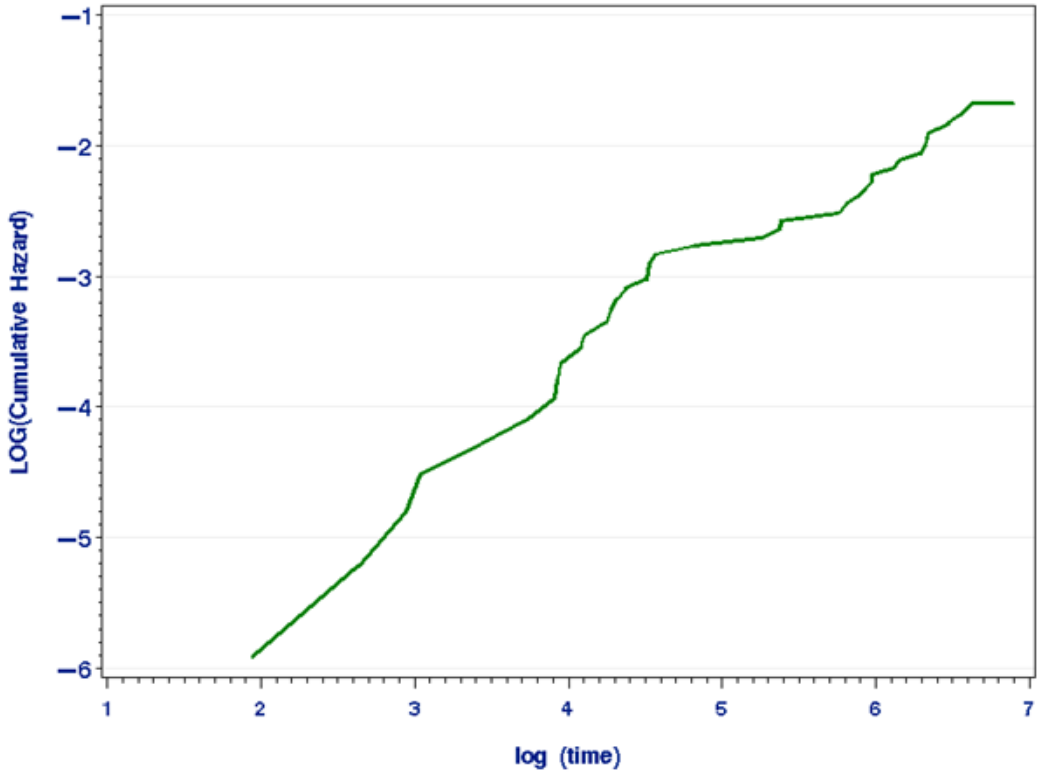
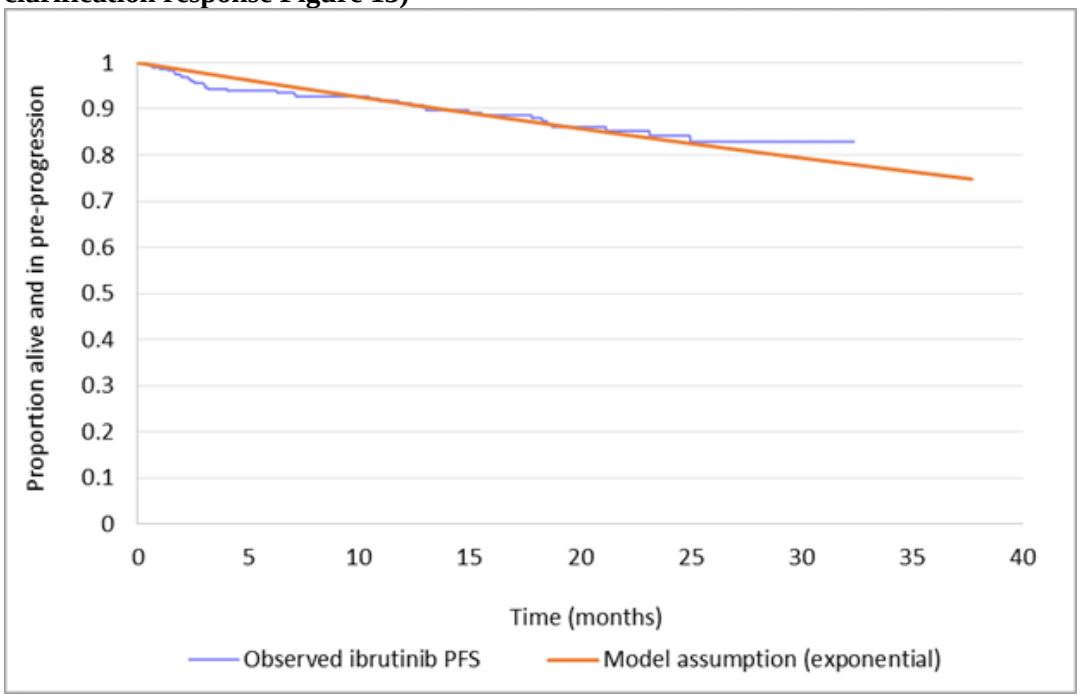


Figure 22: Pre-progression mortality observed in pooled ibrutinib data (reproduced from clarification response Figure 13)



PFS – progression-free survival

(b) The use of post-progression survival data may introduce a selection bias

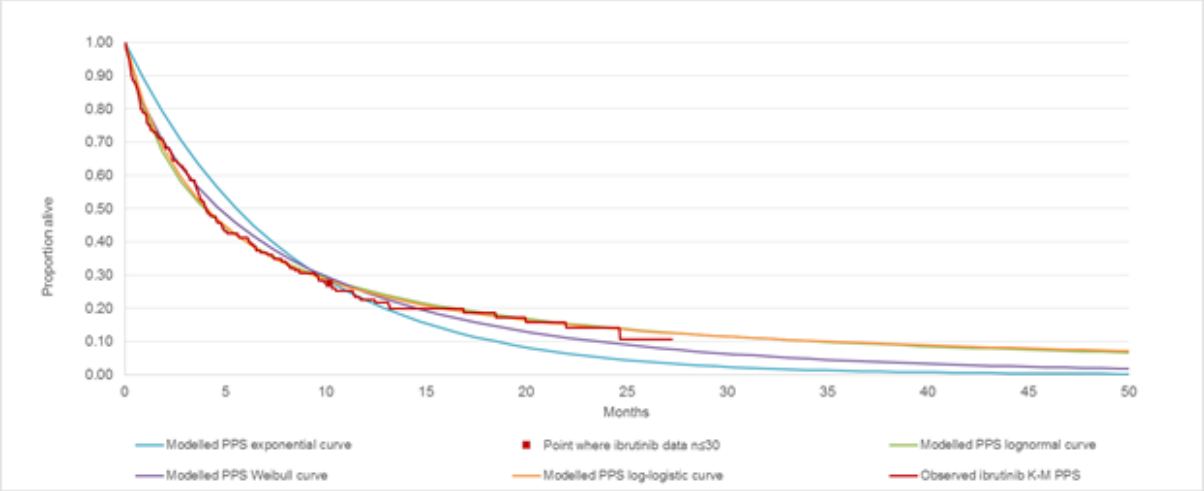
By definition, PPS does not reflect a randomised endpoint and considers only the survival prognosis of patients who have already experienced disease progression. Regression models fitted to Kaplan-Meier data for PPS use data only for those patients who have progressed; patients who have not yet progressed are excluded from the dataset. If there is a true difference in survival outcomes between patients who progress earlier and those who progress later, the consequence is a selection bias. This concern regarding the potential difference in survival prognosis between rapid progressors and late progressors is discussed in the clinical section of the CS. The risk of this type of selection bias is not present in an ITT analysis of OS from the point of randomisation, as both patients who have experienced the event of interest and those who are censored contribute to the likelihood function used to estimate the parameters of the regression model.[66] Within the company's model, this problem may be mitigated by the fact the same PPS rate is assumed in both the ibrutinib and R-chemo groups, although the true impact of the potential bias is not clear. The ERG also notes that the limitations in the evidence base, particularly for OS, restrict the potential for producing robust estimates of treatment effect for ibrutinib versus R-chemo (see Section 4.5).

(c) Structural constraints imposed by the adopted Markov approach

The company's Markov model, as implemented, imposes structural constraints on the way in which the hazard rate for post-progression mortality is modelled. PPS is assumed to follow an exponential distribution (see Table 53); the CS[1] (page 142) states that this assumption was made *"to avoid the requirement to use tunnel states to track patient movements."* The ERG considers this to represent a

poor justification for the selected model structure as it has been made on the basis of convenience rather than a proper consideration of the PPS hazard rate. As previously shown in Figure 12, the use of the exponential curve does not reflect the PPS data well and other parametric functions may provide a both statistically better fit and a more plausible extrapolation. In response to a request for clarification from the ERG (see clarification response,[21] question C17), the company presented further statistical analysis of the available PPS data using Weibull, log logistic and log normal survivor functions (see Figure 23). The clarification response states that these curves were *"not vastly dissimilar"* to the exponential curve in terms of mean survival, but noted that the log logistic and log normal functions had implausibly long tails. The company also notes that the use of the exponential function appears more conservative than the Weibull function. The company's clarification response includes an additional scenario analysis which attempts to use the Weibull function to model PPS; within this analysis the undiscounted ICER (without PAS) is estimated to be £102,456 per QALY gained. However, given that the model does not include the functionality to reflect time-variant transition probabilities for PPS (as this would require a Semi-Markov structure), it is unclear how the Weibull function for PPS has been incorporated into the model.

Figure 23: Ibrutinib pooled data: PPS parametric curve fits (reproduced from clarification response Figure 6)



PPS – post-progression survival; K-M – Kaplan-Meier

With respect to the relationship between the selected model structure and the available evidence base, the company's clarification response[21] (question C12) states:

"This approach uses the evidence available to show that PFS is a good surrogate for OS to model OS outcomes without making considerable leaps of faith regarding the evidence available for OS…A substantial amount of PFS data are available from all ibrutinib trials to be able to quantify the PFS benefit and these data are mature. Because of this, the approach taken within the health economic model using PFS data and then adding on a fixed PPS to both arms is more appropriate as it avoids making any potentially unjustified assumptions around PPS, which would be implicit in modelling

PFS and OS separately. As well as the avoidance of making any unjustified assumptions relating to the PPS benefit of ibrutinib, using the current methodology of PFS + fixed PPS also reduces bias associated with fitting parametric curves to OS data which may arise as a result of differential subsequent therapies received by patients within the clinical trials." (clarification response[21])

The ERG suggests that the company's use of a Markov approach still makes several assumptions (particularly regarding the application of treatment effects only to PFS and the relationship between PFS and OS), and may not reduce bias or uncertainty. The evidence used by the company to support the use of PFS as a surrogate for OS (Lee *et al*[67]) is actually based on aggressive or indolent NHL (rather than R/R MCL) and includes EFS as well as PFS as a surrogate marker for OS. The ERG considers that rather than reducing uncertainty, the translation of a surrogate endpoint to a final endpoint may add another layer of uncertainty onto an already uncertain survival projection. Whilst the company's clarification response[21] (question C19) appears to suggest a reasonable level of individual-level correlation within the pooled ibrutinib dataset[19] (coefficients ranging from 0.70 to 0.90, 95% CIs not reported), the ERG notes that correlation is not the same as causation. It should also be noted that the company's claim that using PPS reduces potential bias due to the use of subsequent therapies in the clinical trials is invalid; the PPS data are also subject to the same potential bias. Whilst the level of censoring in the OS data for ibrutinib means that any survival projection is uncertain, the ERG considers that the observed OS Kaplan-Meier curves for the ibrutinib group (with appropriate extrapolation) are likely to represent the best estimate of OS for patients receiving ibrutinib.

The ERG takes the view that the precise modelling approach adopted is not important provided the adopted structure does not impose inappropriate constraints on the synthesis of the available evidence and that the model-predicted outcomes are considered to be credible. Given the discrepancy between the model-predicted OS and the observed Kaplan-Meier OS curves (see ERG critical appraisal point 10), this raises the question as to whether an alternative modelling approach (for example the partitioned survival approach adopted previously by Peng *et al*[22]) could have produced more credible estimates of OS. Alternative estimates of health gains estimated using survivor functions fitted to the available OS data are presented in the ERG's exploratory analyses (see Section 5.4).

(2) Issues surrounding use of parametric survival modelling

The ERG has several concerns regarding the parametric survival modelling presented within the CS: (a) only a limited set of survivor functions are considered for PFS; HRs are applied to models which do not assume proportional hazards, and; (c) the hazards of pre-progression mortality and PPS are assumed to be constant.

(a) Limited set of candidate functions considered for progression-free survival

With respect to modelling PFS, the CS[1] considered the exponential, Weibull, log normal and log logistic survivor functions. The ERG considers that other survivor functions, for example, the Gompertz, the generalised gamma, the gamma and the generalised F models should have been considered. In response to a request for clarification from the ERG (see clarification response,[21] question C24), the company explored the use of the Gompertz and generalised gamma functions. Whilst the generalised gamma curve provided the best fit to the observed data in terms of AIC, the company noted that both the generalised gamma and Gompertz survivor functions produced clinically implausible PFS projections. The company's clarification response notes that the generalised F function cannot be fitted using SAS (the statistical package used to undertake the company's survival analysis); this however could have been fitted using an alternative software package (e.g. R).

(b) Application of hazard ratios to accelerated failure time models

Within the company's scenario analyses, the HR for PFS derived from the indirect comparison is applied to the log logistic and log normal PFS functions. This is inappropriate as these are accelerated failure time (AFT) models which do not assume proportional hazards. The company's clarification notes that given the implausibility of these functions, this issue is secondary consideration (see clarification response,[21] question C27). The ERG considers the company's view to be reasonable.

(c) Pre-progression mortality and PPS hazards assumed to be constant

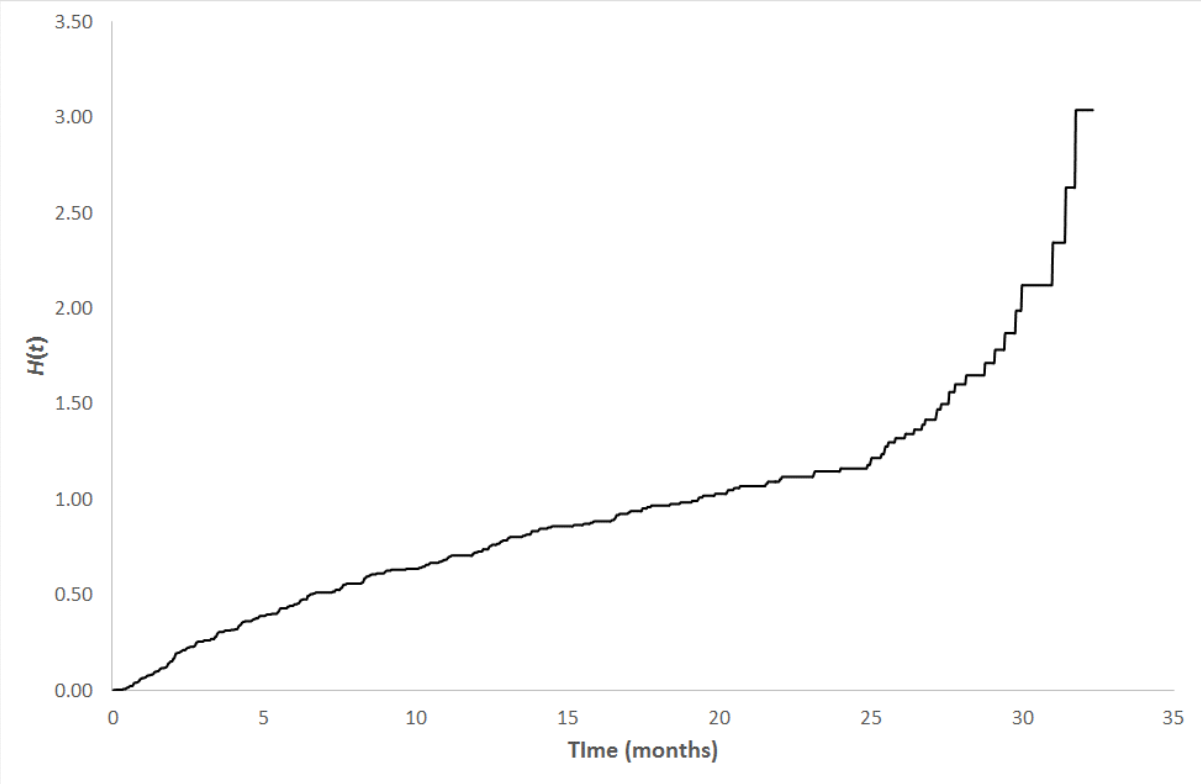
As noted in Section 5.2, the company's model assumes that the hazards of pre-progression mortality and PPS are constant. The original CS did not include any consideration of other survivor functions, although additional analyses of PPS were presented in the company's clarification response (see Figure 23). As noted previously, the model does not allow for the incorporation of time-dependent transitions for PPS, hence it is not possible to explore the impact of alternative survivor functions for PPS in the company's model.

(3) Methods for modelling time to treatment discontinuation (or death)

The ERG has concerns regarding the parametric survival curves fitted to the Kaplan-Meier data for TTD/D. The CS[1] (page 155) states that *"all four curves provide a good fit to the data available."* However, the ERG considers that none of the fitted parametric curves provide a reasonable fit to the observed Kaplan-Meier curve for TTD/D. This is unsurprising given that the hazard of treatment discontinuation or death appears to decrease slightly between 0 and 25 months, and then increases sharply beyond this point (see Figure 24). Within the base case model, the company selected the use of the Weibull function (previously shown in Figure 11). This does not provide a good visual fit to the data and leads to a much longer tail compared with the observed Kaplan-Meier curve: using the Weibull TTD/D function, approximately 7% of patients will still be receiving treatment at 50 months,

whilst the empirical Kaplan-Meier curve indicates that all patients discontinued by around 32 months. The consequence is that the modelled drug costs are overestimated for ibrutinib, thereby inflating the ICER for ibrutinib versus R-chemo.

Figure 24: Cumulative hazard function for time to treatment discontinuation or death (*H*(*t*) = -log *S*(*t*))



In response to a request for clarification (see clarification response,[21] question C23), the company argues that the use of parametric models for TTD/D *"avoids making unjustified model assumptions about long-term discontinuation rates based on the small patient numbers at latter time points still at risk in K-M data"* and states that the observed data beyond 27 months are "unstable" due to small numbers of patients at risk (n<30). Whilst the ERG agrees that the tail of the TTD/D curve is uncertain, the best estimate of the cumulative survival probability for this outcome is that estimated using the observed Kaplan-Meier data directly rather than a parametric model which does not provide a good fit to those data. If censoring is truly random, collecting additional data over a longer follow-up should not produce a systematic shift in the Kaplan-Meier curve in any particular direction. The impact of using the observed Kaplan-Meier curves for TTD/D is presented as part of the ERG's exploratory analyses (see Section 5.4).

(4) Uncertainty surrounding relative effectiveness of ibrutinib versus treatments currently used in clinical practice in England

The ERG considers that irrespective of the approach used to model the relative effectiveness of ibrutinib versus R-chemo, the resulting estimates of incremental health gain will be subject to considerable uncertainty due to the limitations of the evidence base for ibrutinib. In particular, this uncertainty is driven by four main issues: (a) the absence of randomised head-to-head trial comparisons for ibrutinib versus R-chemo (b) the presence of treatment switching within the RAY (MCL3001) trial;[15] (c) immaturity of the available OS data within the pooled ibrutinib dataset,[19] and; (d) the use of other therapies beyond disease progression which are not used in England.

(a) Absence of randomised head-to-head trial comparisons for ibrutinib versus R-chemo

As detailed in Sections 4.3 and 4.4, the relative effectiveness of ibrutinib versus R-chemo was estimated using an indirect comparison. The RAY (MCL3001) study is the only RCT of ibrutinib in R/R MCL. Within this study, ibrutinib was compared with TEM, a treatment which is not used in clinical practice in England. With respect to this issue, the CS notes *"This is uncertainty that we as Janssen can do little about as we could not design an international clinical trial using an unlicensed comparator arm."* Consequently, it was necessary to undertake an indirect comparison using other external evidence.

The ERG considers the following to represent the main limitations of the company's implemented indirect comparison:

- The treatment effect for ibrutinib versus R-chemo, and the associated uncertainty around this estimate, could have been more meaningfully synthesised using a random effects NMA.
- The OPTIMAL trial[8] involved only single-agent chemotherapy, however, all options included in the final NICE scope[11] (except for cytarabine) relate to combination chemotherapy regimens.
- The adjusted HR for PFS which is used to reflect the "rituximab effect" was drawn from the HMRN audit.[7] This analysis does not specifically relate to patients with relapsed/refractory disease, does not differentiate between chemotherapy regimens, and has been estimated only in those patients achieving response (n=108). It is also noteworthy that since this is not a trial, differences in outcomes between patients receiving R-chemo and those receiving chemotherapy alone may be subject to confounding.
- The CS[1] (page 130) states that R-CHOP is perceived to be the most effective chemotherapy option available in the UK. Clinical advisors to the ERG suggested that R-bendamustine is likely to represent the main comparator for ibrutinib, although other R-chemo regimens may be considered. The ERG notes that R-bendamustine is not included in the final NICE scope,[11] nor is it reflected in the company's model. The ERG's clinical advisors noted that outcomes

for R-bendamustine and R-CHOP are likely to be similar. It is also noteworthy that the company's indirect comparison assumes that all R-chemo options are equivalent in terms of efficacy.

- Whilst pre-progression mortality for patients receiving R-chemo is not included as an outcome in the indirect comparison, this is instead assumed to be equal to the rate observed in the TEM arm of the RAY (MCL3001) trial.[15] Given the evidence available, the validity of this assumption is unclear.
- The indirect comparison used in the health economic model is restricted to PFS. The company's clarification response[21] (question C11) states that *"there is no evidence to prove that the use of rituximab has an effect on survival beyond extension of PFS."* However, this is not true. Forstpointner *et al*[14] compared rituximab plus FCM versus FCM alone in the R/R MCL population. This study reported a statistically significant improvement in OS for patients in the rituximab plus FCM group (p=0.0042). The ERG's additional analyses demonstrate that it is possible to estimate OS gains for ibrutinib versus R-chemo within an NMA, however the results are very uncertain due to the quality of evidence (see Section 4.5).

In light of these issues, the ERG notes that any estimate of treatment effect for ibrutinib relative to R-chemo derived from the available evidence base will be subject to considerable uncertainty.

(b) Treatment switching within the RAY (MCL3001) trial

Within the RAY (MCL3001) trial,[15] 22.3% patients who were randomised to the TEM arm subsequently crossed over to the ibrutinib arm following IRC-confirmed disease progression. Consequently, the ITT estimates of OS in the TEM group may be confounded. Whilst this does not impact upon OS outcomes for ibrutinib, it does affect outcomes for TEM which in turn would affect the estimated HR for OS for R-chemo versus ibrutinib derived from an indirect comparison. The ERG sought clarification regarding why a formal analysis of treatment switching was not undertaken (see clarification response,[21] question C20). The company's response includes a preliminary examination of three potential approaches to handling confounding due to treatment switching suggested in NICE Technical Support Document 16.[68] The company's response notes that the Inverse Probability of Censoring Weights (IPCW) method is not appropriate as the relevant time-dependent variables were not consistently captured throughout the RAY (MCL3001) trial,[15] and insufficient information was available to estimate the weights and to deal with censoring-related selection bias. The company's clarification response also argues that the 2-stage method is also not appropriate because, on average, a large amount of time passed between patients' progression and treatment switching. The company's clarification response does however include two analyses which attempt to address the potential confounding caused by treatment switching: (i) a "censor at switch" analysis mentioned but not fully reported in the original CS, and; (ii) a rank preserving structural failure time (RPSFT) analysis applied

to the RAY (MCL3001) trial. The ERG notes that censoring at the point of treatment switching may produce a selection bias because switching is likely to be associated with prognosis; this is therefore an inherent weakness in the analysis. The company's clarification response also notes that RPSFT method requires an assumption of a "common treatment effect", the validity of which cannot be empirically tested. In addition, OS estimates in both groups may be affected by the use of other subsequent-line treatments which are not used in clinical practice in England. Whilst both approaches suffer from potential biases, there is value in examining the results of these analyses (see Table 54).

Table 54: Overall survival estimates from RAY (MCL3001) including adjustment for treatment switching in the TEM group

Analytic approach	HR (95% CI)
ITT analysis	0.74 (0.50 to 1.09)
Censor at switch	0.76 (0.53 to 1.10)
RPSFT	0.76 (0.53 to 1.09)

ITT - intention to treat; CI - confidence interval; RPSFT - rank preserving structural failure time

As shown in Table 54, all analyses report very similar HRs and similar 95% CIs. This suggests that, on the basis of the currently available evidence from RAY (MCL3001),[15] switching in the TEM group has not produced significant confounding of OS outcomes. The ERG considers that this analysis should be repeated following the final datacut of the RAY (MCL3001) trial[15] (due in the first quarter of 2017).

(c) Immaturity of the available OS data within the pooled ibrutinib dataset

The CS[1] (page 132) notes that median OS was only just reached in the pooled ibrutinib dataset.[19] In addition, the number of patients at risk by 2.5 years follow-up is very small. As such, the available OS data are immature. The ERG notes that the modelling approach adopted cannot reduce this uncertainty; rather, a central of objective of the model analysis should be the faithful representation of that uncertainty. Whilst a key uncertainty in the evidence base relates the incremental survival gains for ibrutinib versus R-chemo, the company's model structure (which does not use OS as an input) does not allow for any exploration of this uncertainty.

(d) Use of other therapies following disease progression which are not used in the UK

Table 11 summarises the use of antineoplastic therapies used in the three ibrutinib studies; approximately 30% of patients in the pooled ibrutinib dataset received further antineoplastic therapy following disease progression. The company's clarification response[21] (question B19) notes that these therapies may have impacted on OS estimates and many of these treatments would not be used in the clinical practice in England. The ERG considers this to be a matter of external validity. The ERG notes that this is not accounted for in the company's model its impact on OS is unclear.

(5) Exclusion of costs of subsequent therapies beyond progression

The company's base case model does not include the costs of subsequent-line therapies in either group. Clinical advisors to the ERG noted that patients who fail R-chemo or ibrutinib are likely to subsequently receive further treatment using a different chemotherapy regimen (in combination with rituximab if not refractory). Given that no adjustment has been made to account for the survival contribution of post-progression therapies to PPS, the ERG considers that the costs of these subsequent-line therapies should have been included in the company's base case model. The ERG notes that a scenario analysis is presented in which FCR is included as subsequent-line therapy for both model groups. In this scenario, the ICER is slightly reduced to £73,628 per QALY gained (see Table 48).

(6) Concerns regarding the company's implementation of the "sequential" model

The CS[1] includes a scenario which compares ibrutinib followed on progression by R-chemo versus R-chemo alone, based on the argument that ibrutinib provides an additional line of therapy which would otherwise not be available. The ERG has several concerns regarding the validity of the company's sequential model:

- The R-chemo "PFS2" curve applied to reflect subsequent-line therapy in the ibrutinib sequence is based on the same Kaplan-Meier curve used to reflect PFS1 for the R-chemo comparator group, albeit based on a different parametric function fitted to the observed data (exponential rather than Weibull). Clinical advisors to the ERG suggested that the duration of PFS would decrease with each additional prior line of therapy. If PFS for subsequent line R-chemo is less favourable than that used in the comparator group (without prior ibrutinib), the company's model will over-estimate the health gains for the ibrutinib sequence group. Whilst not explicitly stated in the CS,[1] the ERG considers that the use of an exponential distribution to model the R-chemo PFS2 period for the ibrutinib sequence was presumably driven by the inability of the company's model to reflect time-variant hazard transition probabilities out of intermediate health states.
- The costs of subsequent-line R-chemo in the ibrutinib sequence group are not modelled in the same way as those for the comparator therapy group. In the comparator group, R-chemo costs are modelled on a per-cycle basis taking into account the modelled TTD/D curve and the maximum treatment duration (6 cycles). In the ibrutinib sequence group, the costs of subsequent-line R-chemo are modelled as a single once-only cost applied to all patients who survive their first progression event. This is likely to marginally overestimate subsequent-line treatment costs in the ibrutinib sequence.
- Mean survival and mean QALY gains in the R-chemo comparator group generated using the sequential model are reduced compared with those estimated in the base case analysis (see Table 55). The ERG considers this to be counter-intuitive: the costs and outcomes for the

comparator therapy should be unaffected by alternative assumptions made regarding the intervention group.

- The disutility associated with R-chemo is applied to the subsequent-line therapy in the sequential model, but is based on a different calculation which has been implemented incorrectly. Within the sequential model, health utility for PFS2 is calculated as:

(Health state population at time t x ((utility PFS) x (cycle duration – R-chemo QALY loss)) x age utility adjustment) [iv]

This is incorrect as the R-chemo health loss is already defined in terms of QALYs lost per 4-week cycle. In addition, the ERG identified a further error in this calculation, whereby the =VLOOKUP() function used to determine the age-adjusted utility multiplier in the model refers to the column containing cumulative survival probabilities (column F) rather than the current age of the cohort (column E). Rectifying these errors reduces the modelled QALY gain for the sequence compared with the company's reported estimate and produces an estimated ICER for ibrutinib followed by R-chemo versus R-chemo of £79,214 per QALY gained. The ERG also notes that the corrected QALY gains for the ibrutinib sequence are lower than those estimated for the ibrutinib group in the company's base case; this again seems somewhat counter-intuitive.

Table 55: Comparison of results generated using the company's base case model and sequential model (scenario analysis)

Base case analysis[21] (excluding post-progression treatment)							
Option	**LYGs**	**QALYs**	**Costs**	**Inc. LYGs**	**Inc. QALYs**	**Inc. costs**	**ICER (per QALY)**
Ibrutinib	[redacted]	[redacted]	[redacted]	1.23	0.94	£70,522	**£75,317**
R-CHOP	[redacted]	[redacted]	[redacted]	-	-	-	-
Company's sequential model (scenario analysis, including errors)[21]							
Option	**LYGs**	**QALYs**	**Costs**	**Inc. LYGs**	**Inc. QALYs**	**Inc. costs**	**ICER (per QALY)**
Ibrutinib	[redacted]	[redacted]	[redacted]	1.43	1.08	£82,751	**£76,671**
R-CHOP	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG corrected sequential model (scenario analysis, errors corrected)							
Option	**LYGs**	**QALYs**	**Costs**	**Inc. LYGs**	**Inc. QALYs**	**Inc. costs**	**ICER (per QALY)**
Ibrutinib	[redacted]	[redacted]	[redacted]	1.43	1.04	£82,751	**£79,214**
R-CHOP	[redacted]	[redacted]	[redacted]		-	-	-

LYGs - life years gained; QALYs – quality-adjusted life years; ICER - incremental cost-effectiveness ratio; R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

Notwithstanding the errors detailed above, given the basis of the strong assumptions and structural constraints applied in the sequential model, the ERG considers that the results of this analysis should be disregarded.

(7) Inappropriate use of blended comparison of R-chemo options

The company's scenario analyses (see clarification response,[21] Table 17) include the use of a blended comparison of three alternative R-chemo options. Within this analysis, the proportionate use of each therapy is assumed to be R-CHOP (85%), R-CVP (10%), and FCR (5%). Whilst RC is reported to be part of the blend, this is assigned a weight of 0%, hence it is not actually included. Owing to the dearth of comparative evidence for each of the options, the CS assumes that each R-chemo regimen is equivalent in terms of efficacy, however the costs of each regimen differs. The ERG considers the use of blended comparisons to be inappropriate as they may lead to misleading conclusions on the cost-effectiveness of ibrutinib in the R/R MCL population. If all R-chemo options are indeed equally effective, the most efficient choice would involve using the least expensive regimen that can be tolerated by the patient. This can be simply demonstrated within a fully incremental analysis (see Table 56). Given the assumption of equivalent efficacy between the R-chemo options, this would lead R-CVP to dominate R-CHOP and FCR. Based on the company's model, the ICER for ibrutinib versus R-CVP is £76,732 per QALY gained.

Table 56: Fully incremental analysis of ibrutinib, R-CHOP, R-CVP and FCR

Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
Ibrutinib	[redacted]	[redacted]	0.94	£71,847	£76,732
R-CVP	[redacted]	[redacted]	-	-	-
R-CHOP	[redacted]	[redacted]	-	-	Dominated
RC	[redacted]	[redacted]	-	-	Dominated
FCR	[redacted]	[redacted]	-	-	Dominated

QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; R-CVP - rituximab, cyclophosphamide, vincristine and prednisolone; R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; RC - rituximab, cytarabine; R-FC - fludarabine, cyclophosphamide, rituximab

(8) Questionable approach to modelling HRQoL

The company's model assumes that HRQoL is differentiated according to the presence/absence of disease progression (utility progression-free=0.78; utility post-progression=0.68), with an additional disutility applied to patients receiving R-chemo (utility decrement=0.20, equivalent to a QALY loss of 0.015 per 4-week cycle). The progression-free utility estimates were based on an analysis of EQ-5D-5L data collected within the RAY (MCL3001) and SPARK (MCL2001) studies.[15, 33] The disutility for R-chemo was based on expert clinical opinion.[1] The ERG has several concerns regarding the reliability of these HRQoL estimates: (a) the disutility for R-chemo is not a preference-based disutility; (b) the R-chemo disutility is applied to the entire TTD/D curve; (c) the company's review of HRQoL evidence does not consider alternative estimates from non-MCL populations.

(a) Derivation of the disutility for R-chemo

The disutility associated with R-chemo reflects clinicians' judgements which have not been derived using a preference-based method. This is parameterised in the model as a QALY loss per 4-week cycle without age-adjustment. The CS includes a sensitivity analysis in which the QALY decrement is

calculated by subtracting the EQ-5D VAS valuation reported in a previous study of progressed patients with CLL and MCL by Schenkel *et al*,[63] (VAS estimate=0.61) from the progression-free utility of 0.78 derived from the RAY (MCL3001) and SPARK (MCL2001) studies. This results in a slightly lower QALY loss of 0.013 per 4-week period. However, the quality of life estimate reported by Schenkel *et al*[63] relates to a mixed population of patients (52 of 75 patients had CLL rather than MCL) and the EQ-5D VAS does not estimate utility as it is not a preference-based instrument.

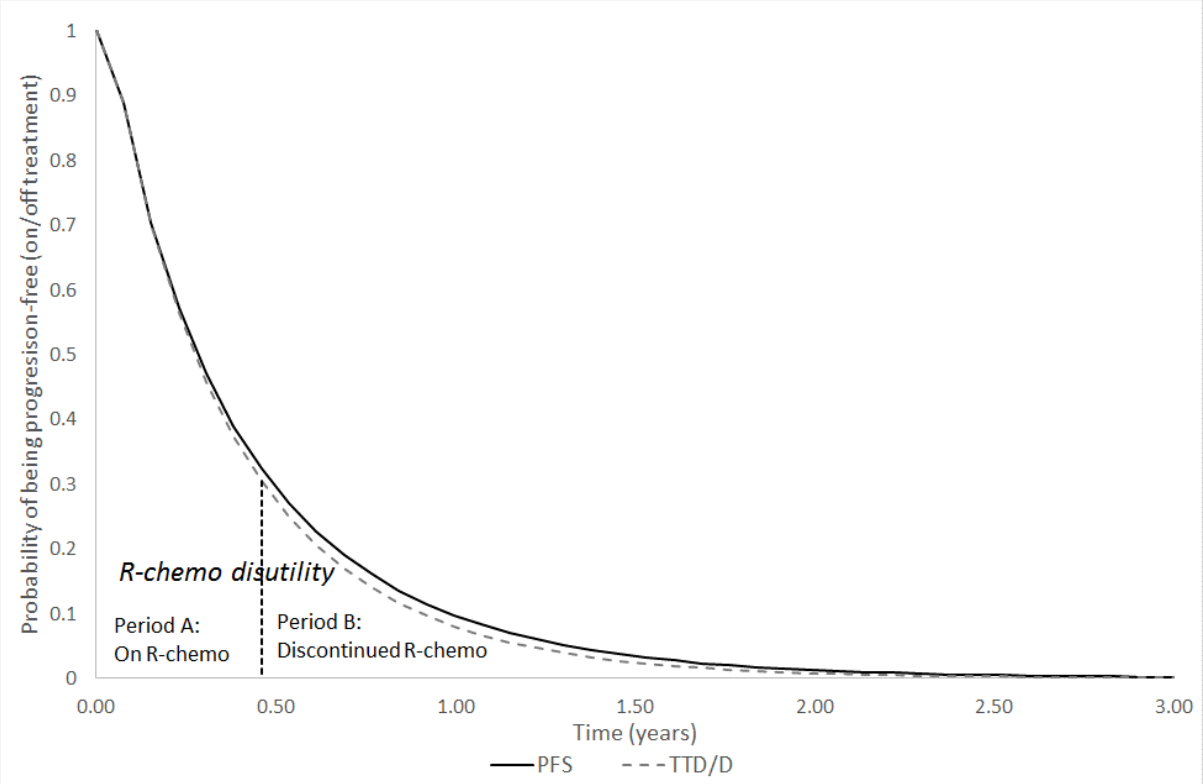
(b) Uncertainty surrounding progression-free and post-progression utility values

The company's model assumes that patients who are progression-free and on R-chemo experience a lower level of HRQoL compared with patients who are progression-free and on ibrutinib as a consequence of avoiding chemotherapy-related toxicity and fatigue. Consequently, modelled patients in the R-chemo group experience a lower level of HRQoL whilst progression-free (utility=0.58 [0.78 minus 0.20]) compared with patients who have experienced disease progression and have discontinued treatment (utility=0.68). The ERG notes that only 36 patients contributed data to the post-progression utility value (compared with 234 patients who contributed data to the progression-free utility value). This utility associated with progressed disease is therefore very uncertain.

(c) R-chemo disutility applied to entire TTD/D curve

The disutility for the R-chemo group is applied to the entire duration of the TTD/D curve. As shown in Figure 25, patients are assumed to receive chemo for a maximum of 6 cycles ("Period A"), however the disutility is also applied throughout "Period B." Whilst the clinical advisors to the ERG stated that the effects of toxicity may persist beyond treatment cessation (one suggested 6-12 months whilst the other suggested approximately 3 months), the ERG notes beyond 6 cycles the TTD/D curve for the R-chemo is essentially arbitrary as it does not reflect time to progression nor does it reflect time on treatment since all patients have discontinued R-chemo before this timepoint.

Figure 25: Time to treatment discontinuation/death and application of R-chemo disutility



R-chemo - rituximab and chemotherapy; PFS - progression-free survival; TTD/D - time to treatment discontinuation or death

In response to a request for clarification from the ERG (see clarification response,[21] question C2), the company stated: *"The model assumes that all patients QoL will return to normal immediately upon ending R-chemo treatment (either on or prior to progression), resulting in an increase in utility for R-chemo patients who will no longer be suffering the associated side effects of chemotherapy."* This is not true. The ERG notes however that the assumed disutility duration does not have a material impact upon the ICER for ibrutinib versus R-chemo (see Section 5.4, ERG Exploratory Analysis 2).

(d) Company's review of HRQoL evidence limited to R/R MCL population only

Owing to the uncertainty surrounding the available HRQoL estimates detailed above, the ERG considers that it may have been prudent to explore the use of utility estimates elicited from patients with other types of lymphoma. Table 57 summarises the utility values applied in the published economic analyses included in the company's review (obtained through personal communication with the corresponding author for each study).

Table 57: Summary of utility values applied in published models of R/R MCL

Study	Progression-free utility	Post-progression utility	Source
Yoong *et al*[50]	0.81 (0.60 whilst receiving chemotherapy)	0.60	Doordujin *et al*[69] (NHL, EQ-5D)
LaChaine *et al*[49]	0.805	0.618	Wild *et al*[70] (follicular lymphoma, EQ-5D)
Peng *et al*[22]	Baseline: 0.777 Utility during PFS -- Week 0-8: 0.777 -- Week 9-88: 0.836 -- Week 89+: 0.878	Utility decrement of -12.8% from baseline	QLQ-C30 data in PCYC1104 mapped to EQ-5D for progression-free utilities Post-progression disutility based on Beusterien *et al*[71] (CLL, standard gamble)

NHL - Non-Hodgkin's Lymphoma; CLL - chronic lymphocytic leukaemia

The ERG notes that within their clarification response[21] (question C2), the company provided further analyses around health utility values. Within these analyses, alternative utility values of 0.45 to 0.636 were assumed for the post-progression state. It should however be borne in mind that these ICERs retain the progression-free utility value of 0.68 and the R-chemo QALY loss of 0.015 per cycle. These additional analyses indicate that the utility value applied in the progression state does not materially impact upon the ICER for ibrutinib versus R-chemo (including the PAS, assuming post-progression utility scores of 0.45 and 0.636 results in estimated ICERs for ibrutinib versus R-chemo of £73,865 and £75,035 per QALY gained, respectively).

As noted within the CS and the company's clarification response,[21] the company makes an argument that the EQ-5D does not fully capture the quality of life impact of varying severity of fatigue or important quality of life improvement through reduction in fatigue and increased energy (see clarification response,[21] question C1). With reference to this issue, the clinical advisors to the ERG expressed some disappointment with respect to the limited benefit in EQ-5D observed within the RAY (MCL3001) trial[15] and noted that the mean change from baseline EQ-5D scores for patients receiving ibrutinib did not reflect their experience of using the drug. Whilst the ERG acknowledges that there may be a disconnect between the EQ-5D-5L evidence from RAY (MCL3001) and clinical experience using ibrutinib, the ERG is aware of no other evidence of the benefits of ibrutinib using a preference-based measure of HRQoL in the R/R MCL population. The company's clarification response mentions a prospective longitudinal study in which a number of preference-weighted instruments are being considered for data collection alongside the EQ-5D-5L; these include the FACT-Lym with utility scored from Functional Assessment of Cancer Therapy - General (FACT-G) items,[72] the European Organisation for Research and Treatment of Cancer 8 Dimensions (EORTC-8D) scored from the European Organisation for Research and Treatment of Cancer quality of life

questionnaire[73] (EORTC QLQ-C30) and the Short Form 6-Dimensions (SF-6D) scored from the Short-Form 36 (SF-36).[74] However, company's clarification response notes that the protocol for the study has not yet been finalised and the utility instrument has not yet been decided upon.

Whilst the company's approach to modelling HRQoL may be questioned, the ERG considers that these are driven largely by the limitations in the available evidence base.

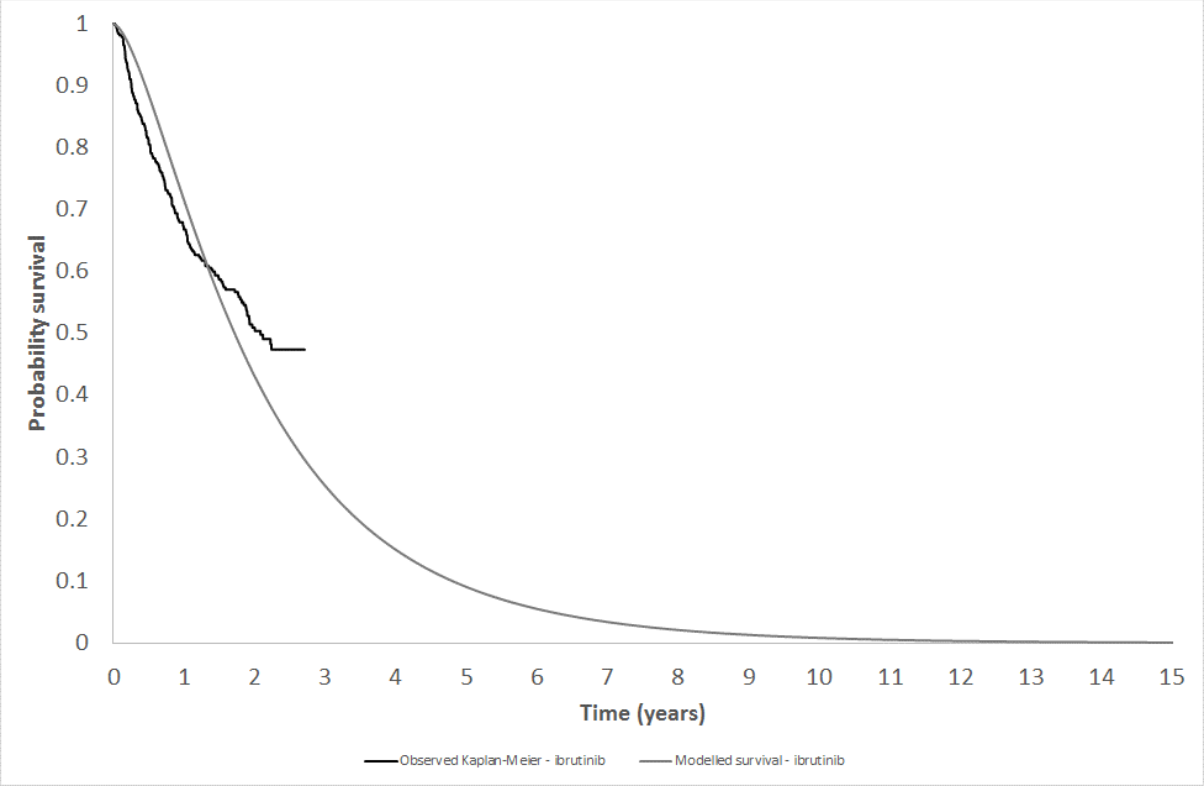
(9) Ibrutinib treatment not constrained to progression-free period within the PSA

The SmPC for ibrutinib states that treatment with ibrutinib should continue until disease progression or no longer tolerated by the patient.[17] Whilst this condition is met within the deterministic version of the company's model, this is not the case for the company's probabilistic model. A re-run of the PSA undertaken by the ERG indicated that 69.1% of the probabilistic model iterations included at least one timepoint in which TTD/D>PFS. The ERG considers that it would have been more appropriate to constrain the sampled TTD/D curve to be less than or equal to the sampled PFS curve.

(10) Discrepancy between observed and predicted OS

Figure 26 presents a comparison of the company's predicted OS and the observed Kaplan-Meier OS curve derived from the pooled ibrutinib dataset.[19] The company's model-predicted OS does not appear to provide a good visual fit to the observed Kaplan-Meier OS curve. Specifically, the model over-estimates OS up to around 15.6 months (1.3 years) and subsequently under-predicts OS beyond this timepoint. This suggests that the survival gain in the ibrutinib group is likely to be underestimated. The ERG considers that this discrepancy it is likely to be a consequence of one or more of the following issues previously discussed: (i) inappropriate assumptions concerning the nature of the pre-progression mortality hazard; (ii) the imperfect projection of PFS; (iii) poor model fit for PPS, and/or; (v) selection bias in the PPS dataset. As such, the ERG has some concerns with respect to the credibility of the company's model results. This issue is explored within the ERG's exploratory analyses (see Section 5.4).

Figure 26: Comparison of observed and predicted overall survival for ibrutinib group



(11) Uncertainty surrounding company's subgroup analyses and risk of confounding

The ERG notes that the company's analysis according to the number of prior LOTs received by patients reflects a *post hoc* defined subgroup. Whilst the ibrutinib studies each included pre-specified subgroups according to previous therapies received (RAY (MCL3001) LOT≤2, >2; SPARK (MCL2001) LOT≤2, >2; PCYC1104 ≤2 previous regimens or >2 regimens), the company's economic analysis is defined according to a different threshold for prior LOTs received (LOT=1, LOTs≥2). In response to a request for clarification from the ERG, the company stated that they did not undertake a test for treatment by subgroup interaction within the RAY (MCL3001) trial. Similarly, no interaction test is presented for the pooled ibrutinib dataset in the CS.[1] Table 58 presents the numbers of patients from each of the ibrutinib studies who contributed data to each LOT subgroup. As can be seen in the table, the LOT=1 subgroup is comprised of only 99 patients (26.8% of the total pooled dataset). The ERG also notes that none of the parametric models fitted to the LOT=1 PFS subgroup data provide a good visual fit (see Figure 13).

Table 58: Contribution of data from individual studies and pooled dataset to LOT subgroup analyses

Population / subgroup	RAY (MCL3001)[15]	SPARK (MCL2001)[33]	PCYC1104[43]	Pooled ibrutinib dataset[19]
Full population	139	120	111	370
1 prior LOT	57	20	22	99
2+ prior LOTs	82	100	89	271

LOT - line of therapy

Consequently, the ERG considers that any estimates of relative effectiveness or cost-effectiveness should be treated with some caution.

5.4 Exploratory analyses undertaken by the ERG

This section presents the methods and results of the exploratory analyses undertaken by the ERG. Owing to concerns relating to the company's model structure outlined in Section 5.3, the ERG undertook two sets of exploratory analyses. "Analysis Set A" was undertaken using the company's submitted model. "Analysis Set B" was undertaken by restructuring the company's model to use OS as an input. All analyses are presented for the comparison of ibrutinib versus R-CHOP and include the PAS for ibrutinib. The results for all analyses using 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.

Exploratory Analysis Set A - methods

The ERG undertook the following analyses using the company's submitted model (following the correction of the error identified by the company during the clarification process). Additional details on the implementation of the analyses are presented in Appendix 3.

Exploratory Analysis A1. HR for PFS derived from ERG'S random effects NMA

The ERG's random effects NMA (see Section 4.5) produced a slightly different estimate of the HR for PFS for ibrutinib versus R-CHOP compared with the company's 2-stage indirect comparison (company's HR=0.28; ERG's HR=0.27). Within this analysis, the HR for PFS derived from the ERG's random effects NMA was applied to the company's model.

Exploratory Analysis A2. TTD/D for ibrutinib group based on Kaplan-Meier curve

The ERG has concerns that the company's use of a parametric (Weibull) curve to model the probability of remaining alive and on treatment does not provide a good fit to the observed data and appears to overestimate treatment costs for ibrutinib. Within this analysis, the probability of being alive and on treatment was modelled using the Kaplan-Meier survival curve for TTD/D directly.

Exploratory Analysis A3. Truncation of R-chemo disutility following treatment discontinuation

The company's model applies the R-chemo disutility of 0.20 to the entire duration of the TTD/D curve. However, the company's clarification response states that that patients' HRQoL will return to normal immediately upon discontinuing R-chemo treatment.[21] Consequently, the company's intended assumption about the duration of this disutility is unclear; the ERG considers that an assumption that HRQoL returns to normal upon discontinuation would be more reasonable. This analysis therefore

applies the disutility for R-chemo only whilst patients are receiving treatment (6 cycles); beyond this point, no QALY loss is incurred.

Exploratory Analysis A4. ERG's preferred analysis using the company's model

This analysis combines Exploratory Analysis A1 (HR derived from the ERG's random effects NMA), Exploratory Analysis A2 (TTD/D based on Kaplan-Meier curve) and Exploratory Analysis A3 (R-chemo disutility truncated upon discontinuation). This analysis is presented for both the deterministic and probabilistic version of the model.

Exploratory Analysis A5. Use of alternative utility values for progression-free and post-progression states

The analysis of alternative HRQoL values within the CS is limited to the EQ-5D-5L data from RAY (MCL3001)[15] and SPARK (MCL2001)[33] within the base case, and a further scenario analysis in which the disutility for R-chemo is estimated as the difference between the utility for the progression-free state and the progressed VAS score reported by Schenkel *et al*.[63] This exploratory analysis includes the application of utility values used in the previous economic evaluation reported by Lachaine *et al*[49] (progression-free utility=0.805; post-progression utility=0.618) and Yoong *et al*[50] (progression-free utility=0.81; post-progression utility=0.60). Insufficient information was available to allow for an analysis using the utility values applied in the Peng *et al* study.[22] This analysis is based on the ERG's preferred base case model (Exploratory Analysis A4, detailed above).

Exploratory Analysis A6. Cost-effectiveness of ibrutinib versus chemotherapy for rituximab-resistant patients

The company's base case analysis compared ibrutinib versus R-CHOP. Scenario analyses are presented for alternative comparators of FCR, R-CVP and RC. However, some patients may be resistant to rituximab; these patients may receive chemotherapy without further rituximab. Whilst the evidence to support this comparison is severely lacking, two exploratory analyses are presented: (i) the cost of rituximab is set to zero, and; (ii) the cost of rituximab is set to zero and the HR for PFS is set equal to 0.19 (the rituximab effect is removed from the indirect comparison). The ERG notes that the first of these analyses is problematic in that it ignores the relative benefit of adding rituximab to chemotherapy, whilst the second analysis does not account for the fact that patients do not typically receive single-agent chemotherapy. This analysis is based on the ERG's preferred base case analysis (Exploratory Analysis A4, detailed above).

Exploratory Analysis A7: Ibrutinib versus R-CHOP in the 1 prior LOT subgroup using the ERG's preferred analysis

This analysis applies the assumptions from Exploratory Analysis A4 (HR derived from the ERG's random effects NMA, TTD/D based on Kaplan-Meier curve and R-chemo disutility truncated upon

discontinuation) to the 1 prior LOT subgroup. As noted in Section 5.3, this reflects a *post hoc* analysis and the company's PFS model fit is poor.

Exploratory Analysis Set B - methods

Owing to the ERG's concerns regarding the assumptions and restrictions inherent in the use of a Markov approach based on PFS and PPS, the ERG explored the impact of using a partitioned survival approach to evaluate the cost-effectiveness of ibrutinib versus R-chemo based on the available OS data for ibrutinib from the pooled dataset[19] and the HRs for PFS and OS derived from the ERG's NMAs (see Section 4.5). Given that the company's model calculates a Markov trace for the progression-free and post-progression states in both groups over time, and that all subsequent estimates of costs and QALYs are based on this trace, it was possible to apply the partitioned survival model methodology directly within the company's existing model structure. The other elements of the company's model were unchanged.

Survival modelling methods and results

Aggregate OS Kaplan-Meier data from the pooled ibrutinib dataset[19] are contained but not directly used in the company's model. These were used to replicate the underlying patient-level time-to-event data for OS using the methods reported by Guyot *et al*.[75] Parametric survival models were then fitted to these data using the flexsurv package in R. Model discrimination was undertaken by exploring the goodness-of-fit of each survivor function based on the AIC and BIC and through consideration of clinical plausibility of the extrapolation in the unobserved period. Eight survivor functions were fitted to the data: (i) generalised gamma; (ii) generalised F; (iii) gamma; (iv) log logistic; (v) log normal; (vi) Gompertz; (vii) Weibull, and; (viii) exponential.

Figure 27 presents a comparison of the fitted parametric survivor functions and the observed Kaplan-Meier OS curves. Table 59 presents the AIC and BIC statistics for each parametric survivor function (the lowest values are highlighted in bold). Table 60 presents the 15-year restricted mean survival estimate for each function; these values reflect the area under the curve (AUC) up to the 15 year timepoint (the time horizon of the company's model).

Figure 27: Observed and predicted overall survival

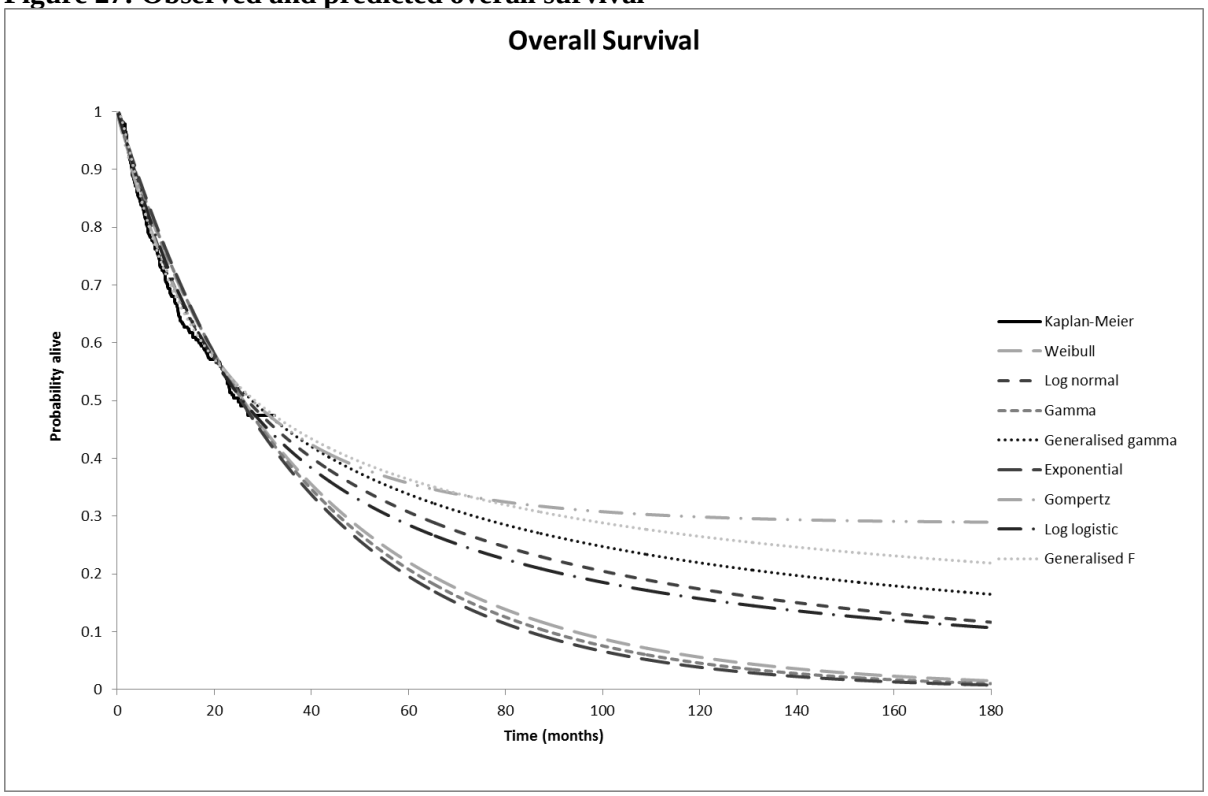


Table 59: Goodness-of-fit – ERG curves fitted to the ibrutinib overall survival data

Parametric function	AIC	BIC
Generalised gamma	1473.1	1484.8
Gamma	1486.6	1494.4
Log normal	**1472.3**	**1480.1**
Weibull	1486.0	1493.8
Exponential	1485.0	1488.9
Gompertz	1479.9	1487.7
Log logistic	1478.8	1486.6
Generalised F	1474.6	1490.2

AIC - Akaike information criterion; BIC - Bayesian information criterion

Table 60: Predicted mean OS for ibrutinib (with and without constraints applied to ensure the mortality hazard remains greater than for the general population)

Survivor function	Constrained	Unconstrained
Generalised gamma*	4.97	4.98
Gamma	3.14	3.14
Log normal*	4.49	4.49
Weibull	3.26	3.26
Exponential	3.04	3.04
Gompertz*	5.56	5.76
Log logistic*	4.27	4.27
Generalise F	5.42	5.45

** Mortality hazard in these parametric functions were constrained to be equal to the general population mortality for at least one day*

On the basis of the AIC and BIC statistics, the log normal function appears to provide the best fit to the observed data. However it is also important to consider the plausibility of survival projection beyond the observed period. As shown in Figure 27, the generalised gamma, generalised F, log logistic, log normal and Gompertz models predict that over 10% of patients receiving ibrutinib would be alive 15 years after treatment. Given that MCL is incurable, the ERG considered these curves to be clinically implausible. The exponential, Weibull and gamma models appear to provide broadly similar projections of OS; the 15-year restricted mean predicted OS for the exponential, Weibull and gamma models are 3.04, 3.26 and 3.14 years, respectively. These estimates are consistently higher than those predicted by the company's model. The ERG notes that based on these models, the hazard of death remains consistently greater than that for the general population (see Table 60). Given that the projections are similar, the ERG selected the exponential model for use in the exploratory analysis on the basis of parsimony. Clinical advisors to the ERG noted considerable uncertainty surrounding the survival extrapolation for ibrutinib.

Application of fitted OS curves within the company's health economic model

In order to incorporate the OS data into the company's model, the following amendments were necessary:

- The probability of being in the dead state at each time *t* was amended to reflect the cumulative probability of death using the OS curves
- The probability of being in the post-progression state was amended to reflect the difference between the cumulative survival probabilities for OS and PFS at each timepoint *t*
- An HR for OS for ibrutinib versus R-chemo was applied to the R-chemo group.
- Logical consistency constraints were applied to ensure that: (i) the probability of death estimated from the OS curve could not be less than that for the general population at the modelled cohort age; (ii) the PFS curve was consistently below the OS curve, and; the TTD/D curve was below the PFS curve.

Analyses undertaken using the partitioned survival model

Exploratory Analysis B1. Cost-effectiveness results using ERG's NMAs for OS

Analyses were undertaken using ERG's Exploratory Analysis 4 as a starting point (ERG's NMA for PFS, Kaplan-Meier curves for TTD/D and truncation of QALY loss after discontinuation of R-chemo). Separate analyses are presented to explore the impact deriving the HR for OS from the following analyses:

(a) NMA in which the rituximab effect is estimated using data reported by Forstpointner *et al*[14]
(b) NMA in which the rituximab effect is estimated using data from the HMRN audit[7]
(c) NMA in which the rituximab effect is estimated using data reported by Forstpointner *et al*[14] and the HMRN audit[7]

Exploratory Analysis B2. Threshold analysis around hazard ratio for OS

In addition, a threshold analysis was undertaken to explore the HR necessary in order for the ICER for ibrutinib versus R-CHOP to be below £50,000 per QALY gained.

Additional threshold analyses in the 1 prior LOT subgroup were not undertaken using this amended version of the model.

Exploratory analysis results

Exploratory Analysis Set A – results

Exploratory Analysis A1. HR for PFS derived from ERG'S random effects NMA

Table 61 presents the results of the analysis in which the HR for PFS was derived from the ERG's random effects NMA. As expected, the use of a slightly improved treatment effect for PFS (HR=0.27 versus 0.28) has only a marginal impact on the cost-effectiveness of ibrutinib versus R-CHOP (ICER=£75,094 per QALY gained). It should be noted that the additional uncertainty reflected in the random effects NMA is not captured within this deterministic analysis but is captured in ERG Exploratory Analysis 4.

Table 61: Exploratory Analysis A1 - HR for PFS derived from ERG's random effects NMA

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Ibrutinib	[redacted]	[redacted]	0.94	£70,619	**£75,094**
R-CHOP	[redacted]	[redacted]	-	-	-

QALY - quality-adjusted life year; R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

Exploratory Analysis A2. TTD/D for ibrutinib group based on Kaplan-Meier curve

Table 62 presents the results of the analysis in which the probability of being alive and on treatment for the ibrutinib is group based on the observed Kaplan-Meier curve rather than the Weibull model. Within this analysis, only the costs for the ibrutinib group are affected; compared with the company's base case analysis, the costs of ibrutinib are reduced by [redacted] per patient. Consequently, the ICER for ibrutinib versus R-chemo is estimated to be £61,472 per QALY gained.

Table 62: Exploratory Analysis A2 - TTD/D for ibrutinib group based on Kaplan-Meier curve

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Ibrutinib	[redacted]	[redacted]	0.94	£57,558	**£61,472**
R-CHOP	[redacted]	[redacted]	-	-	-

QALY – quality-adjusted life year; R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

Exploratory Analysis A3. Truncation of R-chemo QALY loss following treatment discontinuation

Table 63 presents the results of the analysis in which the QALY loss for R-chemo is restricted to the 6 cycles during which patients are receiving R-chemo. As shown in the table, truncating the duration over which the R-chemo QALY loss is applied has only a minor impact on the cost-effectiveness of ibrutinib. Within this analysis, the ICER for ibrutinib versus R-chemo is increased to £77,111 per QALY gained.

Table 63: Exploratory analysis A3 - Truncation of R-chemo disutility following treatment discontinuation

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Ibrutinib	[redacted]	[redacted]	0.91	£70,522	**£77,111**
R-CHOP	[redacted]	[redacted]	-	-	-

QALY - quality-adjusted life year; R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

Exploratory Analysis A4. ERG's preferred analysis using the company's model

Table 64 presents the results of the ERG's preferred analysis using the company's model. As shown in the table, the combination of the HR derived from the ERG's random effects NMA, the use of the TTD/D Kaplan-Meier curve and the truncation of the QALY loss after discontinuation results in a probabilistic ICER for ibrutinib versus R-chemo of £63,340 per QALY gained.

Table 64: Exploratory analysis A4 - ERG's preferred analysis using the company's model

Probabilistic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	0.92	£58,183	**£63,340**
R-CHOP	[redacted]	[redacted]	-	-	-
Deterministic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	0.92	£57,656	**£62,697**
R-CHOP	[redacted]	[redacted]	-	-	-

QALY - quality-adjusted life year; R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

Exploratory Analysis A5. Use of alternative utility values for progression-free and post-progression states (using ERG's preferred base case)

Table 65 presents the results of the analyses in which alternative utility values sourced from the literature[49, 50] are applied in the company's model. The application of the utility values used by Lachaine *et al* (progression-free=0.805; post-progression=0.618) results in an ICER for ibrutinib versus R-CHOP of £60,417 per QALY gained. Unsurprisingly, the application of the utility values used by Yoong *et al*[50] (progression-free utility=0.81; post-progression utility=0.60) produce very similar results; within this analysis, the ICER for ibrutinib versus R-CHOP is estimated to be £59,952 per QALY gained.

Table 65: Exploratory analysis A5 – Use of alternative utility values for progression-free and post-progression states

(i) Utilities for progression-free and post-progression based on Lachaine *et al*[49]					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	0.95	£57,656	**£60,417**
R-CHOP	[redacted]	[redacted]	-	-	-
(ii) Utilities for progression-free and post-progression based on Yoong *et al*[50]					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	0.96	£57,656	**£59,952**
R-CHOP	[redacted]	[redacted]	-	-	-

QALY - quality-adjusted life year; R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

Exploratory Analysis A6. Cost-effectiveness of ibrutinib versus chemotherapy for rituximab-resistant patients

Table 66 presents the results of the analyses comparing ibrutinib versus chemotherapy alone (excluding rituximab). Removing the costs but retaining the benefits of rituximab result in an ICER for ibrutinib versus chemotherapy of £69,054 per QALY gained. Improving the HR for ibrutinib versus chemotherapy to 0.19 results in an ICER of £64,727 per QALY gained. The ERG notes that given the limitations of the evidence base, these exploratory analyses should be interpreted with caution.

Table 66: Exploratory analysis A6 – Cost-effectiveness of ibrutinib versus chemotherapy for rituximab-resistant patients

(i) Cost of rituximab set to zero					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	0.92	£63,501	**£69,054**
R-CHOP	[redacted]	[redacted]	-	-	-
(ii) Cost of rituximab set to zero and PFS HR=0.19					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	0.99	£64,182	**£64,727**
R-CHOP	[redacted]	[redacted]	-	-	-

QALY - quality-adjusted life year; R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

Exploratory Analysis A7: Ibrutinib versus R-CHOP in the 1 prior LOT subgroup using the ERG's preferred analysis

Table 67 presents the results of the ERG's preferred assumptions within the 1 prior LOT subgroup. Within this analysis, ibrutinib is estimated to produce an additional [redacted] QALYs at an additional cost of [redacted] per patient; the corresponding ICER for ibrutinib versus R-CHOP is estimated to be £44,711 per QALY gained.

Table 67: Exploratory Analysis A7 - ibrutinib versus R-CHOP in the 1 prior LOT subgroup using the ERG's preferred analysis

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Ibrutinib	[redacted]	[redacted]	1.63	£73,069	**£44,711**
R-CHOP	[redacted]	[redacted]	-	-	-

QALY - quality-adjusted life year; R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

Exploratory Analysis Set B – results

Exploratory Analysis B1 – cost-effectiveness results using ERG's NMAs for OS

Table 68 presents the results of the partitioned survival model together with the HRs for OS derived from the ERG's NMAs (see Section 4.5). As shown in the table, the ICER for ibrutinib versus R-CHOP is expected to be dominated in all scenarios. The ERG notes that given the problems relating to the NMAs, these results should be interpreted with caution.

Table 68: Exploratory analysis B1 – partitioned survival analysis using alternative NMA-derived hazard ratios for OS, probabilistic model

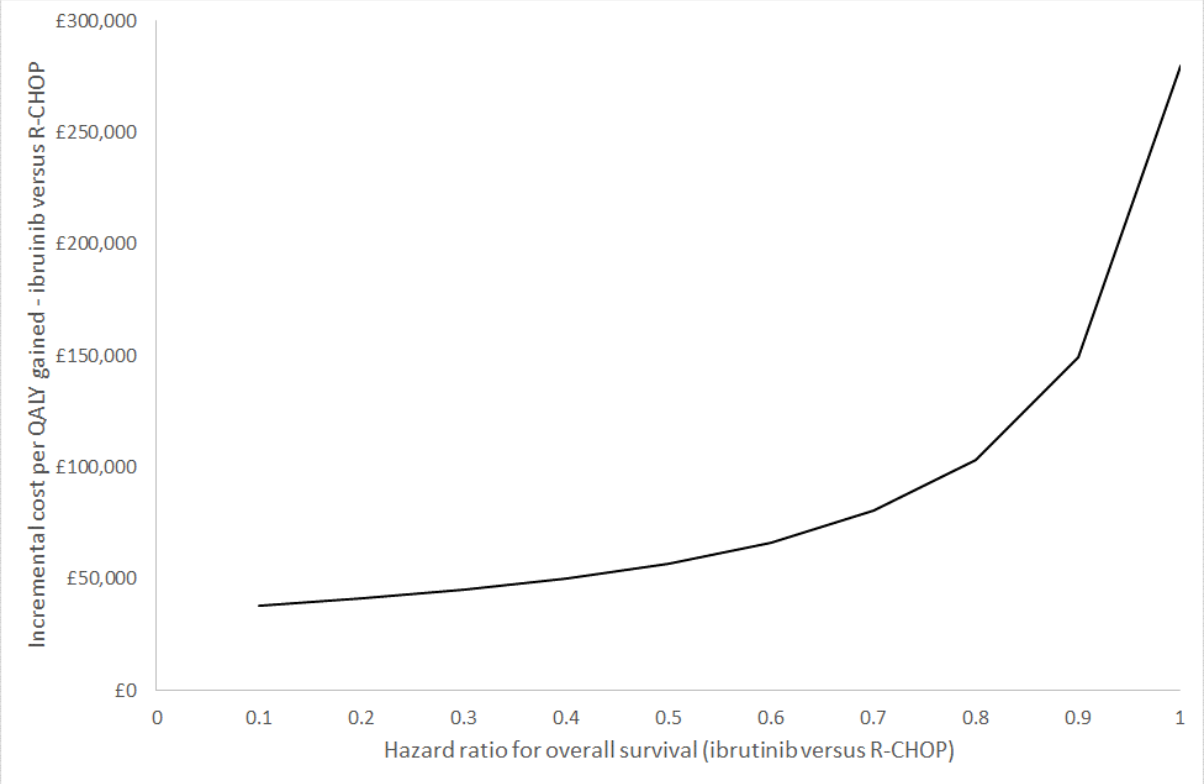
NMA – rituximab effect informed by Forstpointner *et al*[14]					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	-1.28	£29,999	**Dominated**
R-CHOP	[redacted]	[redacted]	-	-	-
NMA – rituximab effect informed by HMRN[7]					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	-0.05	£45,909	**Dominated**
R-CHOP	[redacted]	[redacted]			
NMA – rituximab effect informed by Forstpointner *et al*[14] and HMRN[7]					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	-0.31	£42,476	**Dominated**
R-CHOP	[redacted]	[redacted]		-	-

NMA - network meta-analysis; QALY – quality-adjusted life year; R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; HMRN - Haematological Malignancy Research Network

Exploratory Analysis B2 – threshold analysis around hazard ratio for OS

Figure 28 presents a threshold analysis in which the HR for OS for ibrutinib versus R-CHOP is varied between values of 0.1 and 1.0. As shown in the figure, the ICER for ibrutinib versus R-CHOP is below a threshold of £50,000 per QALY gained only when the HR for OS is below 0.39.

Figure 28: Exploratory analysis B1 - threshold analysis based on hazard ratio for OS - ibrutinib versus R-CHOP



QALY - quality-adjusted life year; R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

Table 69 summarises the results of additional threshold analyses in which the HR for PFS for ibrutinib versus R-CHOP is varied (taking arbitrary values of 0.20 and 0.35) and in which the health state utilities are sourced from Lachaine *et al*[49] and Yoong *et al*.[50] These analyses consistently suggest that irrespective of the true value of the HR for PFS and the source of utility values, the HR for OS necessary for ibrutinib versus R-CHOP to have an ICER below £50,000 per QALY gained is around 0.39-0.40. The current most favourable estimated HR for OS for ibrutinib versus TEM is 0.74.[21] Assuming that future data collection will only impact upon the evidence for ibrutinib versus TEM within the next datacut of the RAY (MCL3001) study[15] (expected in the first quarter of 2017), this means that an HR for OS for ibrutinib versus TEM would need to be 0.31 or better in order for the ICER for ibrutinib to be below £50,000 per QALY gained.

Table 69: Exploratory analysis B2 – necessary OS hazard ratio for ibrutinib versus R-CHOP in order to the ICER for ibrutinib versus R-CHOP to be below £50,000 per QALY gained

Scenario	PFS HR=0.27	PFS HR=0.20	PFS HR=0.35
ERG preferred analysis	0.39	0.39	0.39
ERG preferred analysis with utilities from Lachaine *et al*[49]	0.40	0.40	0.39
ERG preferred analysis with utilities from Yoong *et al*[50]	0.40	0.40	0.39

PFS – progression-free survival; HR - hazard ratio

5.5 Discussion

The CS includes a systematic review of published economic evaluations of treatments for R/R MCL together with a *de novo* health economic evaluation of ibrutinib versus R-chemo in adult patients with R/R MCL.

The company's review of existing economic evaluations did not identify any studies relating to ibrutinib in the R/R MCL indication. However, during the course of the assessment, the ERG identified one study (Peng *et al*[22]) which modelled the effectiveness of ibrutinib versus R-bendamustine, FMC and TEM based on a partitioned survival approach. This study reported estimated incremental health gains of 0.86 to 0.92 LYGs and 0.70 to 0.72 QALYs for ibrutinib. This study was not a full economic evaluation and was limited to modelling health gains only. In addition, the documentation provided alongside the CS included an unpublished economic evaluation of ibrutinib versus TEM, R-bendamustine and R-CHOP using registry data from the Skåne registry in Sweden;[54] this analysis also adopted a partitioned survival approach. Whilst the ERG considers the previously published and unpublished economic evaluations to be insufficient to address the decision problem,[11] these previous models could have been further developed to inform the appraisal**.**

The company's *de novo* economic model adopts a Markov approach to estimate the costs and health outcomes for ibrutinib versus R-chemo from the perspective of the NHS and PSS over a 15-year (lifetime) horizon. The base case compares ibrutinib versus R-CHOP; scenario analyses are also presented for ibrutinib versus R-CVP, FCR, RC, and a blended comparison of all four R-chemo options. Separate subgroup analyses are presented for patients who have received one prior LOT and for patients who have received ≥2 prior LOTs. The company's base case model includes three health states: (i) progression-free; (ii) post-progression, and; (iii) dead. The model also implicitly includes a further partition between patients who are progression-free and on treatment and those who are progression-free after discontinuation of treatment, based on TTD/D data. Transitions between states are modelled according to a 28-day cycle length (195 cycles). Within the ibrutinib group, health state transitions are modelled using parametric survivor functions fitted to data on pre-progression-mortality (exponential model), PFS (Weibull model) and PPS (exponential model) from the pooled ibrutinib dataset.[19] TTD/D is also modelled using a parametric survivor function (Weibull model), but does not impact on transitions. The benefits of ibrutinib versus R-chemo are modelled using a treatment effect derived from an indirect comparison based on the RAY (MCL3001) trial[15] (ibrutinib versus TEM), the OPTIMAL trial[8] (TEM versus physician's choice single-agent chemotherapy) and the HMRN audit[7] (R-chemo versus chemo). This HR for PFS is applied to the PFS and TTD/D curves for ibrutinib. Health utilities for the progression-free and post-progression states were derived from the RAY (MCL3001) and SPARK (MCL2001) studies; a disutility associated with R-chemo toxicity was derived from clinical opinion. The company's model includes costs associated with drug

acquisition, drug administration, follow-up, management of AEs, BSC and death. Resource use was estimated using a survey of actively practicing NHS haematologists and oncologists and was assumed to include full blood counts, X-rays, blood glucose tests, lactate dehydrogenase, lymphocyte counts, bone marrow exams, consultations with a haematologist, non-surgical inpatient visits, biopsies, blood transfusions and platelet infusions. Unit costs were taken from MIMs,[56] the CMU[57] and NHS Reference Costs.[58]

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 R-CHOP; the ICER for ibrutinib versus R-CHOP is expected to be £76,014 per QALY gained. The results of the deterministic model are similar, with ibrutinib yielding an ICER of £75,317 per QALY gained compared with R-CHOP. Assuming a WTP threshold of £50,000 per QALY gained, the company's base case model suggests that the probability that ibrutinib produces more net benefit than R-CHOP is approximately zero.

Across all but one of the company's scenario analyses, the ICER for ibrutinib versus R-chemo was greater than £70,000 per QALY gained. The only exception to this relates the analysis in which the modelled OS for R-CHOP is "calibrated" against the HMRN OS estimate of 8.4 months by adjusting the post-progression mortality rate in this group only (ICER=£59,345 per QALY gained). The ERG notes that this is an analysis in the 1 prior LOT subgroup rather than the base case population. The ERG also notes that the choice of comparator regimen does not have a material impact upon the company's deterministic ICER for ibrutinib.

The company's subgroup analysis according to number of prior LOTs indicates the potential for an improved cost-effectiveness profile for ibrutinib. Within the subgroup of patients who have received only one prior LOT, the probabilistic version of the company's model suggests that ibrutinib is expected to generate an additional [redacted] QALYs at an additional cost of [redacted] per patient; the corresponding ICER is £65,977 per QALY gained. Within the subgroup of patients who have received two or more prior LOTs, ibrutinib is expected to produce and additional [redacted] QALYs at an additional cost of [redacted] per patient; the corresponding ICER is £84,263 per QALY gained.

The ERG critically appraised the company's economic analysis and 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) concerns regarding the constraints and assumptions imposed by the company's Markov model approach, particularly surrounding the use of PPS rather than OS as a model input; (ii) uncertainty surrounding the relative benefits of ibrutinib relative to treatments currently used for R/R

MCL in the NHS; (iii) the use of parametric survival curves to model TTD/D rather than the Kaplan-Meier curves; (iv) questionable assumptions regarding HRQoL; (v) discrepancies between the model-predicted and observed OS for ibrutinib, and; (vi) uncertainty surrounding the company's subgroup analysis based on the number of prior LOTs.

The ERG undertook two sets of exploratory analyses. The first set of exploratory analyses ("Set A") involved amending the parameter values of the company's submitted model. The ERG's preferred analysis within Set A involved using the ERG's NMA-derived HR for PFS, the use of the Kaplan-Meier curve for TTD/D for ibrutinib and the truncation of the R-chemo QALY loss upon treatment discontinuation. The second set of exploratory analyses ("Set B") involved amending the structure of the company's model such that OS was used as an input and PPS at any time t was defined as $S(t)_{OS}$-$S(t)_{PFS}$; this is analogous to a partitioned survival model. This structural amendment of the model allowed for the exploration of the impact of applying alternative HRs for OS for ibrutinib versus R-chemo, including those derived from the ERG's random effects NMAs (see Section 4.5).

The ERG's exploratory analyses based on the company's model structure suggest the following:

- As expected, the impact of using the HR for PFS from the ERG's NMA had a negligible impact upon the cost-effectiveness of ibrutinib (ICER=£75,094 per QALY gained).
- The use of the Kaplan-Meier curves for TTD/D improves the cost-effectiveness of ibrutinib versus R-chemo; within this analysis the ICER was estimated to be £61,472 per QALY gained.
- The truncation of the R-chemo disutility upon treatment discontinuation increased the ICER for ibrutinib versus R-CHOP to £77,111 per QALY gained.
- The ERG's preferred analysis, which includes all three amendments produced a probabilistic ICER for ibrutinib versus R-CHOP of £63,340 per QALY gained.
- The use of alternative utility values for the progression-free and post-progression states within the ERG's preferred analysis produced ICERs for ibrutinib versus R-CHOP ranging from £59,952 to £60,417 per QALY gained.
- The analyses in which rituximab is excluded from the comparator regimen produced ICERs ranging from £64,727 to £69,054 per QALY gained.
- Within the LOT=1 subgroup, the ERG's preferred analysis suggests that the ICER for ibrutinib versus R-CHOP is £44,711 per QALY gained. This is considerably lower than the ICER for the overall population, but may be subject to confounding due to the *post hoc* definition of the subgroup and bias due to the poor fit of the PFS function.

The ERG's exploratory analyses based on the partitioned survival model structure suggest the following:

- Irrespective of whether the rituximab effect is estimated using data reported by Forstpointner *et al*,[14] the HRMN audit,[48] or both, ibrutinib is expected to be dominated. This is likely to be a consequence of problems in robustly estimating treatment effects for OS given the evidence.
- Irrespective of the true value of the HR for PFS and the source of utility values, the HR for OS for ibrutinib versus R-CHOP necessary in order for ibrutinib to have an ICER below £50,000 per QALY gained is around 0.39-0.40.

The ERG's considers that a balance exists in that the company's PFS-based model makes a number of restrictive structural assumptions which lead to a poor model fit to the available OS data for ibrutinib, whilst the ERG's partitioned survival analysis (Exploratory Analysis Set B) provides a better fit to the OS data but involves using the outputs of a highly uncertain NMA.

The ERG notes that the foreword to the CS states that the company requests the opportunity to remain on the CDF in order to collect further evidence to reduce the level of uncertainty that currently exists. The CS notes four areas in which further data collection may reduce uncertainty:

1. The final datacut of RAY (MCL3001) is not yet available but is expected in the first quarter of 2017. The CS states that a statistically significant OS benefit of ibrutinib over TEM is expected.
2. New analyses of the HRMN audit are expected to also include data on ibrutinib and may potentially allow a direct comparison of ibrutinib versus R-chemo in UK real-life clinical practice.
3. The Janssen "PHEDRA initiative" (Platform for Haematology in EMEA: Data for Real World Analysis) intends to generate R/R MCL data from countries including France, Italy, Germany, Netherlands and Sweden. This will look to describe treatment practices, outcomes and medical resource use.
4. Given the company's concerns regarding the appropriateness of the EQ-5D in capturing fatigue-related quality of life, the company is planning to undertake a further prospective longitudinal study using an alternative preference-based measure. Current options under consideration include: the FACT-Lym with utility scored from FACT-G items; the EORTC-8D scored from the EORTC QLQ-C30, and; the SF-6D scored from the SF-36.

The ERG's exploratory analyses suggest that the key uncertainty surrounding the cost-effectiveness of ibrutinib relates to its expected OS gain compared with R-chemo. The current most favourable estimated HR for OS for ibrutinib versus TEM is 0.74. Assuming that future data collection will only impact upon the evidence for ibrutinib versus TEM within the next datacut of the RAY (MCL3001) study, the ERG's threshold analyses suggest that the HR for OS for ibrutinib versus TEM would need to be 0.31 or better in order for the ICER for ibrutinib versus R-CHOP to be below £50,000 per QALY gained. The ERG suggests that this outcome is unlikely.

6. END OF LIFE

The CS[1] states that ibrutinib meets NICE's criteria for life extending therapies given at the end of life.[20] The company's evidence supporting this is presented in Table 70.

Table 70: Evidence supporting company's end of life argument (adapted from CS Table 50)

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	UK data from HMRN reveals that median OS was 8.4 months in patients with R/R disease who achieved a response to first-line treatment (n=57). This is supported by data from two additional sources: • Median OS was reported to be 9.7 months in the single-agent chemotherapy arm of the OPTIMAL trial[8] • Median OS was reported to be 5.2 months the Skåne University Hospital registry in Sweden (data from 2000 to 2012)[54] These data provide survival estimates of approximately 5-10 months in current UK clinical practice.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	The pooled analysis of the ibrutinib studies[19] produced a median OS estimate of 25 months. This is considerably greater than the 5-10 month estimate of survival in clinical practice (see above). Available literature within MCL indicates that PFS provides a good surrogate for OS and this approach has previously been accepted within front-line MCL,[67, 76] It is therefore helpful to also consider estimates of PFS on ibrutinib with those from sources reflective of clinical practice. Table 71 provides a summary of the OS and PFS estimates for ibrutinib from the RAY (MCL3001) study and the pooled analysis compared to estimates reflective of routine clinical practice. Based on both PFS and OS, ibrutinib demonstrates a greater than three month extension to life. **Table 71: PFS and OS to support end of life criteria 1 and 2** **Source** / **Median PFS (months)** / **Median OS (months)** Ibrutinib, RAY (MCL3001) / 14.6 / NR Ibrutinib, pooled analysis / 12.81 / 25.00 HMRN / N/A / 8.4 OPTIMAL (single-agent chemo) 2009 / 1.9 / 9.7 Skåne registry / 2.8 / 5.2
The treatment is licensed or otherwise indicated for small patient populations	An estimated 356 R/R MCL patients are eligible to receive ibrutinib in England, Wales and Northern Ireland in 2017. This equates to a patient population smaller than 1 in 50,000. The incidence of CLL is estimated at 7 per 100,000 in England and only 7% of people diagnosed with CLL have the 17p deletion or TP53 mutation described in ibrutinib's licence.[48, 77] WM, the other condition for which ibrutinib holds a marketing authorisation, has an estimated incidence of 0.55 per 100,000. Therefore, the size of the combined population for which ibrutinib is licensed is small.

HMRN - Haematological Malignancy Research Network; OS - overall survival; MCL - mantle cell lymphoma; PFS – progression-free survival; R/R MCL relapsed/refractory mantle cell lymphoma

The ERG agrees that using treatments currently available on the NHS, the expected OS for the R/R MCL population is typically less than 24 months.

The ERG notes that there is considerable uncertainty surrounding the incremental survival benefit associated with ibrutinib compared with existing therapies currently used on the NHS. This uncertainty is principally driven by the absence of a direct head-to-head trial against any relevant comparator, the immaturity of the OS data within the pooled ibrutinib dataset,[19] and the weaknesses in the other studies included in the ERG's NMAs of OS (see Section 4.5). The ERG notes that whilst comparing the median OS from the pooled analysis against the HMRN,[7] the OPTIMAL trial[8] and the Skåne registry[54] suggests an incremental gain in median OS of more than 16 months, this form of naïve indirect comparison may be subject to confounding due to differences between the populations recruited into the studies and the design of those studies. In addition, the ERG does not believe that considering PFS data is meaningful in supporting the argument that ibrutinib meets the end of life criteria for incremental survival benefits.

The ERG agrees that the eligible patient population is expected to be small, but notes that this criterion is no longer considered by NICE.

7. DISCUSSION

Clinical effectiveness evidence

As R/R CML is a relatively rare disease, there is very little real world data available. Only three studies of ibrutinib in R/R MCL patients were identified. These included one open-label RCT (RAY [MCL3001]) and two open-label single-arm studies (SPARK [MCL2001] and PCYC1104).

In RAY (MCL3001), the comparator was TEM, which is not used in clinical practice in England. In addition, RAY (MCL3001) was an open-label trial and was therefore potentially subject to bias, although the quality of the study was deemed adequate by CS and ERG. The primary endpoint in RAY (MCL3001) was assessed by an IRC masked to study treatment. PFS was significantly better in the ibrutinib arm than in the TEM arm. OS, however, was not significantly better in the ibrutinib arm than the TEM arm. It is uncertain if this lack of significant OS benefit was due to the use of subsequent therapies beyond progression (including treatment switching in the TEM arm) or the lack of adequate power for this outcome. Analysis suggested it was probably not due to TEM crossover. The TEM arm in the RAY (MCL3001) study reported better outcomes than the TEM arm within earlier studies (including the OPTIMAL trial). It is uncertain if this is due to improved supportive care in RAY (MCL3001) and the use of experimental therapies.

The two open-label studies were of lower quality design (single-arm), however, the results from these two studies are generally consistent with the ibrutinib arm of RAY (MCL3001). OS in both arms of the RAY (MCL3001) study was better than data reported within the HMRN audit. It is not clear if this was due to differences in populations, treatments or additional therapies received. Evidence from both the RAY (MCL3001) and SPARK (MCL2001) studies showed clinically meaningful improvement in HRQoL for approximately 62% of patients treated with ibrutinib. There are potential advantages for both patients and clinicians with ibrutinib as it is administered orally. This may impact on HRQoL. There was also an improved AE profile in the ibrutinib arm of RAY (MCL3001) compared to the TEM arm.

The company conducted an indirect comparison of ibrutinib versus single-agent chemotherapy for PFS, OS and ORR. Rituximab is used in routine clinical practice in England, therefore to account for the differential effectiveness of using rituximab alongside chemotherapy the company performed an additional adjustment to the HR for PFS. No adjustment was conducted for OS. The adjusted HR for PFS for ibrutinib versus R-chemo was estimated to be 0.28. The ERG considers that a single stage approach using a random effects NMA would provide a better representation of the uncertainty in the resulting treatment comparisons than the two stage procedure implemented by the company. Based on the ERG's additional analyses, ibrutinib is associated with a slower rate of disease progression, compared to R-chemo (random effects HR=0.27, 95% CrI 0.06, 1.26) although the result is

inconclusive as it did not reach statistical significance at the 95% level. The estimated median HRs for OS for ibrutinib versus R-chemo range from 0.98 to 1.96, depending on the data source used for the rituximab arm of the network. This illustrates the high level of uncertainty for this comparison. Due to concerns regarding the evidence used to inform the indirect comparisons, the results of the indirect comparison should be interpreted with caution.

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 R-CHOP; the ICER for ibrutinib versus R-CHOP is expected to be £76,014 per QALY gained. The results of the deterministic model are similar, with ibrutinib yielding an ICER of £75,317 per QALY gained compared with R-CHOP. Assuming a WTP threshold of £50,000 per QALY gained, the company's base case model suggests that the probability that ibrutinib produces more net benefit than R-CHOP is approximately zero. Within the company's DSA, the net monetary benefit remained consistently negative, hence the ICER for ibrutinib versus R-CHOP is greater than £50,000 per QALY gained. The company's scenario analyses report a most favourable ICER in the scenario in which the modelled OS for R-CHOP is "calibrated" against the HMRN OS estimate of 8.4 months by adjusting the post-progression mortality rate in this group only; within this analysis the ICER is estimated to be £59,345 per QALY gained. The ERG notes however that this is actually an analysis in the 1 prior LOT subgroup rather than the base case population. The company's subgroup analyses suggest that the cost-effectiveness of ibrutinib may be improved when used in patients who have received only 1 prior LOT (ICER=£65,977 per QALY gained). This is however a *post hoc* subgroup which is at risk of confounding and includes only 99 (27%) of the 370 patients from the pooled ibrutinib dataset. The ERG also notes that none of the parametric survival models provide a good visual fit to the PFS Kaplan-Meier curves within this subgroup.

The ERG critically appraised the company's economic analysis and double-programmed the deterministic version of the company's model. No programming errors were identified in the base case model, however some programming mistakes were identified in the implementation of the company's sequential 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 identified by the ERG included: (i) concerns regarding the constraints and assumptions imposed by the company's Markov model approach, particularly surrounding the use of PPS rather than OS as a model input; (ii) uncertainty surrounding the relative benefits of ibrutinib relative to current treatments for R/R MCL used in the NHS; (iii) the use of parametric survival curves to model TTD/D rather than the Kaplan-Meier curves; (iv) questionable assumptions regarding HRQoL; (v)

discrepancies between the model-predicted and observed OS for ibrutinib, and; (vi) uncertainty surrounding the company's subgroup analysis based on the number of prior LOTs.

The ERG undertook two sets of exploratory analyses. The first set of exploratory analyses ("Set A") involved amending the parameter values of the company's submitted model. The ERG's preferred analysis within Set A involved using the ERG's NMA-derived HR for PFS, the use of the Kaplan-Meier curve for TTD/D for ibrutinib and the truncation of the R-chemo QALY loss upon treatment discontinuation. The second set of exploratory analyses ("Set B") involved amending the structure of the company's model such that OS was used as an input and PPS at any time *t* was defined as $S(t)_{OS}$-$S(t)_{PFS}$; this is analogous to a partitioned survival model (as used in previous analyses of published and unpublished economic analyses of ibrutinib for R/R MCL[22, 54]). This structural amendment of the model allowed for the exploration of the impact of applying alternative HRs for OS for ibrutinib versus R-chemo, including those derived from the ERG's random effects NMAs.

The ERG's exploratory analyses based on the company's model structure suggest the following:

- As expected, the deterministic analysis using the HR for PFS from the ERG's NMA had a negligible impact upon the cost-effectiveness of ibrutinib (ICER=£75,094 per QALY gained).
- The use of the Kaplan-Meier curves for TTD/D improves the cost-effectiveness of ibrutinib versus R-chemo; within this analysis the ICER was estimated to be £61,472 per QALY gained.
- The truncation of the R-chemo disutility upon treatment discontinuation increased the ICER for ibrutinib versus R-CHOP to £77,111 per QALY gained.
- The ERG's preferred analysis, which includes all three amendments resulted in a probabilistic ICER for ibrutinib versus R-CHOP of £63,340 per QALY gained.
- The use of alternative utility values for the progression-free and post-progression states within the ERG's preferred analysis produced ICERs for ibrutinib versus R-CHOP ranging from £59,952 to £60,417 per QALY gained.
- The analyses in which rituximab is excluded from the comparator regimen produced ICERs ranging from £64,727 to £69,054 per QALY gained.
- Within the LOT=1 subgroup, the ERG's preferred analysis suggests that the ICER for ibrutinib versus R-CHOP is £44,711 per QALY gained. This is considerably lower than the ICER for the overall population, but may be subject to confounding due to the *post hoc* definition of the subgroup and bias due to the poor fit of the Weibull function used to model PFS.

The ERG's exploratory analyses based on the partitioned survival model structure suggest that irrespective of whether the rituximab effect is estimated using data reported by Forstpointner *et al*,[14]

the HRMN audit,[48] or both, ibrutinib is expected to be dominated. This is likely to be a consequence of problems in robustly estimating treatment effects for OS given the evidence available.

The foreword to the CS states that the company requests the opportunity to remain on the CDF in order to collect further evidence to reduce the level of uncertainty that currently exists. The CS suggests four areas in which further data collection may reduce uncertainty: (i) the final datacut of the RAY (MCL3001) study (expected during the first quarter of 2017); (ii) new analyses of the HRMN audit; (iii) the Janssen "PHEDRA initiative" (Platform for Haematology in EMEA: Data for Real World Analysis), and; (iv) a further prospective longitudinal study using an alternative preference-based measure of HRQoL. The key uncertainty surrounding the cost-effectiveness of ibrutinib relates to its OS gain relative to R-chemo. The ERG's threshold analyses using the exploratory partitioned survival model consistently suggest that irrespective of the true value of the HR for PFS and the source of utility values, the HR for OS necessary for ibrutinib versus R-CHOP to have an ICER below £50,000 per QALY gained is around 0.39-0.40. Other things being equal, this would require the final datacut of the RAY (MCL3001) study to report an HR for ibrutinib versus TEM of 0.31. The ERG considers this outcome to be unlikely.

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9. APPENDICES

Appendix 1: Company's cost-effectiveness results based on ibrutinib list price

A1.1 Base case cost-effectiveness results

Table 72 presents the company's base case cost-effectiveness results for ibrutinib versus R-CHOP based on the list price for ibrutinib. 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 R-CHOP; the ICER for ibrutinib versus R-CHOP is expected to be £102,136 per QALY gained. Based on the deterministic version of the model, the ICER for ibrutinib versus R-CHOP is estimated to be £101,709 per QALY gained.

Table 72: Company's central estimates of cost-effectiveness – ibrutinib versus R-CHOP

Probabilistic model*					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	0.94	£95,698	**£102,136**
R-CHOP	[redacted]	[redacted]	-	-	-
Deterministic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	0.94	£95,233	**£101,709**
R-CHOP	[redacted]	[redacted]	-	-	-

** obtained by reprogramming the PSA subroutine and re-running the model*

A1.2 Probabilistic sensitivity analysis results

Figures 29 and 30 present the cost-effectiveness plane and CEACs for ibrutinib versus R-CHOP, respectively; each figure is based on a re-run of the company's PSA. Assuming a WTP threshold of £50,000 per QALY gained, the company's base case model suggests that the probability that ibrutinib produces more net benefit than R-CHOP is approximately zero.

Figure 29: Cost-effectiveness plane – ibrutinib versus R-CHOP (adapted by the ERG)

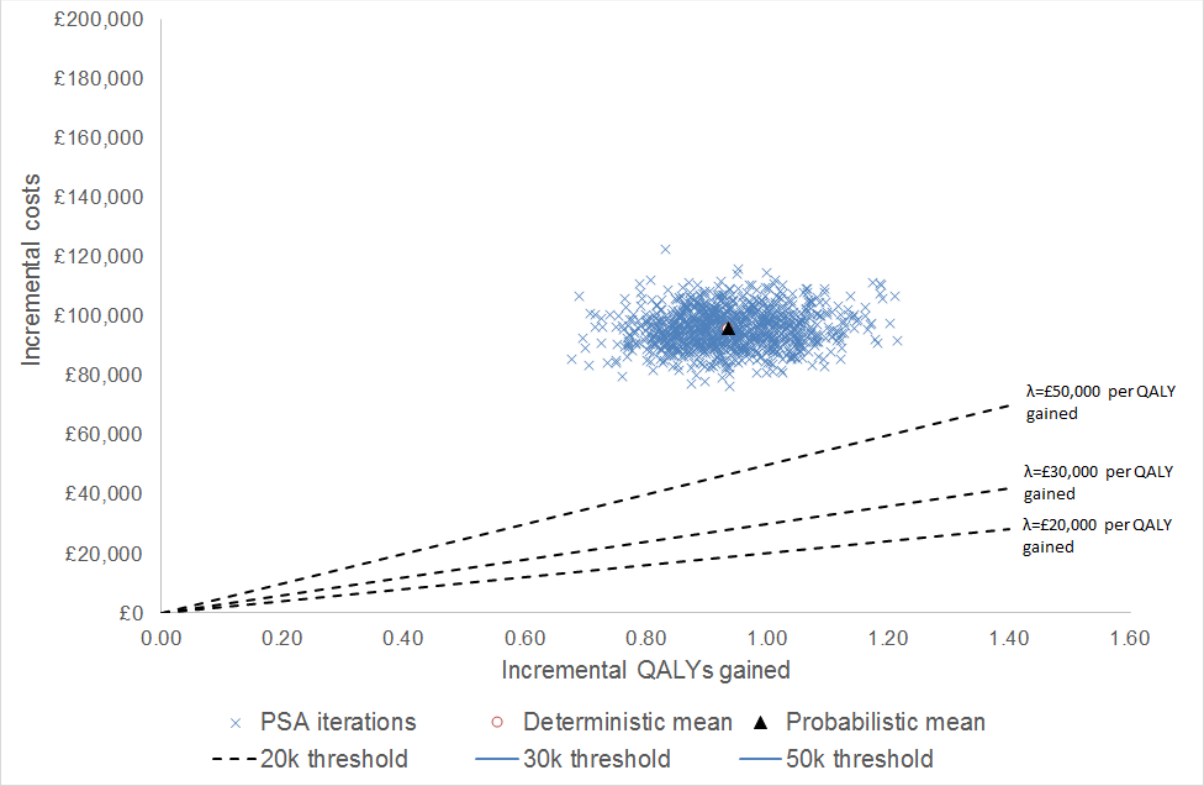
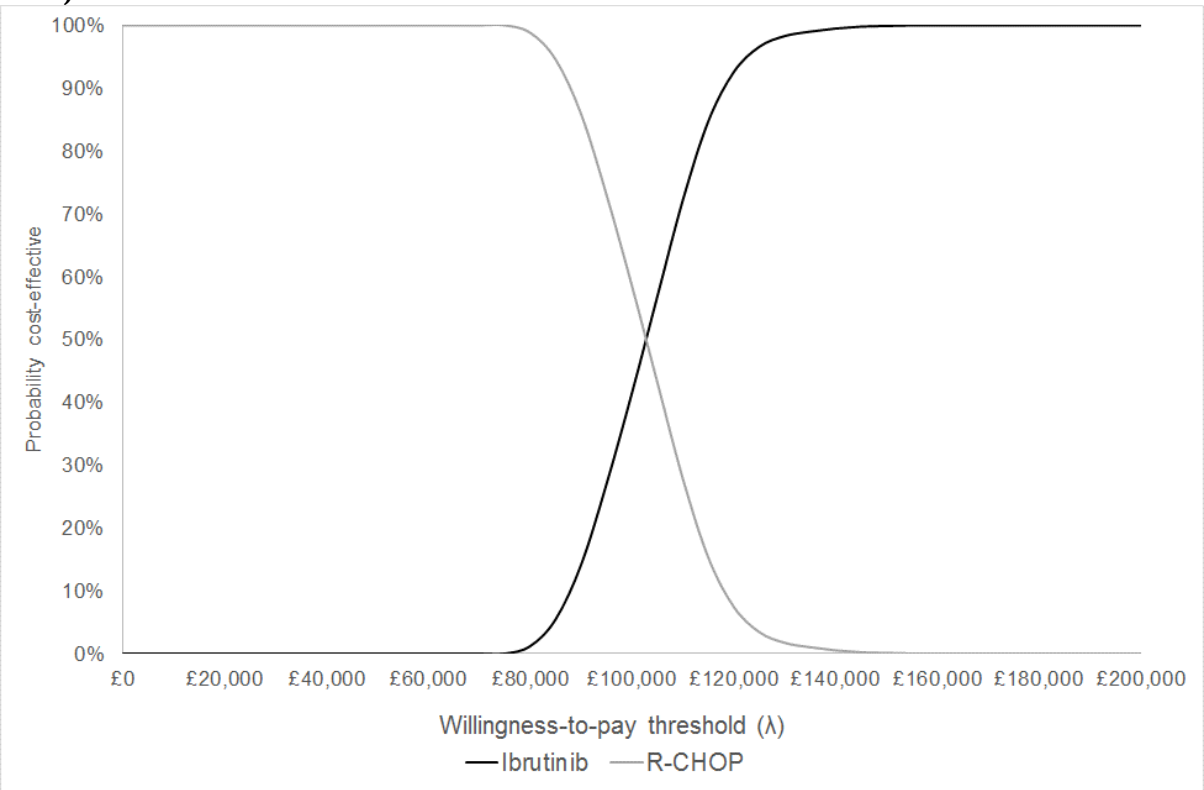


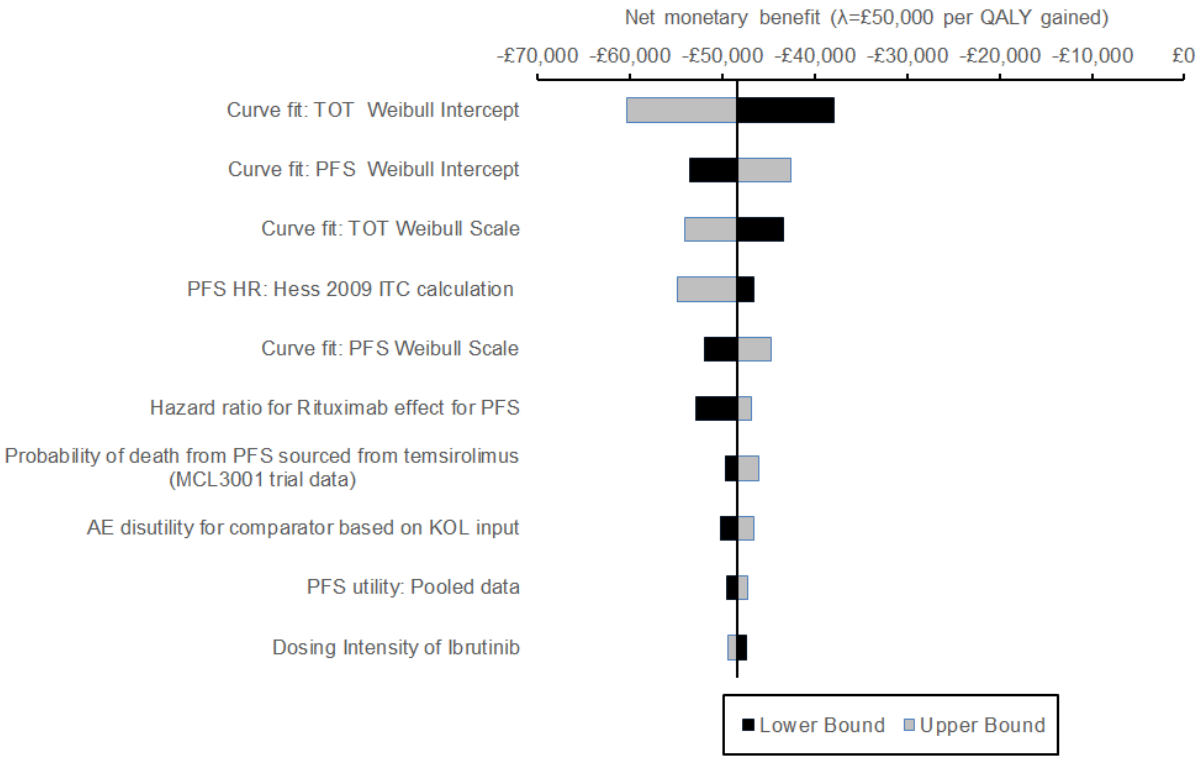
Figure 30: Cost-effectiveness acceptability curves – ibrutinib versus R-CHOP (adapted by the ERG)



A1.3 Deterministic sensitivity analysis results

Figure 31 presents the results of the company's one-way DSA (ranges defined according to upper and lower 95% CIs for estimated parameters), based on net monetary benefit assuming a WTP of £50,000 per QALY gained. Results are presented only for the ten most influential parameters. The results of the DSA suggest that the parameters of the survivor functions for PFS and TTD/D, the individual elements of the composite HR for PFS, the pre-progression mortality probability for R-chemo, the disutility associated with R-chemo, the PFS utility value and the cost of outpatient appointments for the management of AEs are the most influential parameters. The ERG notes that the net monetary benefit remains negative across all DSAs, hence the ICER for ibrutinib versus R-CHOP would be greater than £50,000 per QALY gained.

Figure 31: One-way sensitivity analysis tornado diagram (λ=£50,000 per QALY gained, adapted by the ERG)



A1.4 Scenario analysis results

Table 73 presents the results of the company's scenario analyses. Across almost all scenario analyses, the ICER remains in excess of £94,000 per QALY gained. The only exception to this relates the analysis in which the modelled OS for R-CHOP is "calibrated" against the HMRN OS estimate of 8.4 months by adjusting the post-progression mortality rate in this group only; within this analysis, the HR for PPS for R-chemo versus ibrutinib (after discontinuation of both therapies) is assumed to be 2.40. Within this analysis, the ICER is estimated to be £79,128 per QALY gained. Whilst unclear from the CS, it is important to note that this is actually an analysis in the 1 prior LOT subgroup.

Table 73: Summary of company's scenario analyses – ibrutinib versus R-chemo

Scenario	Incremental (ibrutinib vs R-chemo)		
	QALYs	Costs	ICER
1. Base case	0.94	£95,233	£101,709
2. Comparator efficacy HR for PFS using TEM data*	0.93	£94,909	£102,241
3. Time horizon = 10 years†	0.94	£95,256	£101,653
4. Time horizon = 20 years†	0.94	£96,558	£103,124
5. Comparator - R-CVP†	0.94	£93,065	£99,394
6. Comparator - FCR†	0.94	£94,291	£100,704
7. Comparator - RC†	0.94	£95,257	£101,735
8. Blended comparison†	0.94	£95,233	£101,709
9. No wastage included†	0.94	£95,659	£102,164
10. R-chemo disutility based on Schenkel *et al.*[63]	0.93	£95,233	£102,892
11. Utilities not age-adjusted	0.95	£95,233	£100,384
12. Sequential approach‡	1.08	£107,462	£99,566
13. Including FCR as subsequent treatment	0.94	£93,651	£100,020
14. PFS exponential model	0.83	£90,779	£108,934
15. PFS log normal model	1.30	£124,731	£96,005
16. PFS log logistic model	1.32	£131,215	£99,415
17. Pre-progression mortality for R-chemo equal to ibrutinib	0.92	£94,986	£103,542
18. Response rates of R-chemo equal to TEM response	0.94	£94,779	£101,224
19. Response rates of R-chemo equal to response in OPTIMAL[8]	0.94	£94,318	£100,733
20. Response rates of R-chemo equal to ibrutinib	0.94	£95,337	£101,820
21. PFS HR=1	1.00	£97,020	£97,023
22. Rituximab PFS HR applied to OPTIMAL[8] ITC = 0.75	0.95	£95,644	£100,358
23. Rituximab PFS HR applied to OPTIMAL[8] ITC = 0.89	0.98	£96,471	£98,163
24. Rituximab PFS HR applied to OPTIMAL[8] ITC = 1.6	1.05	£99,032	£94,312
25. Assuming R-chemo post-progression mortality probability = 0.27 (to reflect HMRN median OS of 8.4 months) using the 1 prior LOT subgroup	1.87	£147,936	£79,128

** Correct values not presented in clarification response; † values presented in clarification response correspond to analysis presented on different row of Table 7; ‡ subject to programming errors – see Section 5.3*

A1.5 Subgroup analysis results

Table 73 presents the results of the company's subgroup analysis based on the number of prior LOTs received by the modelled population (LOT=1 or LOT≥2). The probabilistic results are based on a re-run of the PSA subroutine by the ERG. Within the subgroup of patients who have received only one prior LOT, the probabilistic version of the company's model suggests that ibrutinib is expected to generate an additional [redacted] QALYs at an additional cost of [redacted] per patient; the corresponding ICER is £87,412 per QALY gained. This is lower than the company's probabilistic base case estimate (ICER=£102,136 per QALY gained). Within the subgroup of patients who have received two or more prior LOTs, ibrutinib is expected to produce and additional [redacted] QALYs at an additional cost of [redacted] per patient; the corresponding ICER is £114,086 per QALY gained. This is less favourable than the ICERs for the company's base case and the 1 prior LOT subgroup.

Table 73: Summary of company's subgroup analyses

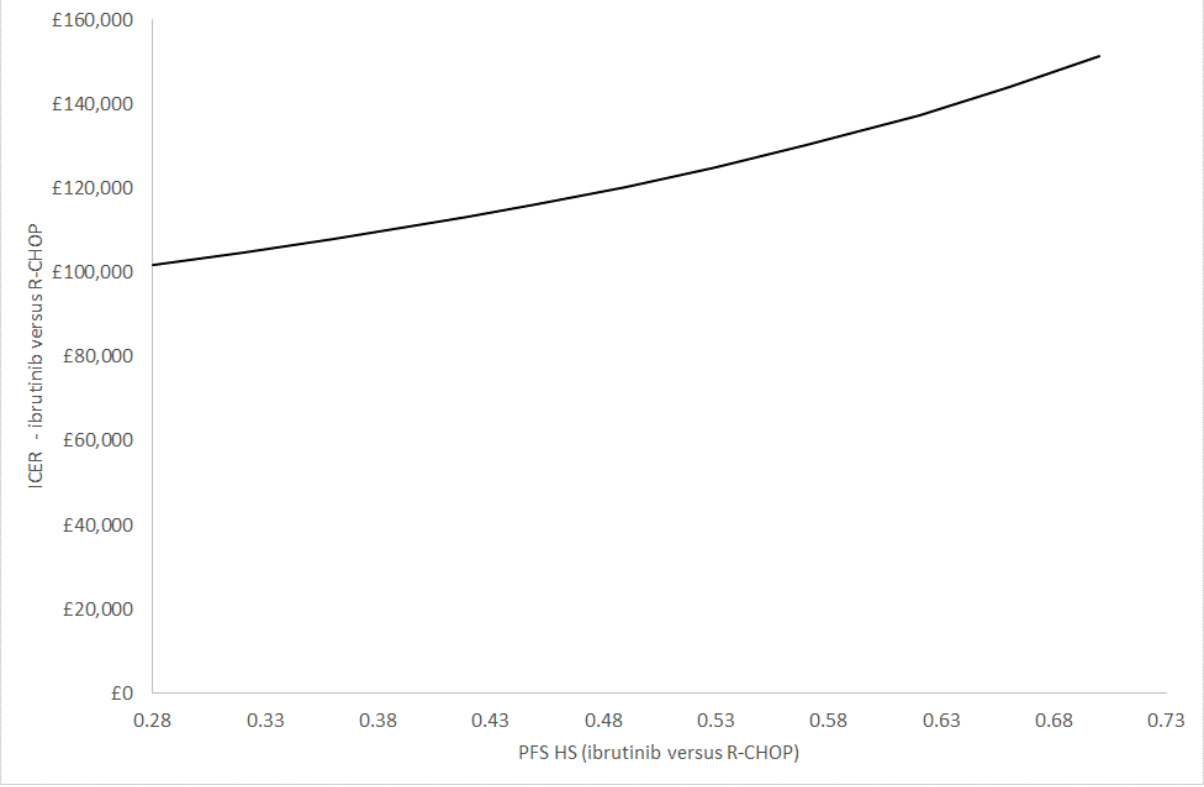
1 prior LOT - probabilistic model*					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	1.69	£147,973	**£87,412**
R-CHOP	[redacted]	[redacted]	-	-	-
1 prior LOT - deterministic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	1.67	£145,385	**£86,851**
R-CHOP	[redacted]	[redacted]	-	-	-
≥2 prior LOTs - probabilistic model*					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	0.72	£81,824	**£114,086**
R-CHOP	[redacted]	[redacted]	-	-	-
≥2 prior LOTs - deterministic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	0.72	£81,046	**£113,053**
R-CHOP	[redacted]	[redacted]	-	-	-

** Results generated by re-programming the PSA subroutine*

A1.6 Threshold analysis

Figure 32 presents the results of the company's threshold analysis. As shown in Figure 31, as the HR for PFS for ibrutinib versus R-CHOP increases (thereby lessening the distance between the PFS and TTD/D curves), so too does the ICER for ibrutinib.

Figure 32: Threshold analysis around PFS HR for ibrutinib versus R-CHOP



Appendix 2 – ERG exploratory analysis results using list price for ibrutinib

Exploratory Analysis Set A – results

Exploratory Analysis A1. HR for PFS derived from ERG'S random effects NMA

Table 75: Exploratory Analysis A1 - HR for PFS derived from ERG'S random effects NMA

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Ibrutinib	[redacted]	[redacted]	0.94	£95,330	**£101,371**
R-CHOP	[redacted]	[redacted]	-	-	-

Exploratory Analysis A2. TTD/D for ibrutinib group based on Kaplan-Meier curve

Table 76: Exploratory Analysis A2 - TTD/D for ibrutinib group based on Kaplan-Meier curve

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Ibrutinib	[redacted]	[redacted]	0.94	£77,948	**£83,249**
R-CHOP	[redacted]	[redacted]	-	-	-

Exploratory Analysis A3. Truncation of R-chemo QALY loss following treatment discontinuation

Table 77: Exploratory analysis A3 - Truncation of R-chemo disutility following treatment discontinuation

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Ibrutinib	[redacted]	[redacted]	0.91	£95,233	**£104,131**
R-CHOP	[redacted]	[redacted]	-	-	-

Exploratory Analysis A4. ERG's preferred analysis using the company's model

Table 78: Exploratory analysis A4 - ERG's preferred analysis using the company's model

Probabilistic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	0.93	£78,579	**£84,866**
R-CHOP	[redacted]	[redacted]	-	-	-
Deterministic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	0.92	£78,045	**£84,870**
R-CHOP	[redacted]	[redacted]	-	-	-

Exploratory Analysis A5. Use of alternative utility values for progression-free and post-progression states (using ERG's preferred base case)

Table 79: Exploratory analysis A5 – Use of alternative utility values for progression-free and post-progression states

(i) Utilities for progression-free and post-progression based on Lachaine *et al*[49]					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	0.95	£78,045	**£81,783**
R-CHOP	[redacted]	[redacted]	-	-	-
(ii) Utilities for progression-free and post-progression based on Yoong *et al*[50]					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	0.96	£78,045	**£81,154**
R-CHOP	[redacted]	[redacted]	-	-	-

Exploratory Analysis A6. Cost-effectiveness of ibrutinib versus chemotherapy for rituximab-resistant patients

Table 80: Exploratory analysis A6 – Cost-effectiveness of ibrutinib versus chemotherapy for rituximab-resistant patients

(i) Cost of rituximab set to zero					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	0.92	£83,891	**£91,227**
R-CHOP	[redacted]	[redacted]	-	-	-
(ii) Cost of rituximab set to zero and PFS HR=0.19					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	0.99	£84,572	**£85,289**
R-CHOP	[redacted]	[redacted]	-	-	-

Exploratory Analysis A7: Ibrutinib versus R-CHOP in the 1 prior LOT subgroup using the ERG's preferred analysis

Table 81: Exploratory Analysis A7 - ibrutinib versus R-CHOP in the 1 prior LOT subgroup using the ERG's preferred analysis

Deterministic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	0.92	£78,045	**£84,870**
R-CHOP	[redacted]	[redacted]	-	-	-

Exploratory Analysis Set B – results

Exploratory Analysis B1 – cost-effectiveness results using ERG's NMAs for OS

Table 82: Exploratory analysis B1 – partitioned survival analysis using alternative NMA-derived hazard ratios for OS, probabilistic model

NMA – rituximab effect informed by Forstpointer *et al*[14]					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	-1.28	£50,242	**Dominated**
R-CHOP	[redacted]	[redacted]	-	-	-
NMA – rituximab effect informed by HMRN[7]					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	-0.05	£66,096	**Dominated**
R-CHOP	[redacted]	[redacted]			
NMA – rituximab effect informed by Forstpointer *et al*[14] and HMRN[7]					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	-0.31	£62,688	**Dominated**
R-CHOP	[redacted]	[redacted]	-	-	-

Exploratory Analysis B2 – threshold analysis around hazard ratio for OS

Figure 33: Exploratory analysis B1 - threshold analysis based on hazard ratio for OS - ibrutinib versus R-CHOP

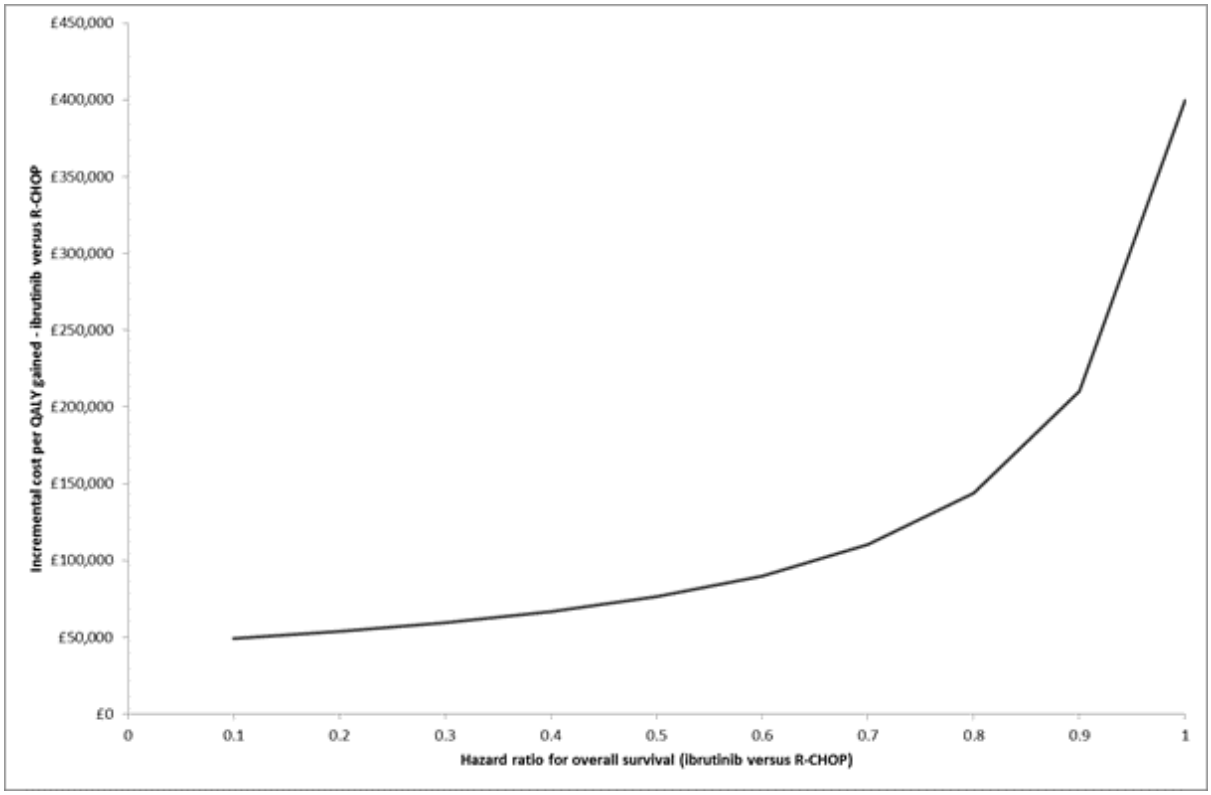


Table 83: Exploratory analysis B2 – necessary OS hazard ratio for ibrutinib versus R-CHOP in order to the ICER for ibrutinib versus R-CHOP to be below £50,000 per QALY gained

Scenario	PFS HR=0.27	PFS HR=0.20	PFS HR=0.35
ERG preferred analysis	0.11	0.11	0.12
ERG preferred analysis with utilities from Lachaine *et al*[49]	0.08	0.08	0.08
ERG preferred analysis with utilities from Yoong *et al*[50]	0.07	0.07	0.07

Appendix 3 – Technical details for implementing ERG Exploratory Analyses

Exploratory Analyses Set A

Exploratory Analysis A1. HR for PFS derived from ERG'S random effects NMA

Go to the "Clinical Inputs" worksheet

In cell I20 change the value to 0.27

Exploratory Analysis A2 - TTD/D for ibrutinib group based on Kaplan-Meier curve

Add a new worksheet to the workbook called "Sheet 1".

In cell B2 apply the following formula ='KM data'!A7. Fill down

In cell C2 apply the following formula ='KM data'!H7. Fill down

In cell A2 apply the following formula =B2/12. Fill down

Go to the "Model ibru" sheet

In cell G18 apply the following formula =VLOOKUP(C18,Sheet1!$A$2:$C$1557,3,TRUE). Fill down.

Exploratory Analysis A3. Truncation of R-chemo QALY loss following treatment discontinuation

Go to the "Model PC" worksheet.

In cell AT25 insert the value 0. Fill down

Exploratory Analysis A4. ERG's preferred analysis using the company's model

Apply the steps detailed above.

Exploratory Analysis A5. Use of alternative utility values for progression-free and post-progression states (using ERG's preferred base case)

Use the model which has was generated in Exploratory Analysis A4

Lachaine et al utility values

Go to the "Parameters" worksheet.

In cell D38 change the value to 0.805

In cell D42 change the value to 0.618

Yoong et al utility values

Go to the "Parameters" worksheet.

In cell D38 change the value to 0.81

In cell D42 change the value to 0.60

Exploratory Analysis A6. Cost-effectiveness of ibrutinib versus chemotherapy for rituximab-refractory patients

Use the model which has was generated in Exploratory Analysis A4

Part (i)

Go to the "Cost Inputs" worksheet

In cell F26 set the value to 0

Part (ii)

Apply the steps in Part (i)

Go to the "Clinical Inputs" worksheet

Set the value in cell I20 to 0.19

Exploratory Analysis A7: Ibrutinib versus R-CHOP in the 1 prior LOT subgroup using the ERG's preferred analysis

Use the model which has was generated in Exploratory Analysis A4

Go to the "Settings" worksheet

Change the value in cell H38 to "1 prior line"

Exploratory Analysis Set B

Add new sheet added called “ERGcurves”

Generate cumulative survival probabilities for OS for ibrutinib (in worksheet “ERG curves”)

Add day, month and year counter, calculate age from model entry, and the ERG-fitted exponential OS curve for ibrutinib to worksheet “ERGcurves” cells A3: E5479

Calculate descriptive AUC for exponential curve using formula in cell F5 “=IF(E6="","",(SUM(E5:E6)/2)*(B6-B5))/365.25”. Fill down.

Generate cumulative survival probabilities for PFS for ibrutinib (in worksheet “ERG curves”)

In cells H4:H5479, calculate cumulative PFS probabilities using the Weibull function (in days)

In cells J5:K1560 lookup time and TTD/D from the observed Kaplan-Meier curve (in months)

Estimate daily probability of death in general population (in worksheet “lifetable”)

Insert two additional columns from column I

In column I, calculate age- and sex- weighted annual probabilities of death for all years

In column J, convert death probability to rate using formula =-(LN(1-*probability*))/365.25 and fill down

In column K, convert to daily probability using formula =1-EXP(-*rate**1) and fill down

Apply logical consistency constraints (in worksheet “ERG curves”)

In column M, constrain OS curve by general population mortality using formula:

=IF(((E5-E6)/E5)<VLOOKUP(ROUNDDOWN(ERGcurves!C5,0),lifetable!$D$8:$K$108,8,0),M5*(1-VLOOKUP(ROUNDDOWN(ERGcurves!C5,0),lifetable!$D$8:$K$108,8,0)),M5*(1-((E5-E6)/E5)))

In column O, set values equal to constrained OS curve

In column P, constrain PFS cumulative survival probabilities to be less than OS curve using formula =IF(H5>O5,O5,H5). Fill down.

In column Q, constrain the TTD/D cumulative survival probabilities to be less than the PFS curve =IF(VLOOKUP(D5,$J$4:$K$1560,2,TRUE)<P5,VLOOKUP(D5,$J$4:$K$1560,2,TRUE),P5)

Add ERG’s NMA-derived HRs for PFS and OS

Add new worksheet called “ERG clinical inputs”

In cell A2 insert the following table:

	A	B	C	D	E	F	G	H	I
2			Method						
3			Company's adjustment	FE NMA		RE NMA			
4	End point		Effect size*	Effect size*	95% CrI	Effect size*	95% CrI	95% PrI	s.d.
5	PFS		0.28	0.27	(0.12, 0.62)	0.27	(0.06, 1.23)	(0.05,1 .64)	-
6	OSS	Forstpointner only	NA	1.96	(0.71, 5.40)	1.98	(0.45, 8.74)	(0.35,1 1.74)	0.22(0.0 1,0.72)
7		HMRN only	NA	0.98	(0.49, 1.97)	1	(0.26, 3.82)	(0.19, 5.34)	0.22(0.0 1,0.72)
8		Forstpointner and HMRN	NA	1.1	(0.56, 2.17)	1.15	(0.35, 4.53)	(0.26,6 .28)	0.23(0.0 1,0.70)

Calculate HRs for ibrutinib versus R-chemo for PFS and OS in cells F10 and F11, respectively (1/HR in table above). Note that different HRs can be used by adapting these cell references. Name cells "HR_PFS" and "HR_OS"

Generate time-to-event curves for R-chemo (In worksheet "ERGcurves")

In cell S5, calculate OS projection for R-chemo using formula =O5^HR_OS. Fill down

In cell T5, calculate constrained PFS for R-chemo using formula =IF((P5^HR_PFS)>ERGcurves!S5,ERGcurves!S5,(P5^HR_PFS))

In cell U5, calculate constrained TTD/D for R-chemo using formula =IF(Q5<T5,Q5,T5). Note that applying an HR<1 means that the TTD/D for R-chemo will always be constrained to the R-chemo PFS curve.

Convert ibrutinib model to partitioned survival approach (in worksheets "Model ibru" and "PC")

In column G18, apply =VLOOKUP with approximate match to the constrained ibrutinib TTD/D curve in worksheet "ERGcurves"

In column I18, apply =VLOOKUP with approximate match to the constrained ibrutinib PFS curve in worksheet "ERGcurves"

In column S18, apply =VLOOKUP with approximate match to the constrained ibrutinib OS curve in worksheet "ERGcurves"

Recalculate trace (in worksheets "Model ibru" and "PC")

In column T, set cumulative death probability equal to 1-OS curve

In column Q, calculate PPS as $S(t)_{OS}$ minus $S(t)_{PFS}$

Fill formulae down

Ibrutinib for treating relapsed or refractory mantle cell lymphoma: A Single Technology Appraisal

Erratum in response to the fact check

Produced by School of Health and Related Research (ScHARR), The University of Sheffield

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21st June 2016

additional non-ibrutinib study (OPTIMAL) was included for the indirect comparison of ibrutinib versus single-agent chemotherapy.

At the time of the company's submission, the median OS was not reached in the ibrutinib arm of the RAY (MCL3001) study (n=139) or in the SPARK (MCL2001) study (n=120). In Study PCYC1104 (n=111), median OS was 22.5 months.

Median PFS for ibrutinib-treated patients was 14.6 months in the RAY (MCL3001) study, 13.0 months in the final analysis of Study PCYC1104, and 10.5 months in the SPARK (MCL2001) study. In the RAY (MCL3001) study, median PFS within the TEM arm was 6.2 months; this was significantly worse than for the ibrutinib arm (hazard ratio [HR]=0.43, 95% confidence interval [CI] 0.32; 0.58; p<0.0001). Overall response rates (ORR) assessed by independent review committee (IRC) were similar for ibrutinib-treated patients across studies (71.9% in RAY [MCL3001], 69% in Study PCYC1104 and ~~69~~62.7% in SPARK [MCL2001]). In RAY (MCL3001), there was a significant advantage for ibrutinib over TEM (ORR 40.4%, odds ratio [OR]=3.98, 95% CI 2.38, 6.65, difference in ORR p<0.0001).

Health-related quality of life (HRQoL) was measured by Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym) in the RAY (MCL3001) and SPARK (MCL2001) studies. The percentage of patients reporting clinically meaningful improvement was 61.9% in ibrutinib-treated patients in the RAY (MCL3001) study, and [redacted] in the SPARK (MCL2001) study. Within RAY (MCL3001), significantly fewer TEM-treated patients reported clinically meaningful improvement (35.5%, p<0.0001).

Across studies, the most common adverse events (AEs) for ibrutinib (≥20% of patients) were: diarrhoea; cough; fatigue; thrombocytopenia; neutropenia; peripheral oedema; nausea; muscle spasms, and; pyrexia.

The company's indirect comparison of ibrutinib versus single-agent chemotherapy suggests that ibrutinib is associated with a slower rate of disease progression compared with single-agent chemotherapy (HR=0.19, 95% CI 0.10, 0.36) and a survival benefit (HR=0.61, 95% CI 0.34, 1.10), although the result for OS is inconclusive as it did not reach statistical significance at the 95% level. Rituximab is used in routine clinical practice in England, therefore to account for the differential effectiveness of using rituximab alongside chemotherapy, the company performed an additional adjustment to the HR for PFS. The adjusted HR for PFS for ibrutinib versus R-chemo was estimated to be 0.28.

Table 8: Characteristics of ibrutinib studies

Trial	Trial design	Sample size	Dates of enrolment	Population	Intervention	Comparator	Outcomes
RAY (MCL3001)	Phase III open-label RCT Multicentre international	280 Allocated to Ibrutinib n=139; TEM n=141	December 2012 – November 2013 (dates assessed for eligibility)	R/R MCL At least one prior R-chemo	Ibrutinib 560mg orally o.d.	TEM (i.v.) days 1, 8 and 15 of 21-day cycles 175 mg first cycle, 75 mg subsequent cycles	Primary PFS (IRC assessed) Secondary OS One year survival rate PFS2, DOR, ORR – CR and PR (IRC assessed) Time to next treatment, FACT-Lym, EQ-5D-5L, AEs
PCYC1104	Single-arm Phase II open-label Multicentre international	115 enrolled (data from n=11~~0~~ who received drug)	February 2011 – March 2012 (enrolment)	R/R MCL At least one prior treatment	Ibrutinib 560mg orally o.d.	N/A	Primary ORR (PR or CR) investigator assessed Secondary DOR, time to response, PFS, OS, AEs Other ORR and DOR IRC-assessed
SPARK (MCL2001)	Single-arm Phase II open-label Multicentre international	120 enrolled	July 2012 (study initiated)	R/R MCL At least one prior R-chemo and progressed after bortezomib	Ibrutinib 560mg orally o.d.	N/A	Primary ORR (PR or CR) Secondary Time to initial response, DOR, PFS, OS FACT-Lym, EQ-5D-5L, AEs

Taken from CS Table 12, Dreyling et al,[15] CS Table 29, Wang et al 2013,[32] and Wang et al 2014[34]
RCT – randomised controlled trial; TEM – temsirolimus; R/R MCL – relapsed/refractory mantle cell lymphoma; i.v. – intravenous; N/A – not applicable; PFS – progression-free survival; IRC - independent review committee; PFS2 – progression-free survival after next line of therapy; DOR - duration of response; CR – complete response; PR – partial response; AE – adverse event

Table 9: Baseline characteristics of ibrutinib studies

Characteristic	RAY (MCL3001) Ibrutinib N=139	RAY (MCL3001) TEM N=141	PCYC1104 N=111 (with data from 115 enrolled)	SPARK (MCL2001) N=120
Median age (range)	67.0 (39-84)	68.0 (34-88)	68 (40-84)	67.5 (35-85)
Age < 65 no. (%)	53 (38.1%)	54 (38.3%)	41 (36.9%)	45 (37.5)
Age ≥ 65	86 (61.9%)	87 (61.7%)	70 (63.1%)	75 (62.5%)
Male sex, no (%)	100 (71.9%)	108 (76.6%)	85 (77%)	104 (86.7%)
Race, no (%)				
White	115 (82.7%)	129 (91.5%)	102 (91.9%)	113 (94.2%)
Asian	16 (11.5%)	5 (3.5%)	1 (0.9%)	0
Other	3 (2.2%)	4 (2.8%)	8 (7.2%)	2 (1.7%)
Unknown/ not reported	5 (3.6%)	3 (2.1%)	0	5 (4.2%)
ECOG PS, no (%)				
0	67 (48.2%)	67 (47.5%)	51 (45.6%)	42 (35.0)
1	71 (51.1%)	72 (51.1%)	48 (43.2%)	67 (55.8)
2	1 (0.7%)	3 (1.4%)	11 (10%)	11 (9.2)
>2	0	0	1 (1%)	0
Median time from initial diagnosis to randomisation (months)	38.90	46.23	42.35 (time to first dose)[37]	43.9 (time to first dose)
Mean time from initial diagnosis to randomisation (months)	49·98 (SD 42·71)[15]	51·17 (SD 33·60)[15]		
Median time from end of last prior therapy to randomisation (months)	8.25	7.03	2.65[37]	[redacted]
Stage of MCL at study entry, no (%)				
I	3 (2.2%)	2 (1.4%)	NR	[redacted] ~~NR~~
II	7 (5.0%)	5 (3.5%)	NR	[redacted] ~~NR~~
I or II	10 (7.2%)	7 (4.9%)	NR	11~~7~~ (9.2%)
III	17 (12.2%)	14 (9.9%)	NR	16 (13.3%)
IV	112 (80.6%)	120 (85.1%)	NR	93 (77.5%)
III or IV	129 (92.8%)	134 (95.0%)	80 (72%)	109 (~~77.3~~90.8%)
Extent of disease				
Bulky disease: LD ≥ 5cm, n (%)	74 (53.2%)[15]	75 (53.2%)[15]	43 (38.7%)[37]	63 (52.5)
Extranodal disease, no (%)	83 (59.7%)	85 (60.3%)[15]	60 (54.1%)[37]	72 (60.0)
Bone marrow involvement, no (%)	[redacted]	[redacted]	54 (48.6%)	50 (41.7)
Blastoid Histology no (%)	16 (11.51%)	17 (12.06%)[15]	17 (15.32%)	11 (9.17%)
Simplified MIPI, no (%)				
Low risk (1-3)	44 (31.7%)	42 (29.8%)	15 (14%)	28 (23.7)
Intermediate risk (4-5)	65 (46.8%)	69 (48.9%)	42 (38%)	57 (48.3)
High risk (6-11)	30 (21.6%)	30 (21.3%)	54 (49%)	33 (28.0)

Concomitant therapies were allowed in all three studies (see clarification response,[21] question B3). In the RAY (MCL3001) trial, standard supportive care therapies (e.g. anti-emetics, loperamide) other than anticancer treatment required for the management of symptoms as clinically indicated, were allowed (see CS,[1] page 57). Haematopoietic growth factors were also allowed. Prohibited medications included: any chemotherapy; anticancer immunotherapy; experimental therapy, and; radiotherapy. Systemic use of corticosteroids (i.e. any systemic corticosteroids ≥20mg/day prednisone or its equivalent per day for more than 10 days) was prohibited.

SPARK (MCL2001) allowed standard supportive care therapies required for the management of symptoms, as clinically indicated, other than anticancer treatment . Haematopoietic growth factors could be administered according to the American Society of Clinical Oncology (ASCO) or institutional guidelines. ~~and haematopoietic growth factors.~~ Prohibited medications included: any chemotherapy; anticancer immunotherapy; experimental therapy, and; radiotherapy. Systemic use of corticosteroids (i.e. any systemic corticosteroids ≥20mg/day prednisone or its equivalent per day for more than 10 days) was prohibited. Patients were excluded if they required concomitant treatment with strong CYP3A4/5 inhibitors or anticoagulation with warfarin or equivalent vitamin K antagonists (see CS,[1] page 94).

In the PCYC1104 study, use of haematopoietic growth factors was permitted after treatment cycle 1 according to the ASCO guidelines,[40] whereas concomitant use of strong CYP3A4/5 or CYP2D6 inhibitors, or strong CYP3A4/5 inducers, was to be avoided, if possible.[37]

At time of primary analysis in the single-arm studies, median time on ibrutinib was 8 months, and for the RAY (MCL3001) trial, median time on ibrutinib was 14.39 months (see Table 10).

Table 10: Reasons for discontinuation of allocated treatment

	RAY (MCL3001) Ibrutinib N=139	**RAY (MCL3001) TEM N=141**	**PCYC1104 N=111 (at time of primary analysis)**	**SPARK (MCL2001) N=120 (at time of primary analysis)**
Median time on allocated treatment, months	14.39 (range 0.0-28.2)[15]	3.02 (range0.0-27.0)[15]	8.3 (range 0.7, 21.4)[37]	8.0 (range 0.5-20.9) (CS[1] page 95)
Reasons for treatment discontinuation	74 discontinued comprising 55 disease progression 9 AEs 6 deaths 4 refused further treatment	124 discontinued comprising 58 disease progression 36 AEs 16 refused further treatment 6 investigator/ funder decisions 8 deaths	65 discontinued comprising 49~~50~~ disease progression 7 patient of investigator decision 9~~8~~ AEs[32]	81 discontinued comprising 53 disease progression 8 AEs (CS[1] page 95) [redacted]

Adapted from CS[1] Sections 4.5.1 and 4.11.2.3, Dreyling et al,[15] Wang et al 2013,[32] CHMP assessment report,[37] SPARK (MCL2001) CSR[33]
TEM – temsirolimus

In all three studies, progressed patients could go on to receive subsequent anticancer therapies, including therapies not routinely available in clinical practice in England; these may have affected outcomes collected post-progression.

In the RAY (MCL3001) trial, at time of the primary analysis (20 months median follow-up), there was crossover of 32 (23%) patients in the TEM arm to ibrutinib treatment. Subsequent anti-neoplastic systemic therapy was received by 31.7% (n=44) of patients in the ibrutinib arm, and by 58.2% (n=82) in the TEM arm, including the 32 patients who received ibrutinib (see Table 11).

4.2.2 Overall survival

The RAY (MCL3001) study defined OS as the duration from the date of randomisation to the date of the subject's death from any cause. Survival time of living subjects was censored on the last date a subject was known to be alive or lost to follow-up. The estimate of OS included all patients in the ITT population, including patients in the TEM arm who crossed over to ibrutinib as part of the amended protocol. A *post hoc* sensitivity analysis of OS was performed in which data from patients who crossed over from the TEM arm to receive ibrutinib during the study or who had received ibrutinib as subsequent therapy were censored at the date of the first dose of next-line ibrutinib treatment (a "censor at switch" analysis). The result was consistent with that recorded using the ITT analysis set. Median OS was not reached at time at which the CS was submitted (see Table 12).

For Study PCYC1104, at final analysis (26.7 months follow-up), the median OS was 22.5 months (95% confidence interval [CI] 13.7 months, not evaluable [NE]). At the primary analysis, median OS was not evaluable. For the SPARK (MCL2001) study, at a median follow-up of 14.9 months, median OS was not reached.

[redacted]

Table 12: Overall survival

Outcome	**RAY (MCL3001) Ibrutinib N=139 (ITT)**	**RAY (MCL3001) TEM N=141**	**PCYC1104 N=111**	**SPARK (MCL2001) N=120** Primary analysis
OS rate at 12 months, %	68% (95% CI: 59%, 75%)	61% (95% CI: 52%, 69%)	Primary analysis 64.2% (95% CI 54.0, 72.7)	[redacted]
OS rate at 18 months	[redacted][2][6]	[redacted][2][6]	Primary analysis 58.2% (95% CI 47.3, 67.6)	61% [redacted]
Median (95% CI) OS, months	NE [redacted][26]	21.3 [redacted][26]	Final analysis 22.5 (13.7, NE)	NE [redacted][33]
HR (95% CI) ibrutinib versus TEM	0.76 (95% CI: 0.53; 1.09, *p*=0.1324)		N/A	N/A

Adapted from CS[1] Sections 4.7.2.2 and 4.11, RAY (MCL3001) CSR,[26] and SPARK (MCL2001) CSR[33]
ITT – intention to treat; TEM - temsirolimus OS – overall survival; CI – confidence interval; NE – not evaluable; HR – hazard ratio; N/A – not applicable

The ITT analysis of the RAY (MCL3001) study reported a non-significant effect for OS. The CS suggests that this is due to sample size and the use of subsequent therapy following progression.

The CS suggests that crossover to ibrutinib of 22.3% of patients in the TEM arm may have influenced the OS results. However, according to Dreyling *et al*:[15] *"A post hoc sensitivity analysis of overall survival was done in which data from patients in the temsirolimus group who crossed over to receive*

PFS for patients with <2 cycles prior bortezomib (n=63) was 7.4 months (95% CI 5.3 months, 19.2 months).

The power calculation for PCYC1104 had expected the bortezomib exposed (≥2 cycles) cohort to have lower response by ORR than the subgroup bortezomib treatment (<2 complete cycles or no treatment). However, the CS uses data from RAY (MCL3001) subgroups to suggest that prior bortezomib was not prognostic (see CS,[1] Appendix 8). It is possible that bortezomib is not the factor explaining the difference in results between the two cohorts of PCYC1104, but instead the difference is due to the prior bortezomib group being more heavily pre-treated, with a median of three, rather than two, prior LOTs. The ERG notes that as the disease progresses it becomes more difficult to treat.

Table 13: Progression-free survival

Outcome	**RAY (MCL3001) Ibrutinib N=139**	**RAY (MCL3001) TEM N=141**	**PCYC1104 N=111 Primary analysis**	**SPARK (MCL2001) N=120 Primary analysis**
PFS rate at 12 months (95% CI)	[redacted][26]	[redacted]	50.6% (40.6, 59.7)[37]	47% [redacted]
PFS rate at 2 years, %	41%	7%	NR	NR
Median (95% CI) PFS, months	14.6 (10.4; NE)	6.2 (4.2; 7.9)	13.9 (7.0, NE)	10.5 (4.4-15)
HR (95% CI) ibrutinib versus TEM	0.43 (0.32; 0.58), *p*<0.0001		N/A	N/A
Adjusted* HR (95% CI) ibrutinib versus TEM	0.41 (0.30, 0.57)		N/A	N/A
Subgroup sMIPI low risk HR (95% CI) ibrutinib versus TEM	0.29 (95% CI 0.16, 0.53)		N/A	N/A
Subgroup sMIPI intermediate risk HR (95% CI) ibrutinib versus TEM	0.50 (95% CI 0.32, 0.78)		N/A	N/A
Subgroup sMIPI high risk HR (95% CI) ibrutinib versus TEM	0.44 (95% CI 0.25, 0.78)		N/A	N/A
Subgroup 1 or 2 prior LOTs HR (95% CI) ibrutinib versus TEM	0.39 (95% CI 0.26, 0.59)		N/A	N/A
Subgroup 3 or more prior LOTs HR (95% CI) ibrutinib versus TEM	0.50 (95% CI 0.32, 0.77)		N/A	N/A

Adapted from CS[1] Table 19, SPARK (MCL2001) CSR,[26] EMA CHMP assessment report[37] and Dreyling et al[15]
**adjusted for baseline ECOG performance status, sMIPI, blastoid histology and previous lines of therapy*
TEM – temsirolimus; PFS – progression-free survival; CI – confidence interval; NR – not reported; NE – not evaluable; HR – hazard ratio; N/A – not applicable; sMIPI - Simplified Mantle Cell Lymphoma International Prognostic Index; LOTs – lines of therapy

RAY (MCL3001) also measured PFS2 which was defined as the time interval between the date of randomisation and the date of an event, where events were defined as progressive disease as assessed by the investigator after the next line of therapy, death from any cause, or start of subsequent therapy if no disease progression is noted. Median PFS2 for the ibrutinib group was 19.1 months; this was significantly higher than the 11.3 months observed in the TEM group (HR 0.49, 95% CI 0.36, 0.69; $p<0.0001$).

Subgroup analyses of PFS from RAY (MCL3001) found most subgroups (sex; race; region; age; baseline extranodal disease; baseline ECOG; sMIPI; prior LOTs; stage of disease; tumour bulk; refractory disease) showed a significant advantage for ibrutinib over TEM. The exceptions were patients with blastoid histology (n=33; PFS median 4.1 months) and patients treated with prior bortezomib (n=5030; PFS median 7.9 months). The CS suggests that the small sample size means that results for both of these should be interpreted with caution. The CS also points out that the SPARK (MCL2001) study enrolled patients with prior bortezomib and found a median PFS of 10.5 months. [redacted]

Randomisation in RAY (MCL3001) was stratified by number of prior LOTs (1 or 2 versus 3 or more) and Simplified Mantle Cell Lymphoma International Prognostic Index (sMIPI). HRs for PFS for ibrutinib versus TEM according to sMIPI (see Table 13) were: low risk HR=0.29 (95% CI 0.16, 0.53); intermediate risk HR=0.50 (95% CI 0.32, 0.78); high risk HR=0.44 (95% CI 0.25, 0.78). HRs for prior LOTs were: 1 or 2 LOTs HR=0.39 (95% CI 0.26, 0.59); 3 or more LOTs HR=0.50 (95% CI 0.32, 0.77).

A *post hoc* analysis of prior LOTs looked at 1 prior line vs 2 or more prior lines; the ERG notes that this breaks stratified randomisation as stratification was for 1 or 2 versus 3 or more prior LOTs. Section 4.8.2 of the CS presents Kaplan-Meier curves for PFS suggesting an advantage for ibrutinib, although not for TEM, for patients with 1 prior LOT compared with 2 prior LOTs.

The pooled analysis of the ibrutinib arm of RAY (MCL3001) (IRC-assessed PFS), PCYC1104 (investigator-assessed PFS) and SPARK (MCL2001) (IRC-assessed PFS), had a median PFS of [redacted] For patients with one prior LOT (n=99), median PFS was [redacted]. For patients with more than one prior LOT (n=271), median PFS was [redacted]

Version 4.03. AEs led to dose reduction for 3.6% patients in the ibrutinib arm of the RAY (MCL3001) trial. In the RAY (MCL3001) trial, 6.5% of patients treated with ibrutinib discontinued treatment because of AEs. This was similar to the rate of discontinuation due to AEs in the SPARK (MCL2001) study (6.7%). In the PCYC1104 study, 10 patients (9.0%) discontinued ibrutinib treatment due to treatment-emergent AEs at the time of cut off for the primary endpoint.[32] However, 8 patients were classified as discontinuing due to AEs [redacted].[32, 43] In the long-term extension of Study PCYC1104, 11.7% total discontinued due to AEs (see CS,[1] Table 43).

Table 19: Adverse events reported in the ibrutinib studies

Adverse event	**RAY (MCL3001) Ibrutinib N=139***	**PCYC1104 primary analysis n=111 and n=9 from Phase I study of ibrutinib in MCL[37] (total n=120)†**	**SPARK (MCL2001) Ibrutinib N=120‡**
Any AE	138 (99.3%)	119 (99.2%)	[redacted][36]
Grade ≥3	94 (67.6%)	92 (76.7%)	[redacted]
Drug related (any grade)	[redacted]	108 (90.0%)	[redacted]
Any SAE	[redacted]	71 (59.2%)	[redacted]
Grade ≥3	[redacted]	62 (51.7%)	[redacted]
Drug related SAE	[redacted]	29 (24.2%)	[redacted]
AEs leading to treatment discontinuation	9 (6.5%)	14 (11.7%)	20 (16.7%)
AEs with outcome death	[redacted]	Death during or with 30 days of treatment 17 (14.2%)	[redacted]

Adapted from CS Table 44 and ibrutinib CHMP assessment report[37] and SPARK (MCL2001) CSR[33]
** RAY (MCL3001) median treatment duration 14.1 months.*
† PCYC1104 and ibrutinib Phase I study median treatment duration 8.3 months.
‡ SPARK (MCL2001) median treatment duration 8 months.
AE – adverse event; SAE – serious adverse event

In the ibrutinib arm of the RAY (MCL3001) trial, the most common AEs (≥20% of patients) were: diarrhoea (29%); cough (22%), and; fatigue (22%). Grade 3 or higher AEs were reported in 67.6% of ibrutinib patients. The most frequently occurring Grade 3 or higher AE (≥ 10% of patients) in the ibrutinib arm was neutropenia (12.9%). [redacted]

The PCYC1104 study had long-term follow-up (median 26.7 months). The most common AEs (≥20% of patients) were: diarrhoea (54.1%); fatigue (49.5%); nausea (33.3%); dyspnoea (32.4%); [redacted] and;

thrombocytopenia (21.6%). The prevalence of Grade 3 or higher infections was 27%. The incidence of additional malignancies was 4%.[37]

(EAP) in the United States, 4/149 (2.7%) patients discontinued treatment due to AEs. Other results from the EAP (detailed on page 116 of the CS[1]) reported were: Grade 3 and above AEs - 59 patients (39.6%); any SAEs - 46 patients (30.9%); serious non-fatal AEs of atrial fibrillation - 3 patients (2.0%), and; serious non-fatal AE of atrial flutter - 1 patient (0.7%). Two cases of major haemorrhage without precedent trauma or anticoagulation exposure were reported.

Table 21: Summary of AEs in both treatment arms in RAY (MCL3001) (reproduced from CS Table 44)

Adverse event	**Ibrutinib (n=139)**	**TEM (n=139)**
Any AE	138 (99.3%)	138 (99.3%)
Grade ≥3	94 (67.6%)	121 (87.1%)
Drug related	[redacted]	[redacted]
Any SAE	[redacted]	[redacted]
Grade ≥3	[redacted]	[redacted]
Drug related	[redacted]	[redacted]
AEs leading to treatment discontinuation	9 (6.5%)	36 (25.5%)
Dose reduction due to AEs	5 (3.6%)	60 (43.2%)
AEs with outcome death	[redacted]	[redacted]

Data taken from Dreyling et al and RAY (MCL3001) CSR[26]
TEM – temsirolimus; AE – adverse event

[redacted]

4.3 Trial identified and included in the indirect comparison

No head-to-head trials comparing ibrutinib against comparators listed in the final NICE scope[11] were identified. Section 4.10 of the CS describes attempts to identify evidence comparing ibrutinib to

treatments currently used in practice in the UK. However, no such trials were identified within the CS. Clinical advisors to the ERG were not aware of any such comparative studies. Consequently, the

Characteristic	RAY (MCL3001) Ibrutinib N=139	RAY (MCL3001) TEM N=141	OPTIMAL TEM 175/75mg N=54	OPTIMAL Single-agent chemo N=53
8 or more prior regimens	1 (0.7%)	[redacted]	0	0
Prior haematopoietic stem cell transplantation	33 (23.74%)	[redacted]	17 (32%)	20 (37%)
Prior bortezomib	30 (21.6%)	20 (14.18%)[15]	10 (19%)	17 (31%)

Data taken from CS[1] Table 39, company's clarification response,[21] Dreyling et al,[15] RAY (MCL3001) CSR,[26] and Hess et al[8]
TEM - temsirolimus; MCL - mantle cell lymphoma; LOT - line of therapy

The baseline characteristics of the TEM 175/75mg and single-agent chemotherapy arms of the OPTIMAL trial were similar, except that no patients in the TEM arm had blastoid histology compared with 7% of the single-agent chemotherapy arm, fewer patients in the TEM arm had received prior bortezomib, and the median number of prior LOTs was lower in the TEM arm (median LOTs=3) compared with the single-agent chemotherapy arm (median LOTs=4). The difference in number of prior LOTs may have biased results in favour of TEM. An analysis excluding patients with blastoid histology did not change results of the statistical analyses.[8]

Outcomes for the OPTIMAL trial are shown in Table 24. There was no significant treatment group difference for OS (p=0.3053 at July 2007 datacut; p=0.3519 at February 2008 datacut), however the study was not adequately powered to detect a difference in this endpoint. There was a non-significant trend for improved PFS for TEM 175/75mg versus single-agent chemotherapy (p=0.0618). Patients in the TEM 175/75mg arm had a significantly better ORR than those in the single-agent chemotherapy arm (p=0.0019).[8]

Table 24: Outcomes of the OPTIMAL trial

Outcome	OPTIMAL TEM 175/75mg N=54	OPTIMAL Single-agent chemo N=53	Between group comparison
OS datacut July 19th 2007 (95% CI) months	11.1 months (8.2, 18.0)	9.5 months (5.3, 15.1)	HR 0.77 (0.46, 1.28)
OS datacut February 1st 2008 (95% CI) months	12.8 months (8.6, 19.3)	9.7 months (5.8, 15.07.2, 14.6)	HR 0.80 (0.50, 1.28)
PFS IRC-assessed (97.5% CI) months	4.8 months (3.1, 8.1)	1.9 months (1.6, 2.5)	HR 0.44 (97.5% CI 0.25, 0.78)
ORR IRC-assessed (95% CI) months	22% (11, 33)	2% (0, 5)	OR 15.14 (1.89, 121.19)

Data taken from CS[1] Section 4.10 and Hess et al[8]
TEM - temsirolimus; OS - overall survival; CI - confidence interval; HR - hazard ratio; PFS – progression-free survival; IRC - independent review committee; ORR - overall response rate; OR - odds ratio

Table 25 reports outcomes from RAY (MCL3001) at a median duration of treatment 14.4 months for ibrutinib and 3.0 months for TEM.[15] Median duration of treatment in OPTIMAL was 12 weeks (range 1 to 97 weeks) in the TEM 175/75mg arms and 5 weeks (range 1 to 35 weeks) in the single-agent chemotherapy arm. Outcomes for the TEM arm of RAY (MCL3001) were better than for the TEM 175/75mg arm of OPTIMAL. Tumour response in OPTIMAL was assessed using the Modified Criteria for NHL published in 1999.[44] RAY (MCL3001) used modified criteria published in 2007.[38]

Table 25: Outcomes of RAY (MCL3001) and OPTIMAL trials

Outcome	**RAY (MCL3001) Ibrutinib N=139**	**RAY (MCL3001) TEM N=141**	**OPTIMAL TEM 175/75mg N=54**	**OPTIMAL Single-agent chemo N=53**
Median OS months	Not reached	21.3	12.8	9.7
Median PFS months	14.6	6.23	4.8	1.9
ORR	71.9%	40.4%	22%	2%

Data taken from CS[1] Sections 4.7 and 4.10 and Hess et al[8]
TEM – temsirolimus; TPC – physician's choice of chemotherapy; OS – overall survival; PFS – progression free survival; ORR – overall response rate

There were some differences in the baseline characteristics of patients in the TEM arms of the OPTIMAL and RAY (MCL3001) trials (see Table 23). In the OPTIMAL study, there were no patients in the TEM arm with Stage I and II cancer, whilst in the RAY (MCL3001) study, a small percentage (5.0%) of patients had Stages I and II cancer in the TEM arm. Patients in OPTIMAL were more heavily pre-treated than patients in RAY (MCL3001). Patients in the TEM arm of the OPTIMAL study had more prior LOTs than patients in the TEM arm of the RAY (MCL3001) study (median 3 and 2 respectively).

An analysis of patients with fewer than three prior LOTs (number of patients not reported) in the TEM 175/75mg arm of the OPTIMAL study reported a median PFS of 7.4 months.[8] The outcome for this subgroup was more similar to that of the RAY (MCL3001) TEM treated patients. For patients with three or more prior LOTs in the TEM 175/75mg arm of OPTIMAL, median PFS was 4.5 months.

4.4 Summary and critique of the indirect comparison

4.4.1 Summary of analyses undertaken

The indirect comparison reported in the company's clinical section compares the treatment effects of ibrutinib versus single-agent chemotherapy for three outcomes: (i) PFS; (ii) OS and (iii) ORR. The indirect comparisons were undertaken for each outcome separately. The indirect comparison was conducted using the RAY (MCL3001) and OPTIMAL trials using TEM as a common comparator

- The OPTIMAL study involved only single-agent chemotherapy; all options defined in the final NICE scope[11] (except cytarabine) relate to combination chemotherapy regimens.
- The adjusted HR for PFS which is used to reflect the "rituximab effect" was drawn from the HMRN audit.[7] This analysis does not specifically relate to patients with relapsed/refractory disease, does not differentiate between chemotherapy regimens, and has been estimated only in those patients achieving response (n=108). It is also noteworthy that since this is not a trial, differences in outcomes between patients receiving R-chemo and those receiving chemotherapy alone may be subject to confounding. The HR reported in the audit includes adjustments only for age and sex.
- The CS[1] (page 130) states that R-CHOP is perceived to be the most effective chemotherapy option available in the UK. However, the indirect comparison assumes that all R-chemo options are equivalent in terms of efficacy. One clinical advisor to the ERG suggested that R-bendamustine would be the treatment of choice rather than R-CHOP.
- The indirect comparison used in the health economic model is restricted to PFS. The company's clarification response[21] (question C11) states that *"there is no evidence to prove that the use of rituximab has an effect on survival beyond extension of PFS."* However, this is not true. Forstpointner *et al*[14] compared rituximab plus FCM versus FCM alone in the R/R MCL population. This study reported a statistically significant improvement in OS for patients in the rituximab plus FCM group (p=0.0042). The ERG notes that it would have been possible to compare ibrutinib versus R-chemo in terms of OS within an NMA (see Section 4.5). It should be noted however that only 52 patients in this trial had R/R MCL (although the published OS curve indicates that only 48 patients contributed data). It should also be noted that this study included a second re-randomisation for patients achieving complete or partial response; this may have impacted upon resulting OS estimates.

It should be noted that these issues relate to the evidence rather than the analytic method hence these concerns apply equally to the ERG's additional analyses. However, the ERG's analyses better represent the uncertainty surrounding the estimated treatment effect.

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG undertook an NMA comparing ibrutinib to R-chemo for both PFS and OS using random effects models based on the network shown in Figure 5. Since there were too few studies to estimate the between-study standard deviation from the sample data alone, and in the absence of further information on which to base the choice of prior, a weakly informative half-normal prior with variance 0.32^2 was used. The choice of this prior is discussed in more detail in NICE Decision

Support Unit (DSU) Technical Support Document (TSD) 3.[46] For all outcomes, a burn-in of 50,000 iterations of the

Only one RCT of ibrutinib was included in the company's review of clinical effectiveness. Given the scarcity of evidence, it was deemed acceptable to include lower quality study designs, in this case single-arm studies which are subject to selection bias. All trials were adequately powered for the primary endpoint of PFS (RAY [MCL3001]) or ORR (PCYC1104, SPARK [MCL2001]). All studies were open-label, and therefore prone to performance bias and measurement bias. HRQoL measures were prone to bias due to the study design. However, all studies addressed the issue of measurement bias for the primary outcome through the use of IRC assessment for the primary outcome.

At the time of the company's submission, median OS had not been reached in the ibrutinib arm of the RAY (MCL3001) study (n=139) or in the SPARK (MCL2001) study (n=120). In Study PCYC1104 (n=111), median OS was 22.5 months. The OS rate at 18 months for ibrutinib-treated patients was similar across studies (RAY - [redacted]; PCYC1104 - 58.2%; SPARK - 61%). In the RAY (MCL3001) study, TEM-treated patients (n=141) had a median OS of 21.3 months, but this did not differ significantly from the ibrutinib-treated patients (HR=0.76, 95% CI 0.53, 1.09; p=0.1324). The CS highlights that the RAY (MCL3001) study was not adequately powered to detect a treatment difference for OS. A "censor at switch" analysis reported by Dreyling *et al*[15] reported an HR for OS which was consistent with the ITT analysis. However, the use of subsequent anticancer therapies in both treatment arms may have affected OS.

Median PFS of ibrutinib-treated patients was 14.6 months in the RAY (MCL3001) trial, 13.0 months in the final analysis of PCYC1104, and 10.5 months in the SPARK (MCL2001) study. In the RAY (MCL3001) study, median PFS within the TEM arm was 6.2 months, which was significantly worse than the ibrutinib arm (HR=0.43, 95% CI 0.32; 0.58, p<0.0001).

ORR assessed by IRC was similar for ibrutinib-treated patients across studies (71.9% in RAY [MCL3001], 69% in PCYC1104, and 62.769% in SPARK [MCL2001]). In RAY (MCL3001), there was a significant advantage for ibrutinib over TEM (ORR 40.4%), odds ratio=3.98 (95% CI 2.38, 6.65).

HRQoL was measured by FACT-Lym in the RAY and SPARK studies, a measure validated for use in MCL. The percentage of patients reporting a clinically meaningful improvement was 61.9% in ibrutinib-treated patients in the RAY (MCL3001) study, and [redacted] in the SPARK (MCL2001) study. Within RAY (MCL3001), significantly fewer TEM-treated patients (35.5%, p<0.0001) reported a clinically meaningful improvement. A significant benefit for ibrutinib versus TEM was found in the percentage of patients reporting clinically meaningful worsening (26.6% versus 51.8%, p<0.0001). For SPARK (MCL2001), [redacted] of patients reported clinically meaningful worsening. EQ-5D-5L was

also assessed in RAY (MCL3001) and SPARK (MCL2001). In RAY (MCL3001), there was a significant treatment group difference favouring ibrutinib over TEM, starting in Week 4 of treatment

treatment of patients with R/R MCL. 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. 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 relapsed/refractory MCL
Intervention	Ibrutinib 4 x 140mg capsules (560mg) o.d.
Comparator	The base case assumes patients receive R-CHOP according to the regimen: • Rituximab - 375mg/m^2 i.v. on day 1, every 21 days for 6 cycles • Cyclophosphamide - 750mg/m^2 i.v. on day 1, every 21 days for 6 cycles; • Doxorubicin - 50mg/m^2 i.v. on day 1, every 21 days for 6 cycles; • Vincristine - 1.4mg/m^2 i.v. on day 1, every 21 days for 6 cycles; • Prednisolone - 100mg p.o. on days 1-5, every 21 days for 6 cycles Other R-chemo options are considered in the company's scenario analyses
Primary health economic outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Time horizon	Lifetime
Discount rate	3.5% per year
Price year	2014/2015

MCL - mantle cell lymphoma; R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; QALY – quality-adjusted life year; PSS - Personal Social Services

Population

The population considered within the company's model reflects those patients with R/R MCL who were enrolled into the RAY (MCL3001), SPARK (MCL2001) and PCYC1104 ibrutinib studies. Within the modelled ibrutinib group, data for patients receiving ibrutinib in these studies were pooled into a single dataset (see CS,[1] Section 4.12). At model entry, the population is assumed to be 68 years of age and 78.11% of patients are assumed to be male. The mean body mass of the population is assumed to be ~~77.39~~80.41kg.

The CS also includes subgroup analyses based on the pooled ibrutinib dataset for patients who have received 1 prior LOT or >1 LOT. Within this subgroup analysis, event probabilities are altered to reflect outcomes observed within the subgroup, however the structure of the model remains unchanged (see Section 5.2.2).

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 560mg daily (four capsules). The SmPC for ibrutinib states that treatment with ibrutinib should continue until disease progression or no

Table 32: R-chemo comparators evaluated in the company's base case and scenario analyses (adapted from CS Table 55)

R-chemo option	Assumed dosing and frequency
R-CHOP (base case analysis)	• Rituximab - 375mg/m^2 i.v. on day 1, every 21 days for 6 cycles; • Cyclophosphamide - 750mg/m^2 i.v. on day 1, every 21 days for 6 cycles; • Doxorubicin - 50mg/m^2 i.v. on day 1, every 21 days for 6 cycles; • Vincristine - 1.4mg/m^2 i.v. on day 1, every 21 days for 6 cycles; • Prednisolone - 100mg p.o. on days 1-5, every 21 days for 6 cycles. Treatment continued until disease progression or maximum treatment duration
R-CVP (scenario analysis)	• Rituximab - 375mg/m^2 i.v. on day 1, every 21 days for 6 cycles; • Cyclophosphamide - 750mg/m^2 i.v. on day 1, every 21 days for 6 cycles; • Vincristine: 1.4mg/m2 IV on day 1, every 21 days for 6 cycles • ~~Doxorubicin - 50mg/m^2 i.v. on day 1, every 21 days for 6 cycles;~~ • Prednisolone - 100mg p.o. on days 1-5, every 21 days for 6 cycles. Treatment continued until disease progression or maximum treatment duration
FCR (scenario analysis)	• Fludarabine - 30mg/m^2 i.v. on days 1-3, every 28 days for 6 cycles; • Rituximab - 375mg/m^2 i.v. on day 1, every 28 days for 6 cycles; • Cyclophosphamide - 250mg/m^2 i.v. on days 1-3, every 28 days for 6 cycles. Treatment continued until disease progression or maximum treatment duration
RC (scenario analysis)	• Rituximab - 375mg/m^2 i.v. on day 1, every 28 days for 6 cycles; • Cytarabine - 500mg/m^2 i.v. on days 2-4, every 28 days for 6 cycles. Treatment continued until disease progression or maximum treatment duration

R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-CVP - rituximab, cyclophosphamide, vincristine and prednisolone; FCR - fludarabine, cyclophosphamide and rituximab; RC - rituximab, cytarabine

In addition, the CS presents a further scenario analysis based on a blended comparison of ibrutinib versus R-CHOP, R-CVP and FCR. The use of RC is assumed to be zero. Within the blended comparison, the costs associated with each R-chemo regimen are weighted according to their expected usage (R-CHOP – 85%, R-CVP – 10%, FCR – 5%), however the health outcomes for each regimen are assumed to be the same. The ERG's concerns regarding the interpretation of this blended comparison are discussed in Section 5.3.

The base case analysis compares ibrutinib versus R-CHOP followed on progression by no further lines of therapy in either group. A secondary analysis is also presented in the CS in which ibrutinib followed on progression by R-CHOP is compared with R-CHOP (referred to in the CS as the "sequential" model).

An alternative scenario analysis is also presented in which both ibrutinib and R-CHOP are assumed to be followed on progression by FCR. In this analysis, only the costs for each group are affected; health outcomes in each group are assumed to be the same as those estimated within the base case analysis.

the pooled ibrutinib dataset[19] (CR [redacted]; PR [redacted], and; stable disease [redacted]). The response rate for R-chemo was obtained from the HMRN audit. Two steps were applied to obtain the response rate for R-chemo. Firstly the response rate to first-line R-CHOP was taken from the HMRN audit (response rate = 75.86%). Secondly the relative risk of response at second-line therapy (response rate = 32.97%) given the response rate at first-line chemotherapy (response rate = 41.87%) was used to calculate the relative risk of response of second-line chemotherapy compared to first-line chemotherapy (relative risk = 0.79). Based on these data, overall response to second-line R-CHOP treatment was calculated to be 59.73%;[7] the remainder (40.27% patients) were assumed to have stable disease. The proportionate split of the ~~58.13~~59.73% R-chemo patients between CR and PR was based on the relative proportions of patients achieving CR and PR in the pooled ibrutinib dataset.[19] This resulted in an estimated [redacted] patients with CR and [redacted] with PR. Unit costs for each resource item were valued using NHS Reference Costs 2014/15.[58] Annual resource use for each response outcome, unit costs associated with each resource component and the total per cycle costs by response outcome are presented in Table 41.

7. DISCUSSION

Clinical effectiveness evidence

As R/R ~~CML~~ MCL is a relatively rare disease, there is very little real world data available. Only three studies of ibrutinib in R/R MCL patients were identified. These included one open-label RCT (RAY [MCL3001]) and two open-label single-arm studies (SPARK [MCL2001] and PCYC1104).

In RAY (MCL3001), the comparator was TEM, which is not used in clinical practice in England. In addition, RAY (MCL3001) was an open-label trial and was therefore potentially subject to bias, although the quality of the study was deemed adequate by CS and ERG. The primary endpoint in RAY (MCL3001) was assessed by an IRC masked to study treatment. PFS was significantly better in the ibrutinib arm than in the TEM arm. OS, however, was not significantly better in the ibrutinib arm than the TEM arm. It is uncertain if this lack of significant OS benefit was due to the use of subsequent therapies beyond progression (including treatment switching in the TEM arm) or the lack of adequate power for this outcome. Analysis suggested it was probably not due to TEM crossover. The TEM arm in the RAY (MCL3001) study reported better outcomes than the TEM arm within earlier studies (including the OPTIMAL trial). It is uncertain if this is due to improved supportive care in RAY (MCL3001) and the use of experimental therapies.

The two open-label studies were of lower quality design (single-arm), however, the results from these two studies are generally consistent with the ibrutinib arm of RAY (MCL3001). OS in both arms of the RAY (MCL3001) study was better than data reported within the HMRN audit. It is not clear if this was due to differences in populations, treatments or additional therapies received. Evidence from both the RAY (MCL3001) and SPARK (MCL2001) studies showed clinically meaningful improvement in HRQoL for approximately 62% of patients treated with ibrutinib. There are potential advantages for both patients and clinicians with ibrutinib as it is administered orally. This may impact on HRQoL. There was also an improved AE profile in the ibrutinib arm of RAY (MCL3001) compared to the TEM arm.

The company conducted an indirect comparison of ibrutinib versus single-agent chemotherapy for PFS, OS and ORR. Rituximab is used in routine clinical practice in England, therefore to account for the differential effectiveness of using rituximab alongside chemotherapy the company performed an additional adjustment to the HR for PFS. No adjustment was conducted for OS. The adjusted HR for PFS for ibrutinib versus R-chemo was estimated to be 0.28. The ERG considers that a single stage approach using a random effects NMA would provide a better representation of the uncertainty in the resulting treatment comparisons than the two stage procedure implemented by the company. Based on the ERG's additional analyses, ibrutinib is associated with a slower rate of disease progression, compared to R-chemo (random effects HR=0.27, 95% CrI 0.06, 1.26) although the result is

Appendix 3 – Technical details for implementing ERG Exploratory Analyses

Exploratory Analyses Set A

Exploratory Analysis A1. HR for PFS derived from ERG'S random effects NMA

Go to the "Clinical Inputs" worksheet

In cell I20 change the value to 0.27

Exploratory Analysis A2 - TTD/D for ibrutinib group based on Kaplan-Meier curve

Add a new worksheet to the workbook called "Sheet 1".

In cell B2 apply the following formula ='KM data'!A7. Fill down

In cell C2 apply the following formula ='KM data'!H7. Fill down

In cell A2 apply the following formula =B2/12. Fill down

Go to the "Model ibru" sheet

In cell G18 apply the following formula =VLOOKUP(C18,Sheet1!$A$2:$C$1557,3,TRUE). Fill down.

Exploratory Analysis A3. Truncation of R-chemo QALY loss following treatment discontinuation

Go to the "Model PC" worksheet.

In cell AT25 insert the value 0. Fill down

Exploratory Analysis A4. ERG's preferred analysis using the company's model

Apply the steps detailed above.

Exploratory Analysis A5. Use of alternative utility values for progression-free and post-progression states (using ERG's preferred base case)

Use the model which has was generated in Exploratory Analysis A4

Lachaine et al utility values

Go to the "Parameters" worksheet.

In cell D38 change the value to 0.805

In cell D41~~2~~ change the value to 0.618

Yoong et al utility values

Go to the "Parameters" worksheet.

In cell D38 change the value to 0.81

In cell D41~~2~~ change the value to 0.60

Issue 1 Relevance and limitations of the additional NMA presentation

Description of problem	Description of proposed amendment	ERG response
On page 67 the ERG notes that the results of the analysis for the indirect comparison of ibrutinib versus R-chemo using Forstpointner et al and HMRN should be “interpreted with caution”.	The company agree that the results of this analysis should be interpreted with caution and believe that a list of the limitations of this analysis may aid in understanding. Some of these limitations are: - Mitoxantrone is known as being a very toxic drug and therefore likely to affect the outcomes of the analysis. Mitoxantrone is not used in clinical practice and is not included in the NICE scope. - Paper includes a second randomisation to rituximab maintenance which is not part of UK clinical practice – rituximab effect therefore does not represent a standard course. There is no reporting of how many patients on each arm received this and this could have a major impact on outcomes for OS. - Small patient numbers in the Forstpointer et al paper: 24 patients in each arm (FCM and R-FCM). These small numbers may introduce several biases into the results (see Figure 3B – ERG reference to 52 patients may need correcting). - Median OS has not been reached within this analysis only 22 patients experience events over both arms (only 6 patients in the R-FCM arm). - It is unclear how the hazard ratio of 0.31 was derived given that median OS was not reached within the trial and a HR is not reported. Were the curves digitized? If so what method was used – with small numbers of events this could have a major impact. - Study was not stratified by histology which means that referring to the extremely small subgroup with MCL could have a large amount of bias associated – noted there are imbalances in the small number of patient characteristics reported including 13% of patients on the R-FCM having been fit enough to receive an SCT compare to 0% on the FCM arm.	This is not a factual error. The ERG however agrees that there are numerous problems associated with the use of the Forstpointer study (as indeed there are for the HMRN study). The inclusion of the second randomisation for patients achieving either complete or partial response does potentially lead to a treatment pathway for some patients that may not be typical in clinical practice in England. However, the treatment pathway in the HMRN audit is also not clear and only reflects those patients who achieved a response to first line therapy. For these reasons, the ERG did not place much weight on the NMA based on OS using either source. We have already highlighted the substantial influence of the rituximab effect on the results of the NMA within the report. No further amendment has been made to the report as the committee can see the company’s concerns within

	Similar issues apply to the HMRN data used including: - Reported only for newly diagnosed MCL patients not relapsed refractory MCL therefore this is a healthier group of patients - Non-randomised comparison We also note the statement provided by the ERG on page 14 that "Clinical advisors to the ERG noted that adding rituximab to chemotherapy was likely to offer a small benefit compared with the use of chemotherapy alone." This statement is also noted "Clinical advisors to the ERG also commented that the benefit of R-chemo would to be expected to reduce with increasing lines of therapy" – particularly given the heavily pre-treated nature of patients included in the pooled ibrutinib dataset. We would request that these statements are recalled when presenting this analysis as these statements perhaps provide some context in that we would not clinically expect the addition of rituximab to have the magnitude of impact estimated within the analyses presented.	this fact check document.

Issue 2 Inaccurate conclusion in the executive summary

Description of problem	Description of proposed amendment	ERG response
Page 9 states that ""The ERG's threshold analyses using the exploratory partitioned survival model consistently suggest that irrespective of the true value of the HR for PFS and the source of utility values, the HR for OS necessary for ibrutinib versus R-CHOP to have an ICER below £50,000 per QALY gained is around 0.39-0.40. Other things being equal, this would require the final datacut of the RAY (MCL3001) study to report an HR for ibrutinib versus TEM of 0.31. The ERG considers this outcome to be unlikely."	Correct statement to make clear that the decision problem specifies comparison to R-chemo not to TEM. TEM is considerably more expensive than R-chemo and also as per the ERG's statement on page 15 considered to be more effective: "Despite not being available in clinical practice, TEM is considered to be more effective than treatments currently used in England." In addition the discount level used to calculate this hazard ratio should be quoted.	The company has misinterpreted the point of the statement made within the executive summary. Where we refer to TEM, the point relates to the future datacut of the RAY (MCL3001) study. In the context of further research to inform the NMA, this is the more relevant HR to quote. All results presented in the executive summary include the PAS. This is clear since all results are redacted

	We would also appreciate reiteration that an additional discount is currently under negotiation which would affect the hazard ratio required.	and the PAS is quoted earlier in the executive summary.

Issue 3 Inaccurate statement regarding Forstpointer analysis

Description of problem	Description of proposed amendment	ERG response
On page 65 the ERG state: "The indirect comparison used in the health economic model is restricted to PFS. The company's clarification response (question C11) states that "there is no evidence to prove that the use of rituximab has an effect on survival beyond extension of PFS." However, this is not true. Forstpointner et al compared rituximab plus FCM versus FCM alone in the R/R MCL population. This study reported a statistically significant improvement in OS for patients in the rituximab plus FCM group (p=0.0042). The ERG notes that it would have been possible to compare ibrutinib versus R-chemo in terms of OS within an NMA (see Section 4.5). It should be noted however that only 52 patients in this trial had R/R MCL."	Change patient number to 48 (number reported in Figure 3B OS analysis). Please remove statement that this trial demonstrates impact of rituximab on OS beyond impact on PFS. The Forstpointer trial demonstrates an impact on OS of rituximab when maintenance therapy is also allowed in addition to FCM. It does not demonstrate a post progression survival benefit. Additionally all the limitations presented in point 1 apply (non-relevant treatment regimens, non-randomised comparison, extremely small patient numbers (n=6 events on R-FCM arm), median OS not reached, limited follow-up etc.). This paper does not appear to be relevant in calculating a rituximab effect on OS; or whether prolongation of OS beyond PFS is viable.	We have quoted the figure from the main text *"After correction by reference histology, 72 (49%) patients had a FL, 52 (35%) patients had an MCL, and 16 (11%) patients were diagnosed as lymphoplasmocytic/cytoid lymphoma."* (page 3066). We have added a sentence to reflect the apparently lower number of patients contributing OS data. With respect to the latter point, we have also included a caveat that a second re-randomisation was undertaken for patients achieving partial or complete response.

Issue 4 Clarification of statement regarding impact of subsequent therapy on PPS

Description of problem	Description of proposed amendment	ERG response
Page 117 states that "the company's claim that using	Correct statement regarding company claims that using PPS reduces potential bias. Claims did not relate to the ibrutinib arm in isolation but to comparison of data with	The ERG considers that the point made in the fact check response

PPS reduces potential bias due to the use of subsequent therapies in the clinical trials is invalid; the PPS data are also subject to the same potential bias"	that available for R-chemo. We agree that PPS data includes subsequent therapy as per the pooled dataset – the issue comes in when OS data are sourced from different trials which include different subsequent therapies (unknown in some cases); the impact of these on OS is unquantifiable and highly likely to be biased. At least by assuming fixed PPS the impact of subsequent therapy on all arms is assumed consistent.	does not reflect the point made in the company's clarification response. The statement included in the ERG report is factually correct with respect to the wording of the clarification response. With respect to the point made in the fact check response, the ERG does not consider that any evidence has been provided that the company's approach reduces bias. This is largely a consequence of the limited evidence for OS for any R/R MCL therapy.

Issue 5 Additional information on sequential approach (<u>no amendment needed</u>)

Description of problem	Description of proposed amendment	ERG response
Page 123 states that: "Mean survival and mean QALY gains in the R-chemo comparator group generated using the sequential model are reduced compared with those estimated in the base case analysis (see Table 55). The ERG considers this to be counter-intuitive: the costs and outcomes for the comparator therapy should be unaffected by alternative assumptions made regarding the intervention group."	For the information of the ERG. The sequential approach is used to demonstrate that the use of ibrutinib provides a further line of treatment for patients with R/R MCL. Once patients have received ibrutinib they will be likely to go on to receive subsequent R-chemotherapy treatment. Within the pooled ibrutinib data, patients go on to receive subsequent therapy (as they would in standard practice). The sequential approach uses the same health outcomes for ibrutinib assuming that benefit of subsequent treatment is captured by the PPS data. Costs and corresponding HRQL decrements are applied to the subsequent treatment within the ibrutinib arm to account for patients in ibrutinib going on to receive R-chemotherapy regimens. The comparator arm PPS is adjusted to reflect that it is unlikely in practice that patients receiving R-chemotherapy can receive subsequent similarly beneficial R-chemotherapy regimens. Therefore	The ERG's concerns regarding the sequential model still stand.

	the PPS survival would be lower than that observed within the ibrutinib arm. We do note the ERG's concern on the duration of PFS benefit assumed in the ibrutinib arm, however, and agree that a more appropriate assumption might have been a lower PFS period. It should be noted, however, that the results of this analysis differ little from the model base case as the costs and benefits of additional lines of treatment cancel each other out.	

Issue 6 Typographical errors

Description of problem	**Description of proposed amendment**	**ERG response**
The independent review committee (IRC) overall response rate (ORR) for the SPARK (MCL2001) study is reported incorrectly. Page 3: "Overall response rates (ORR) assessed by independent review committee (IRC) were similar for ibrutinib-treated patients across studies (71.9% in RAY [MCL3001], 69% in Study PCYC1104 and 69% in SPARK [MCL2001])." Page 68: "ORR assessed by IRC was similar for ibrutinib-treated patients across studies (71.9% in RAY [MCL3001], 69% in PCYC1104, and 69% in SPARK [MCL2001])."	The correct IRC ORR for SPARK (MCL2001) is 62.7%. The correct sentences have been rewritten below: "Overall response rates (ORR) assessed by independent review committee (IRC) were similar for ibrutinib-treated patients across studies (71.9% in RAY [MCL3001], 69% in Study PCYC1104 and 62.7% in SPARK [MCL2001])." "ORR assessed by IRC was similar for ibrutinib-treated patients across studies (71.9% in RAY [MCL3001], 69% in PCYC1104, and 62.7% in SPARK [MCL2001])."	Corrected pages are presented in the ERG addendum.
Page 19: The ERG report states that "Ibrutinib also holds a European marketing authorisation for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have	This is now incorrect as the licence of ibrutinib has recently been updated.	

received at least one prior therapy, or in first-line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy"	The correct wording regarding the licensing of ibrutinib in CLL should be as follows: "Ibrutinib as a single agent is indicated for the treatment of adult patients with previously untreated CLL. Ibrutinib is indicated for the treatment of adult patients with CLL who have received at least one prior therapy."[1]	
Page 20: The ERG report states that "the dose of ibrutinib should be lowered to 140mg o.d. or withheld for up to 7 days when used concomitantly with moderate CYP3A4 inhibitors". This statement should refer to strong CYP3A4 inhibitors (rather than moderate). Page 20: "Dose adjustments are recommended for patients with mild and moderate hepatic impairment". This is incorrect as dose adjustments are not needed for patients with mild and moderate hepatic impairment.	As per the SmPC for ibrutinib, the correct statement should be as follows: "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" As per the SmPC for ibrutinib, the correct statement here should be as follows: "No dose adjustment is needed for patients with mild or moderate renal impairment".	
Page 27: The ERG report states "On the whole, the outcomes listed in the final NICE scope[11] are included in the inclusion criteria for the review; however, HRQoL is not listed. Also, the exclusion criteria state that studies were excluded if they did not report safety or efficacy outcomes. It is thus unclear whether studies only reporting HRQoL would be excluded. There is no indication that studies reporting only HRQoL outcomes were excluded, although the company's PRISMA diagram states that seven studies were excluded on the basis of outcomes reported (see CS,[1] Figure 6)." However, it should be acknowledged that a separate systematic literature review (reported in Section 5.1 and Section 5.4.3 of the company submission) was conducted to identify HRQoL data.	The paragraph should be amended to note that a separate systematic literature review dedicated to identifying HRQoL outcomes was performed, to ensure the reader is not left in doubt that such outcomes were systematically searched for.	
Page 36, Table 8: Regarding the PCYC1104 study, the ERG report	The correct statement should read: "from	

states that 115 patients were enrolled and that data is “from n=110 who received drug”. This number should be n=111 instead. Page 42, Table 10: Regarding reasons for discontinuation in the PCYC1104 study, the ERG report states that 65 patients discontinued treatment in the study, comprising 50 patients due to disease progression, 7 patients due to patient or investigator decision and 8 patients due to adverse events (AEs). These patient numbers are reported incorrectly.	n=111 who received drug” The correct patient numbers regarding reasons for treatment discontinuation in the PCYC1104 study as per the PCYC1104 CSR are as follows: “65 patients discontinued, comprising 49 disease progression, 7 due to patient or investigator decision and 9 due to AEs”	
Page 39, Table 8: The ERG report states that 7 patients (9.2%) in the SPARK (MCL2001) study had stage I or II MCL at the start of study entry. This number should be 11 patients. Page 39, Table 8: The number of patients with stage I or II MCL disease, respectively, at the start of study entry has been detailed as NR. These values are in the CSR. Page 39, Table 8: The percentage of patients with stage III or IV disease has been reported as 77.3%. This is incorrect and should be 90.8%.	The correct statement should read: 11 (9.2%). The number of patients (%) with stage I disease was 2 (1.7%). The number of patients (%) with stage II disease was 9 (7.5%). The number of patients (%) with stage III or IV disease was 109 (90.8%).	
Page 41: The ERG report states that “SPARK (MCL2001) allowed standard supportive care therapies required for the management of symptoms, as clinically indicated, other than anticancer treatment and haematopoietic growth factors.” This statement is incorrect because haematopoietic growth factors were allowed in SPARK (MCL2001) according to the ASCO guidelines. Page 41: The ERG report states that “Systemic use of	The correct statement should read: “SPARK (MCL2001) allowed standard supportive care therapies required for the management of symptoms, as clinically indicated, other than anticancer treatment. Haematopoietic growth factors could be administered according to the American Society of Clinical Oncology (ASCO) or institutional guidelines.”	

corticosteroids (i.e. any systemic corticosteroids ≥20mg/day prednisone or its equivalent per day) was prohibited." Again this statement is technically incorrect since this prohibition only applied if systemic corticosteroids of this dosing were used for more than 10 days.	The correct statement should read: "Systemic use of corticosteroids (i.e. any systemic corticosteroids ≥20mg/day prednisone or its equivalent per day for more than 10 days) was prohibited."	
Page 44, Table 12: There is currently no overall survival (OS) rate at 12 months reported for the SPARK (MCL2001) study. There is also no confidence interval presented for the OS rate at 18 months. Both of these data are available in the SPARK (MCL2001) CSR.	The OS rate at 12 months in the SPARK (MCL2001) study was [redacted]. Please update these values accordingly. The OS rate at 18 months in the SPARK (MCL2001) study was 61% [redacted]. Please update these values accordingly.	
Page 46, Table 13: The ERG report states the PFS rate at 12 months (95% CI) for the ibrutinib arm in RAY (MCL3001) as "[redacted]". The value of [redacted] here is incorrect and should be [redacted]. Page 61, Table 25: The ERG report lists median PFS for the temsirolimus arm in RAY (MCL3001) to be 6.3 months. The correct value should be 6.2 months.	The correct statement for the PFS rate at 12 months for the ibrutinib arm in RAY (MCL3001) should read: "[redacted]" The correct value for median PFS in the temsirolimus arm of the RAY (MCL3001) study should be 6.2 months.	
Page 46, Table 13: The ERG report states the PFS rate at 12 months (95% CI) in the SPARK (MCL2001) study is 47%. For completeness, the confidence interval surrounding this result should be presented.	The correct statement for the PFS rate at 12 months in the SPARK (MCL2001) study should read: 47% [redacted].	
Page 47: "patients treated with prior bortezomib (n=30; PFS median 7.9 months)." The n number here should be n=50.	The correct statement should read: patients treated with prior bortezomib (n=50; PFS median 7.9 months)."	
Page 54, Table 19: The ERG report states that AEs leading to	The correct data should read: 20 (16.7%).	

treatment discontinuation in the SPARK (MCL2001) study were “20 (6.7%).” The percentage reported here is incorrect and should be 16.7%.		
Page 55: The ERG report states “This CUP, an international, multicentre open-label programme, reported data from 175 patients”. This number is incorrect and should be 715.	The correct sentence should read: “This CUP, an international, multicentre open-label programme, reported data from 715 patients”.	
Page 60, Table 24: The confidence interval for the OS datacut February 1st 2008 is reported as (7.2, 14.6). This is incorrect and should be (5.8–15.1).	The correct values should be reported.	
Page 69: The ERG report states: “Within the pooled analysis (n=370), [redacted]”. The value reported for median PFS in the pooled analysis here is incorrect. The correct value is 12.81 months.	The sentence should read: “Within the pooled analysis (n=370), median OS was 25.00 months, median PFS was 12.81 months and ORR was 66.22%”.	
Page 75 of the report, the mean body mass of the population reported in the model is stated to be 77.39kg Page 77 states that the dosing regimen for R-CVP should be: • Rituximab: 375mg/m^2 IV on day 1, every 21 days for 6 cycles • Cyclophosphamide: 750mg/m^2 IV on day 1, every 21 days for 6 cycles • Doxorubicin: 50mg/m^2 IV on day 1, every 21 days for 6 cycles • Prednisolone: 100 mg po on days 1-5, every 21 days for 6 cycles	The mean body mass of the population reported in the model is 80.41kg (as reported in Table 114 in the appendices within the CS) The dosing regimen should state: • Rituximab: 375mg/m^2 IV on day 1, every 21 days for 6 cycles • Cyclophosphamide: 750mg/m^2 IV on day 1, every 21 days for 6 cycles • Vincristine: 1.4mg/m^2 IV on day 1, every 21 days for 6 cycles • Prednisolone: 100 mg po on days 1-5, every 21 days for 6 cycles This is a result of Table 55 in the CS being incorrect.	
Value presented on page 93 stating that the proportionate split of 58.13% is an incorrect percentage	The proportionate split of 59.73%, R-chemo patients between CR and PR was based on the relative proportions of patients achieving	

	CR and PR in the pooled ibrutinib dataset.	
Page 149: “As R/R CML is a relatively rare disease, there is very little real world data available. Only three studies of ibrutinib in R/R MCL patients were identified.”	This is a typographical error and the correct sentence should read: “As R/R MCL is a relatively rare disease, there is very little real world data available. Only three studies of ibrutinib in R/R MCL patients were identified.”	
Page 165 states that “Use the model which has was generated in Exploratory Analysis A4 Lachaine et al utility values Go to the “Parameters” worksheet. In cell D38 change the value to 0.805 In cell D42 change the value to 0.61”	This refers to the incorrect cell in the model, and the post-progression utility value that should be changed is D41 such that: In cell D41 change the value to 0.61”	
Page 165 states that “Yoong et al utility values Go to the “Parameters” worksheet. In cell D38 change the value to 0.81 In cell D42 change the value to 0.60”	This refers to the incorrect cell in the model, and the post-progression utility value that should be changed is D41 such that: In cell D41 change the value to 0.60”	

Issue 7 Published data that reduce amount of AiC data

Description of problem	**Description of proposed amendment**	**ERG response**
Due to the recent publication of data on the pooled analysis of the three ibrutinib trials and the compassionate use programme (CUP), some of the following data do not need to be highlighted as academic in confidence. Page45: [redacted]	Some of the confidentiality highlighting relating to the pooled analysis can be removed, based on the presentation presented at the 21st Congress of the European Hematology Association (EHA), June 9-12, 2016 by Rule et al.[2] All confidentiality highlighting can be removed with the exception of the pieces of text noted for the specific pages below: Page 45: [redacted]	NICE will re-mark the relevant sections prior to circulating the committee papers.

[redacted] Page 47: "The pooled analysis of the ibrutinib arm of RAY (MCL3001) (IRC-assessed PFS), PCYC1104 (investigator-assessed PFS) and SPARK (MCL2001) (IRC-assessed PFS), had a median PFS of [redacted]. For patients with one prior LOT (n=99), median PFS was [redacted]. For patients with more than one prior LOT (n=271), median PFS was [redacted]." Page 50: [redacted] Page 69: Within the pooled analysis (n=370), [redacted]" Page 145: "The pooled analysis of the ibrutinib studies19 produced a median OS estimate of [redacted]" and the data in Table 71 relating to median PFS ([redacted] months) and median OS ([redacted] months) in the ibruinitb pooled analysis. Page 56: [redacted]	[redacted] Page 47: [redacted] Page 50: Page 69: All confidentiality highlighting can be removed from this text. However, please note that the figure for pooled median PFS should be corrected to 12.81 months (see **Error! Reference source not found.**)	

[redacted] Page 55: “The CS reports that in the CUP, [redacted]. ”	Some of the confidentiality highlighting relating to the CUP can be removed, based on the poster presented at the 21st Congress of the European Hematology Association (EHA), June 9-12, 2016 by Rule et al.[3] All confidentiality highlighting can be removed with the exception of the pieces of text noted for the specific pages below: Page 56: [redacted] Please also note that the statement that reported data were from 175 patients is incorrect. This should state 715 patients	