pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Ibrutinib (Imbruvica) for Mantle Cell Lymphoma

July 19, 2016

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of ibrutinib (Imbruvica) as compared to an appropriate comparator in patients with relapsed or refractory mantle cell lymphoma (R/R MCL).

Ibrutinib is an oral, first-in-class, selective Bruton's tyrosine kinase (BTK) inhibitor developed to specifically target and selectively inhibit BTK in malignant B-cells. Ibrutinib has a Health Canada indication for:

- the treatment of patients with relapsed or refractory mantle cell lymphoma. This has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit;
- the treatment of patients with CLL, including those with del(17)p, who have received at least one prior therapy, or for the frontline treatment of patients with CLL with del(17). This has been issued marketing authorization without conditions.

For the treatment of patients with relapsed or refractory mantle cell lymphoma, the recommended dosage of ibrutinib is 560 mg (four 140 mg capsules) once daily.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one open-label, randomized controlled trial, MCL3001 comparing ibrutinib (n=139) with temsirolimus (n=139) in patients with relapsed or refractory MCL who received at least one prior rituximab-containing chemotherapy regimen. Of note, temsirolimus is not used in Canada.

Patient characteristics were reported to be balanced between arms. Overall, most patients were stage IV MCL (83%), relapsed (70%), male (74%), and white (87%). Over half of patients had an ECOG performance status of 1 (51%). Sixty-seven percent of patients had 1 to 2 prior lines of therapies and 31% of patients had 3 to 5 prior lines of therapy.

Efficacy

The primary outcome in the MCL3001 study was progression-free survival (PFS) with secondary outcomes including overall survival (OS), overall response rate (ORR), and quality of life (QoL).

The median duration of PFS was 14.6 and 6.2 months in the ibrutinib and temsirolimus groups, respectively (HR=0.43, 95%CI 0.32 to 0.58, p<0.0001). After a median follow-up of 20 months, the median OS was not reached in the ibrutinib group and was 21.3 months in the temsirolimus group [HR 0.76 (95% CI, 0.53 to 1.09), p=0.1324]. ORR was greater in the ibrutinib group compared with the temsirolimus group [72% versus 40%, difference 31.5% (95% CI, 20.5 to 42.5), p<0·0001; OR=3.98, 95%CI 2.38 to 6.65)]. Patients in the ibrutinib group compared with the temsirolimus group had clinically meaningful improvements in lymphoma symptoms.

Harms

Treatment-emergent adverse events (TEAEs) leading to death were similar between the ibrutinib and temsirolimus groups (6% versus 8%). TEAEs leading to discontinuations were less frequent in the ibrutinib group compared with the temsirolimus group (6% versus 26%).

1.2.2 Additional Evidence

pCODR received input on ibrutinib (Imbruvica) for MCL from two patient advocacy groups: Canadian Cancer Survivor Network (CCSN) and the Leukemia and Lymphoma Society of Canada (LLSC). Provincial Advisory Group (PAG) input was obtained from nine of the nine provinces participating in pCODR.

One supplemental issue was identified during the development of the review process, a critical appraisal of the manufacturer-submitted indirect treatment comparison (ITC) of ibrutinib with other therapies for relapsed or refractory MCL.

1.2.3 Interpretation and Guidance

Effectiveness

The effectiveness of ibrutinib for R/R MCL was established in the randomized phase III clinical trial comparing ibrutinib to temsirolimus, which was chosen as a reasonable comparator based on a lack of a well-defined treatment for relapsed MCL and prior demonstration that temsirolimus induced better control of MCL than investigator's choice in an earlier clinical trial. Of note, temsirolimus is not used in Canada. Ibrutinib induced a 57% reduction in risk of progression or death compared to temsirolimus. Patients in the ibrutinib group experienced a median progression free survival (PFS) of 14.6 months compared to 6.2 months for temsirolimus. These results were consistent with the higher overall response rate (ORR) of ibrutinib compared with temsirolimus, 71.9% vs 40.4%, respectively, and lead to a superior 2-year PFS rate of 41% vs 7%, respectively. The impact of ibrutinib on overall survival (OS) appeared to be positive as the median OS was not reached for the ibrutinib group while the median OS was 21.3 months for the temsirolimus group. However, the hazard ratio (HR) for OS only demonstrated a positive trend but not statistically significant difference for ibrutinib when compared with temsirolimus (24% reduction in risk of death [HR, 0.76; 95% CI, 0.53-1.09]). The crossover design of the trial precluded definitive analysis of the impact on overall survival.

The impact of treatment on quality of life (QoL) in patients with R/R MCL was also assessed in the MCL3001 trial. Compared to temsirolimus, ibrutinib relieved lymphoma related symptoms more quickly, maintained that improvement longer and delayed recurrence of lymphoma related symptoms longer, thus, significantly improving QoL.

Safety

Adverse events (AEs) occur at a moderate rate when ibrutinib is used to treat R/R MCL and are generally manageable. In the randomized MCL3001 trial comparing ibrutinib with temsirolimus 6.5% of patients assigned to ibrutinib discontinued the agent due to AEs. The following grade ≥3 treatment-emergent AEs occurred in the ibrutinib and temsirolimus groups, neutropenia (13% versus 17%), thrombocytopenia (9% versus 42%), diarrhea (3% versus 4%), fatigue (4% versus 7%), and peripheral oedema (0% versus 2%). AEs seen with ibrutinib in this trial and those focused on other lymphoid cancers occurred at the level of grade 3 or 4 in approximately 10% to 20% of patients. The most frequently encountered serious adverse events (SAE), atrial fibrillation and major hemorrhage, were seen at rates of 3% to 7% across multiple trials of ibrutinib for lymphoid cancers. Ibrutinib should not be given to patients who are taking warfarin and should be used very cautiously in patients taking any type of anticoagulation or anti-platelet agents. Lethal reactions to ibrutinib are

rare (<1%-2%). Ibrutinib is known to interact with the cytochrome P-450 (cyp 3A) hepatic enzyme system, an effect which must be taken into consideration when ibrutinib dosing is determined.

Burden of Illness and Need

MCL is diagnosed in approximately 500 to 600 new cases per year in Canada and is incurable. The median survival for patients with MCL is about 2.5 years, with a range of 0.5 to 12 years. The prevalence of MCL in Canada is approximately 1,500 cases; almost all of whom will eventually develop R/R disease and will be potential candidates for ibrutinib. Given current prevalence and survival expectations it is reasonable to estimate that 400 to 500 patients will start ibrutinib for R/R MCL each year if and when ibrutinib becomes widely available in Canada.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net clinical benefit to ibrutinib in the treatment of R/R MCL based on one well conducted randomized controlled trial (MCL3001) that demonstrated a clinically and statistically significant benefit in ORR, median PFS, 2-year PFS rate, and improvement in QoL for ibrutinib compared with temsirolimus. Therefore, ibrutinib is an effective treatment for R/R MCL. Ibrutinib has an acceptable safety profile when used to treat patients with R/R MCL, with the exception that ibrutinib dosing must take CYP3A liver enzyme interactions into consideration and ibrutinib should not be combined with warfarin. Ibrutinib should be used cautiously in patients taking other anticoagulants or anti-platelet agents. There is an established need for ibrutinib for R/R MCL in Canada. In reaching this conclusion, the Clinical Guidance Panel considered that:

- Ibrutinib is likely to become the treatment option of choice in R/R MCL and establish a standard of care where currently no standard of care exists among many treatment options. Ibrutinib would be the preferred option in second-line therapy.
- The moderate level of toxicity associated with ibrutinib is reasonable given there is no standard of care in R/R MCL and there is a substantial need for effective treatment options.
- It is standard practice to screen for concomitant medications for drug-drug interactions and during treatment with ibrutinib, thus liver function and use of anticoagulants (other than warfarin, which is contraindicated) should be monitored.
- As patients are treated until progression, the treatment duration of ibrutinib is unknown. The MCL3001 study reported a median exposure of 14.4 months with ibrutinib.
- Including all the provinces in Canada a moderately large (~500-1,000) prevalent population may start ibrutinib shortly after it is introduced.
- The CGP and Methods Team agreed that the studies (MCL-3001 and OPTIMAL) appeared similar enough to compare and the results of the indirect treatment comparison were reasonable.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding ibrutinib for relapsed or refractory mantle cell lymphoma (MCL). The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding ibrutinib for relapsed or refractory MCL conducted by the Lymphoma & Myeloma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on ibrutinib for relapsed or refractory MCL and a summary of submitted Provincial Advisory Group Input on ibrutinib for relapsed or refractory MCL are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

On July 28, 2015, ibrutinib was issued marketing authorization with conditions by Health Canada for the treatment of patients with relapsed or refractory MCL.[1,2] Ibrutinib also has Health Canada approval for the treatment of patients with chronic lymphocytic leukemia.[2]

Ibrutinib is an oral Bruton's tyrosine kinase (BTK) inhibitor developed to target and selectively inhibit BTK in malignant B-cells. The recommended dose for MCL, as it appears in the Health Canada Product Monograph, is 560 mg (four 140 mg capsules) once daily.[2]

The following severe warnings and precautions were noted in the Health Canada Product Monograph:[2]

- ibrutinib should only be prescribed by a qualified physician who is experienced in the use of anti-cancer agents,
- major bleeding events, some fatal, have been reported,
- ibrutinib should not be used in patients with moderate or severe hepatic impairment,
- ibrutinib should not be used concomitantly with a strong CYP3A inhibitor.

2.1.2 Objectives and Scope of pCODR Review

The objective of the review was to evaluate the efficacy and safety of ibrutinib for the treatment of patients with relapsed or refractory mantle cell lymphoma.

See section 6.2.1 for details on the patient population, the intervention, the comparators and the outcomes and the review protocol.

2.1.3 Highlights of Evidence in the Systematic Review

Trial and Population

MCL3001 is a randomized, open-label, multicentre (including Canada), phase 3 clinical trial comparing ibrutinib with temsirolimus in patients with relapsed or refractory MCL who received at

least one prior rituximab-containing chemotherapy regimen. Overall, 280 patients were randomized in a 1:1 ratio to receive oral ibrutinib (n=139) or intravenous temsirolimus (n=141) until disease progression or unacceptable toxic effects.

Key inclusion criteria were as follows: received at least one prior rituximab-containing chemotherapy regimen; documented relapse or disease progression following the last anti-MCL treatment; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; haematology and biochemical values within a specified range.[3] Key exclusion criteria included: chemotherapy, radiation, or other investigational drugs within 3 weeks, antibody treatment within 4 or immunoconjugates within 10 weeks; central nervous system lymphoma; known history of human immunodeficiency virus, active infection with hepatitis C virus or hepatitis B virus, or any uncontrolled active systemic infection that required IV antibiotics.[3]

The study protocol was amended on July 30, 2014 to allow for patients who received temsirolimus and had independent review committee (IRC)-confirmed disease progression to cross over and receive ibrutinib until disease progression, unacceptable toxicity, or study end. A total of 23% of patients (n=32) crossed over to receive ibrutinib therapy. No interim analysis was planned; the results represented are the final analysis for primary and secondary endpoints.

Overall, most patients were stage IV MCL (83%), relapsed (70%), male (74%), and white (87%). About half of patients had an ECOG performance status of 1. On average, the number of prior lines of therapy received was 2, with 67% of patients having had 1-2 prior lines of therapy and 31% of patients having had 3-5 prior lines of therapy. All except one patient received prior rituximab (<100%), 50 patients received prior bortezomib (18%), and 15 patients received prior lenalidomide (5%).[4,5] Time from initial diagnosis to randomisation and time from end of last previous therapy to randomization were similar between groups.

No major imbalances (>10%) in baseline characteristics between arms were noted.

Despite the open label design, measures to reduce risk of bias were made; complete response, partial response, and progressive disease were assessed by an independent review committee; as well an independent data monitoring committee monitored safety. The open label design may have introduced a risk of bias in patient-reported outcomes. Overall survival results may have been confounded due to the high proportion of cross over; however, cross over did not affect the primary endpoint, PFS.

Efficacy

Details of the key outcomes are listed in Table 2.1.

Progression-free survival (PFS) was the primary endpoint. A statistically significant difference in PFS was found; the hazard ratio for disease progression or death was 0.43 (95%CI, 0.32 to 0.58, p<0.0001). The median PFS was 14.6 months for the ibrutinib group compared with 6.2 months for the temsirolimus group. The PFS rate at 2 years was 41% in the ibrutinib group compared with 7% in the temsirolimus group.

Overall survival (OS) was a secondary endpoint. There was no statistically significant difference in OS. After a median follow-up of 20 months, the median OS was not reached for the ibrutinib group, while the median OS for the temsirolimus group was 21.3 months. The 1 year survival rate was 68% in the ibrutinib arm and 61% in the temsirolimus arm. It is important to note that 23% of patients in the temsirolimus group crossed over to ibrutinib, and thus, overall survival results may be confounded. Cross over did not however affect the primary endpoint, PFS.

According to Hess et al., 2015, patient reported outcome compliance rates were generally acceptable, with <20% missing at most time points.[6] More patients treated with temsirolimus had

clinically meaningful worsening of lymphoma symptoms (defined as a ≥5 decrease from baseline) compared with patients treated with ibrutinib (52% versus 27%). The median time to clinically meaningful worsening was 9.7 weeks in the temsirolimus arm and was not reached in the ibrutinib arm, with a hazard ratio 0.27 (95% CI, 0.18 to 0.41, p<0.0001).[6]

Post-hoc analyses were reported by Dreyling et al. and Hess et al., 2015 to highlight time to clinically meaningful improvement. With a median follow-up of 20 months,[7] more patients treated with ibrutinib had a clinically meaningful improvement (defined as a ≥5 increase from baseline) in lymphoma symptoms compared with patients treated with temsirolimus (62% versus 35%).The median time to clinically meaningful improvement was 6.3 weeks compared with 57.3 weeks, with a hazard ratio 2.19 (95% CI, 1.52 to 3.14, p<0.0001).[6]

According to the literature provided by the submitter, evidence suggests that a likely minimal important difference range for the lymphoma (LYM) subscale is approximately 3–5 points,[8] and based on this, the submitter used a more conservative minimal important difference of 5 points; this appears to be reasonable.

The mean EQ-5D-5L utility values and VAS scores were 0.7(±0.2), 66.6(±19.3) for patient in the ibrutinib group and 0.7 (±0.2), 64.5 (±21.9) patients in the temsirolimus group.[6] Hess et al. noted that with the ibrutinib group, changes from baseline for EQ-5D-5L utility values were positive at all time points up to Week 40, and statistically different from temsirolimus at all time points up to Week 49. Hess et al., 2015 also noted that with the ibrutinib group, changes from baseline for VAS values were positive and statistically different from temsirolimus at all time points. With the temsirolimus group, patients had consistently lower utility and VAS scores from baseline, and EQ-5D-5L values did not return to baseline at any time point, up to Week 106.[6]

The overall response rate was greater in the ibrutinib group compared with the temsirolimus group (72% versus 40%, with an odds ratio of 3.98 (95%CI, 2.38 to 6.65), p-value not reported). The complete response rate was 19% in the ibrutinib group compared with 1% in the temsirolimus group.

The median duration of response was 7.0 months in the temsirolimus group and was not reached in the ibrutinib group. The median time to next treatment was 11.6 months in the temsirolimus group and not reached in the ibrutinib group.

Harms

Grade ≥3 treatment-emergent adverse events (TEAEs) were less frequent in the ibrutinib group compared with the temsirolimus group (68% versus 87%). TEAEs leading to discontinuation was also less frequent in the ibrutinib group compared with the temsirolimus group (6% versus 26%). TEAEs leading to death was similar between arms (6% versus 8%).

In terms of adverse events of special interest, adverse events leading to hospitalization were not reported in the study publication, however, the number and days of hospitalization per treatment group were similar between groups.[5] Atrial fibrillation (of any grade) was reported in 6 (4%) patients in the ibrutinib arm and in 3 (2%) patients in the temsirolimus arm.[3] Major bleeding (of any grade) was reported in 14 (10%) patients in the ibrutinib arm and in 9 (6%) patients in the temsirolimus arm. Other malignancies were reported in 5 (4%) patients in the ibrutinib arm and in 4 (3%) patients in the temsirolimus arm; according to Dreyling et al., most of which were non-melanomatous skin cancers.[4]

Table 2.1 Summary of Efficacy Outcomes Dreyling[4,5]

	Ibrutinib (n=139)	Temsirolimus (n=141)
Profession-Free Survival, Primary Outcome (IRC-assessed)		
PFS† median	**14.6 months**	**6.2 months**
HR* (95%CI), p-value	0.43 (95%CI:0.32-0.58), p<0.0001	
PFS rate at 2 years	41%	7%
Overall Survival, Secondary Outcome		
OS median	**Not reached**	**21.3 months**
HR*(95%CI), p-value	0.76 (95%CI:0.53-1.09), p=0.1324	
OS rate at 1 year	68%	61%
Patient Reported Outcomes, Secondary Outcome (using the FACT-Lym Lymphoma Subscale)		
Clinically meaningful improvement in lymphoma symptoms, n (%)	86(62%)	50(35%)
Median time to clinically meaningful improvement	**6.3 weeks**	**57.3 weeks**
HR (95%CI), p-value	2.19 (95%CI:1.52-3.14), p<0.0001	
Clinically meaningful worsening of lymphoma symptoms, n (%)	37 (27%)	73 (52%)
Median time to clinically meaningful worsening	**Not reached**	**9.7 weeks**
HR* (95%CI), p-value	0.27 (95%CI:0.18-0.41), p<0.0001	
Overall Response Rate, Secondary Outcome (IRC-assessed)		
ORR	**100(72%)**	**57(40%)**
Difference in ORR (95%CI), p-value	31.5% (95%CI:20.5-42.5), p<0.0001	
OR (95%CI) p-value	3.98 (2.38-6.65), p=NR	
Complete response, n (%)	26 (19%)	2(1%)
Duration of Response, Secondary Outcome		
Median DOR	**Not reached**	**7.0 months**
p-value	p=NR	
Estimated rate of DOR at 18 months	58%	20%
Time to Next Treatment, Secondary Outcome		
Median TTNT	**Not reached**	**11.6 months**
p-value	p<0.0001	
Estimated rate of TTNT at 18 months	66%	26%

CI = confidence interval; DOR = duration of response; HR = hazard ratio; IRC = independent review committee; NR = not reported; OR = odds ratio; ORR = overall response rate; TTNT = time to next treatment.
*HR < 1 favours Ibrutinib
†PFS defined as the interval from date of randomisation to the date of disease progression (as assessed by the independent review committee) or date of death, whichever occurred first, irrespective of the use of subsequent antineoplastic therapy. Median follow-up of 20 months.
[a]defined as a 5-point or greater increase from baseline.
[b]defined as a 5-point or greater decrease from baseline.

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

2.1.5 Summary of Supplemental Questions

The manufacturer-submitted indirect treatment comparison (ITC) of ibrutinib compared to other therapies for relapsed or refractory MCL was summarized and critically appraised.

As noted by PAG, there is no standard of care for relapsed or refractory MCL and therapies vary across provinces. The following reasons outline why this critical appraisal was conducted:

- A single randomized controlled trial was identified in the systematic review which compared ibrutinib to temsirolimus, therefore, there is currently no available direct comparison of ibrutinib to other therapies for the treatment of relapsed or refractory MCL (such as fludarabine-based chemotherapy regimens, rituximab with chemotherapy, bortezomib, bendamustine with rituximab, gemicitabine/dexamethasone/cisplatin or alkylating agents),
- The manufacturer submitted an economic evaluation which included Investigator's Choice of single-agent treatment (IC) as a proxy for standard of care as a comparator. The ITC included a comparison between ibrutinib and IC.

Overall, the submitted ITC was well conducted and transparent. The submitted ITC adhered to best practices for the conduct of indirect treatment comparison,[9] as well as the CADTH Guidelines for Reporting Indirect Comparisons.[10]

Heterogeneity was explored in the form of sensitivity analyses. Meta-regression analysis could not be performed due to the small number of studies. Results from these sensitivity analyses were consistent with the results from the primary analysis for PFS and OS.

Furthermore, similarity was explored in the submitted ITC in the form of collection of information (i.e., study design and patient characteristics) and consideration of whether the studies appeared similar enough to be compared. The submitted ITC included details on study design and patient characteristics. Upon review, the Methods team and CGP agreed that the studies appeared similar enough to be compared.

Lastly, consistency was not applicable because the network was not a closed loop; therefore, among the pairwise comparison, no direct evidence was available to compare with indirect evidence.

The population considered was patients with relapsed or refractory MCL; this was consistent with the population in the funding request.

However, although the manufacturer's patient, intervention, comparator, outcome, setting (PICOS) criteria of the systematic review for the ITC included monotherapies and combination therapies, gemcitabine + dexamethasone + cisplatin (a relevant intervention identified by CGP) was not included. Moreover, results of the ITC are limited to the comparison of ibrutinib to single agent chemotherapy, and therefore, combination therapies or other relevant monotherapies were not included in the network. The CGP felt that the doses in the investigator's choice single agent seemed reasonable and reflect current clinical practice. However, bortezomib and bendamustine (if not given first line) were not listed as an option for IC. Bortezomib and bendamustine (if not given first line) may be given either as single agents or in combination with rituximab for second-line MCL. Further, despite having specified several comparators there was a lack of literature and, as such, no direct or indirect comparisons could be made for key regimens noted above.

Additional effect modifiers (i.e., mantle-cell lymphoma international prognostic index scores, type of histology, gene expression, allogeneic transplant) identified by the CGP were not considered. However, the Methods Team recognized that limited reporting of baseline characteristics in the study publications may have precluded the submitter for analyzing these additional effect modifiers identified by the CGP.

In brief, the Methods team agreed that based on the evidence provided in the ITC Report that there is reason to believe that ibrutinib was associated with statistically significant improvements in PFS compared investigator's choice single agent therapy for the treatment of relapsed or refractory MCL and there were no statistically significant differences in overall survival between treatments.

2.1.6 Other Considerations

See Section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) input, respectively.

Patient Advocacy Group Input

From a patient's perspective, the physical and emotional impact of living with MCL was varied and was dependent on the timing of chemotherapy and other treatments. According to CCSN and LLSC, respondents reported that the symptoms having the most impact were fatigue, loss of appetite and weight loss. Respondents also described a range of experiences with different types of therapy, including autologous stem cell transplants, allogeneic stem cell transplant, ibrutinib, chemotherapy (e.g., bendamustine, rituximab-bendamustine, R- CHOP, VcR-CVAD, Hyper-CVAD) and radiation therapy. Most respondents also reported that they had at least one remission and relapse with their current treatments. Respondents who had no experience with ibrutinib expect the treatment to manage key symptoms that were important to them, including "pain" and "bruising/bleeding". Respondents who have experience with ibrutinib reported that "loss of appetite and/or weight loss" and "fatigue" were symptoms that were managed by ibrutinib. Most of these respondents also indicated that ibrutinib improved their quality of life compared to previous therapies that they have used to treat their MCL.

PAG Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could be impact implementation of ibrutinib in the treatment of relapsed or refractory mantle cell lymphoma (MCL):

Clinical factors:

- There is no standard of care; treatment is usually intravenous chemotherapy
- New treatment option that is an oral drug

Economic factors:

- Small number of patients relative to other cancers but potentially large number of prevalent patients
- Unknown treatment duration and number of patients eligible for treatment

2.2 Interpretation and Guidance

Effectiveness

The effectiveness of ibrutinib for relapsed or refractory (R/R) mantle cell lymphoma (MCL) was established in the randomized phase III clinical trial comparing ibrutinib to temsirolimus, which was chosen as a reasonable comparator based on a lack of a well-defined treatment for relapsed MCL and prior demonstration that temsirolimus induced better control of MCL than investigator's choice in an earlier clinical trial. Ibrutinib induced a 57% reduction in risk of progression or death compared to temsirolimus. Patients in the ibrutinib group experienced a median progression free survival (PFS) of 14.6 months compared to 6.2 months for temsirolimus. These results were consistent with the higher overall response rate (ORR) of ibrutinib compared with temsirolimus, 71.9% vs 40.4%, respectively, and lead to a superior 2-year PFS rate of 41% vs 7%, respectively. The impact

of ibrutinib on overall survival (OS) appeared to be positive as the median OS was not reached for the ibrutinib group while the median OS was 21.3 months for the temsirolimus group. However, the hazard ratio (HR) for OS only demonstrated a positive trend but not statistically significant difference for ibrutinib when compared with temsirolimus (24% reduction in risk of death [HR, 0.76; 95% CI, 0.53-1.09]). The crossover design of the trial precluded definitive analysis of the impact on overall survival.

The impact of treatment on quality of life (QoL) in patients with R/R MCL was also assessed in the MCL3001 trial. Compared to temsirolimus, ibrutinib relieved lymphoma related symptoms more quickly, maintained that improvement longer and delayed recurrence of lymphoma related symptoms longer, thus, significantly improving QoL.

Safety

Adverse events (AEs) occur at a moderate rate when ibrutinib is used to treat R/R MCL and are generally manageable. In the randomized MCL3001 trial comparing ibrutinib with temsirolimus 6.5% of patients assigned to ibrutinib discontinued the agent due to AEs. The following grade ≥3 treatment-emergent AEs occurred in the ibrutinib and temsirolimus groups, neutropenia (13% versus 17%), thrombocytopenia (9% versus 42%), diarrhea (3% versus 4%), fatigue (4% versus 7%), and peripheral oedema (0% versus 2%).AEs seen with ibrutinib in this trial and those focused on other lymphoid cancers occurred at the level of grade 3 or 4 in approximately 10% to 20% of patients. The most frequently encountered serious adverse events (SAE), atrial fibrillation and major hemorrhage, were seen at rates of 3% to 7% across multiple trials of ibrutinib for lymphoid cancers. Ibrutinib should not be given to patients who are taking warfarin and should be used very cautiously in patients taking any type of anticoagulation or anti-platelet agents. Lethal reactions to ibrutinib are rare (<1%-2%). Ibrutinib is known to interact with the cytochrome P-450 (cyp 3A) *hepatic enzyme system, an effect which must be taken into consideration when ibrutinib dosing is determined.*

Burden of Illness and Need

MCL is diagnosed in approximately 500 to 600 new cases per year in Canada and is incurable. The median survival for patients with MCL is about 2.5 years, with a range of 0.5 to 12 years. The prevalence of MCL in Canada is approximately 1,500 cases; almost all of whom will eventually develop R/R disease and will be potential candidates for ibrutinib. Given current prevalence and survival expectations it is reasonable to estimate that 400 to 500 patients will start ibrutinib for R/R MCL each year if and when ibrutinib becomes widely available in Canada.

Table 2.2 Assessment of Generalizability of Evidence

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	Performance Status	In MCL3001, patients with an ECOG performance status of 0 or 1 were eligible for inclusion. A total of three patients were an inadvertently enrolled in the study, despite having an ECOG PS of 2.	Do trial results apply to patients with ECOG PS of 2 or greater? If so, why?	Currently no data available for ECOG PS≥2, the CGP felt of all available treatments, ibrutinib may be the mildest one with respect to toxicities and should be available.
	CNS relapsed	In MCL3001, patients with documented relapse or disease progression following the last anti-MCL treatment were eligible for inclusion and patients who had CNS lymphoma were not eligible for inclusion.	Do trial results apply to patients who have CNS relapsed?	Ibrutinib has not been studied in patients with relapse of MCL in the CNS.
	sMIPI	In RAY MCL 3001, randomization was stratified by number of previous lines of therapy and by sMIPI score. Of the patients, 31% (n=86) were low risk (0-3); 48% (n=134) were intermediate risk (4-5); and 21% (n=60) were high risk (6-11).	Are the proportion of sMIPI scores (low, intermediate, and high risk) reflective of Canadian demographics?	sMIPI proportions/distribution from the MCL3001 trial were generally in line with what is seen in clinical practice. sMIPI is not often used in clinical practice as it does not influence treatment practice and is cumbersome to calculate, however, the data are provided in the trial report if clinicians wish to employ them.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
	Prior bortezomib use	In RAY MCL 3001, 18% of patients (50 out of 280) had prior bortezomib. Subgroup PFS analysis results of patients with prior bortezomib use showed a hazard ratio of 0.68 (CI, 0.36 to 1.30). Of note, the subgroup analysis of patients with prior bortezomib use may not have been adequately powered to detect a difference in effect.	Do trial results apply to patients with prior bortezomib use?	Too few patients with prior bortezomib were studied to draw firm conclusions; however, the limited available data do not suggest a strong effect of prior bortezomib exposure on responsiveness to ibrutinib.
	Number of prior lines of therapy	Subgroup analysis results of patients with 1 or 2 prior lines of therapy showed a hazard ratio of 0.39 (CI, 0.26 to 0.59) and subgroup analysis results of patients with ≥3 prior lines of therapy showed a hazard ratio of 0.50 (0.32-0.77). Of note, the subgroup analysis of number of prior lines of therapy may not have been adequately powered to detect a difference in effect.	Do trial results apply to patients with multiple prior lines of therapy	CGP felt reasonable for 2nd and 3rd line.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Comparator	Standard of care	PAG noted that there is no standard of care for MCL and that temsirolimus is not used in Canada. The submitter included an ITC of ibrutinib compared with investigator's choice of single-agent treatment as a proxy for standard of care.	Given the comparison versus temsirolimus, are the MCL3001 results applicable to Canadian practice? If so, how? Given the comparison versus investigator's choice of single-agent treatment, are the ITC results applicable to Canadian practice? If so, how?	Temsirolimus was chosen as a reasonable comparator based on a lack of a well-defined treatment for relapsed MCL and prior demonstration that temsirolimus induced better control of MCL than investigator's choice in an earlier clinical trial. The CGP and Methods Team agreed that the studies (MCL-3001 and OPTIMAL) appeared similar enough to compare and the results of the indirect treatment comparison were reasonable. The results of the indirect treatment comparison suggest ibrutinib compared with investigator's choice showed statistically and clinically significant improvements in PFS but no statistically significant difference in OS (although they favoured ibrutinib). However, drugs chosen by investigators in clinical trials may differ from those chosen in clinical practice (e.g. combination therapies or bortezomib/bendamustine), which impacts the degree of certainty in the conclusions that can be drawn.

CGP = clinical guidance panel; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; MCL = mantle cell lymphoma; sMIPI = simplified mantle-cell lymphoma international prognostic index.
For the domains of intervention, outcome, and setting no factors were identified.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net clinical benefit to ibrutinib in the treatment of R/R MCL based on one well conducted randomized controlled trial (MCL3001) that demonstrated a clinically and statistically significant benefit in ORR, median PFS, 2-year PFS rate, and improvement in QoL for ibrutinib compared with temsirolimus. Therefore, ibrutinib is an effective treatment for R/R MCL. Ibrutinib has an acceptable safety profile when used to treat patients with R/R MCL, with the exception that ibrutinib dosing must take CYP3A liver enzyme interactions into consideration and ibrutinib should not be combined with warfarin. Ibrutinib should be used cautiously in patients taking other anticoagulants or anti-platelet agents. There is an established need for ibrutinib for R/R MCL in Canada. In reaching this conclusion, the Clinical Guidance Panel considered that:

- Ibrutinib is likely to become the treatment option of choice in R/R MCL and establish a standard of care where currently no standard of care exists among many treatment options. Ibrutinib would be the preferred option in second-line therapy.
- The moderate level of toxicity associated with ibrutinib is reasonable given there is no standard of care in R/R MCL and there is a substantial need for effective treatment options.
- It is standard practice to screen for concomitant medications for drug-drug interactions and during treatment with ibrutinib, thus liver function and use of anticoagulants (other than warfarin, which is contraindicated) should be monitored.
- As patients are treated until progression, the treatment duration of ibrutinib is unknown. The MCL3001 study reported a median exposure of 14.4 months with ibrutinib.
- Including all the provinces in Canada a moderately large (~500-1,000) prevalent population may start ibrutinib shortly after it is introduced.
- The CGP and Methods Team agreed that the studies (MCL-3001 and OPTIMAL) appeared similar enough to compare and the results of the indirect treatment comparison were reasonable.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Lymphoma & Myeloma Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

Mantle cell lymphoma (MCL) is the 4th most common non-Hodgkin lymphoma seen in North America, constituting between 5% and 10% of new diagnoses of lymphoma and giving rise to approximately 500 to 600 new cases per year in Canada.[11,12] MCL is incurable and almost all patients (> 95%) eventually succumb to the disease after experiencing a median survival of 2.5 years with a range from 0.5 to 12 years (based on experience with 850 patients in British Columbia and summary data detailing the experience with MCL in Sweden and Denmark.[13] Thus, the current prevalence of MCL in Canada is approximately 1,500 (estimated from current experience in British Columbia, BC Cancer Agency Lymphoid Cancer Database), almost all of whom have received at least one course of systemic treatment and, thus, constitute the prevalent relapsed or refractory (R/R) population that is the target of this review. The median age of onset of MCL is 65 years and there is a clear male predominance (2.5:1 overall, 5:1 in the 6th to 7th decade).[11] Most patients (> 95%) present with advanced stage disease and bone marrow, spleen, gastrointestinal and widespread lymph node involvement is common with marrow involvement seen in > 70%.[11,14] A small proportion (< 10%)[15] of patients with MCL have quite indolent disease and are often managed with initial observation, reserving intervention for the > 90%[14] with symptomatic or threatening disease who, therefore, require systemic intervention. The typical course for patients with MCL is one of alternating periods of systemic treatment and short durations of intermittent observation.

The diagnosis of MCL is based on biopsy proof of disease from a nodal or extranodal site that demonstrates the presence of a monoclonal population of small neoplastic B cells that co-express CD20, CD19 and CD5, have the characteristic t[16,17] translocation that moves the intact *BCL1* gene on chromosome 11 that codes for cyclin D1 into proximity with the IgH immunoglobulin heavy chain gene promoter on chromosome 14, and resultantly over- or inappropriately express cyclin D1. *BCL1* is also known as *CCND1*. The standard Ann Arbor lymphoma staging system is used to assign patient's stage but the very large majority (>95%) of patients are found to have advanced stage disease.

MCL prognosis can be estimated via several different approaches. The proliferative rate in the neoplastic cells is strongly prognostic and a gene expression signature profile based on proliferative rate[18] or genes associated with proliferation[19] can be used to assign patients to markedly different quartiles of overall survival (OS) expectation with the lowest proliferation quartile showing a median OS of 6.7 years and the highest 0.8 years. A clinical prognostic score can be assigned using the mantle cell International Prognostic Index (MIPI)[20] which is based on age, performance status, lactate dehydrogenase (LDH) and leukocyte count; however, the need to use a complex formula to calculate the score has limited its usefulness outside of clinical trials. Several other factors known to affect prognosis have been described including expression of *SOX11;*[21] mutations of *NOTCH1*[22] and *BCL1* (*CCND1*);[23] and numbers of infiltrating macrophages[24] but again these have turned out to have limited usefulness in day to day treatment of MCL. Thus, although these factors are useful to estimate prognosis, they have no defined role in the choice of primary or secondary treatment.

In a manner somewhat similar to chronic lymphocytic leukemia, the B cell receptor pathway linking the cell surface B cell receptor through a cascading series of enzymatic activations to the anti-apoptotic and pro-proliferative *NF-kB* and *MYC* systems has been found to be inappropriately activated in MCL. Bruton's tyrosine kinase (BTK) is a pivotal cytoplasmic non-receptor kinase that

participates in this B-Cell receptor pathway making it an attractive target for the BTK inhibitor ibrutinib.

3.2 Accepted Clinical Practice

The treatment of MCL in Canada is not uniform across all provinces; however, a general approach can be outlined with most provinces following treatment algorithms that are roughly similar. Symptomatic patients under the median age of approximately 65 years are usually considered eligible for intensive treatment and are, thus, treated with intensified regimens, often including high dose chemotherapy and autologous hematopoietic stem cell transplantation (ASCT)[25] after chemotherapy with agents such as cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab (CHOPR), sometimes augmented by inclusion of additional agents such as cisplatin, gemcitabine or cytarabine. Several provinces employ bendamustine plus rituximab (BR) instead of CHOPR as the lead-in chemotherapy regimen. This latter choice is based on extrapolation from the results of a clinical trial in which CHOPR was compared to BR as initial treatment of a subset of older patients with MCL within a larger trial that included patients with indolent B cell lymphomas.[16] BR produced a moderately better progression free survival (PFS) and OS. Alternative intensive chemotherapy regimens such as HyperCVAD are occasionally, but not frequently, employed in Canada. Following the initial lead-in chemotherapy and ASCT some provinces offer consolidation or maintenance treatment with rituximab for 8 to 12 doses over 6 to 24 months.

Symptomatic Canadian patients with MCL over the age of approximately 65 years are usually considered ineligible for ASCT and are treated with CHOPR, CVPR or BR and at least some provinces follow that with maintenance rituximab based on the results of a randomized clinical trial (RCT) comparing maintenance rituximab versus alpha-interferon after induction of an initial response using CHOPR[26] in which maintenance rituximab significantly improved both PFS and OS (4-year PFS 58% vs 29%; 4-year OS 87% vs 63%, respectively).

There is no well-defined secondary treatment used to treat patients with R/R MCL in Canada. In addition to standard older chemotherapy agents such as cyclophosphamide, bendamustine,

gemcitabine and high dose corticosteroids various newer agents have been shown to have at least modest activity in R/R MCL (Table 3.1).

Table 3.1. Selected trials of newer agents for R/R MCL.

Agent	n	ORR	PFS (months, median)
Lenalidomide[25]	134	28%	4.0
Temsirolimus[27]	27	41%	6
Temsirolimus[17]	34	38%	6.5
Temsirolimus (2 doses) versus Investigator choice[28]	54 & 54 53	22% & 6% 2%	4.8 & 3.4 1.9
Bortezomib[29,30]	155	33%	6.7
Bortezomib[31]	30	46%	10
Idelalisib[32]	40	40%	3.7
Ibrutinib versus temsirolimus[4]	139 141	72% 40%	14.6 6.2
Ibrutinib[33]	111	68%	13.9
Ibrutinib[34]	120	66%	10.5

Based on the largest phase II study, bortezomib is funded in some provinces for R/R MCL.[29,30] Although the RCT by Hess et al., 2009[28] showed modest superiority of temsirolimus over investigator's choice, provinces in Canada currently do not fund this use; however, this relatively large trial, with its conclusions based on a randomized comparison, provides useful background information for interpretation of the recently reported phase III RCT of ibrutinib versus temsirolimus.[4] Two additional phase II trials in patients with R/R MCL provide useful verification of the single agent effectiveness of ibrutinib. Both demonstrated quite similar ORRs of 68% and 66%[33,34] and the latter showed that this relatively high response rate was also achieved in patients previously treated with bortezomib.[34]

3.3 Evidence-Based Considerations for a Funding Population

As noted in sections 3.1 and 3.2, MCL is not curable with currently available treatments. Patients persistently experience a series of relapses until the disease becomes unresponsive and almost all patients eventually succumb to progressive, treatment resistant lymphoma. For these reasons, it is appropriate to expect the entire prevalent population to become candidates for any new treatment approved and funded for R/R MCL. Thus, it is anticipated that, almost all of the approximately 1,500 prevalent patients in Canada and most of the approximately 500 new patients with MCL diagnosed annually, will eventually become candidates to receive ibrutinib if it is approved for R/R MCL. This is true regardless of presenting stage of the disease because R/R MCL is a systemic disease and requires systemic intervention. There are no tumor characteristics or prognostic factors that reliably predict likelihood of response to ibrutinib, so all patients with progressive symptomatic or threatening disease will become candidates for ibrutinib. The only findings or tests required to justify treatment of R/R MCL with ibrutinib are accurate initial diagnosis, recurrence of symptomatic or threatening disease after primary treatment and freedom from specific contraindications to its use. Proper monitoring during treatment requires regular

blood tests of hematologic, renal and liver function and intermittent radiologic assessment with CT scanning.

3.4 Other Patient Populations in Whom the Drug May Be Used

Ibrutinib has proven effective for a wide range of B-cell lymphoproliferative neoplasms and the full spectrum of its usefulness is still being documented. Currently, ibrutinib offers potentially effective treatment for chronic lymphocytic leukemia, indolent non-Hodgkin lymphoma (follicular, small lymphocytic, lymphoplasmacytic (Waldenstrom macroglobulinemia) and marginal zone lymphoma).

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Three patient advocacy groups, Canadian Cancer Survivor Network (CCSN), the Leukemia and Lymphoma Society of Canada (LLSC) and Lymphoma Canada (LC) provided input on ibrutinib for the treatment of patients with relapsed or refractory mantle cell lymphoma (MCL).

CCSN and LLSC developed two surveys directed to patients with MCL and family members about the impact of MCL on their lives and the effects of treatments for their lymphoma. Demographic questions of gender, age and location were added to the surveys. They also included specific questions for patients who have used ibrutinib to treat their lymphoma.

The patient and caregiver survey links were advertised from January 11- January 31, 2016. CCSN publicized the surveys on Twitter and on Facebook. LLSC sent survey links to MCL patients/family members in their Canadian database and to MCL peer support volunteers based in the USA. Emails were sent to healthcare professional contacts to inform them of the surveys and to request for distribution to their patient populations.

In addition, LLSC also contacted patients who consented to sharing their information via a support program known as "YOU&I", which is supported by Janssen Inc. for patients who have been prescribed ibrutinib.

A total of 24 MCL respondents completed the patient survey: 12 from Canada, and 12 from the United States. Of the 24 respondents, 14 were male and 10 were female. Nine (9) respondents were between 70-79 years, 11 respondents were between 60-69 years, and four (4) respondents were between 50-59 years of age. A separate caregivers survey was completed by seven (7) family member caregivers, all of whom were Canadian, five (5) were female, and two (2) were male. Two (2) of the caregivers identified were spouses, one (1) was a sibling of a patient, and four (4) were adult children caring for parents with MCL.

CCSN and LLSC reported that six (6) respondents have had experience with ibrutinib. Among these respondents, two (2) were women and four (4) were men. CCSN and LLSC noted that five (5) respondents were Canadian and one (1) was American who had access through a clinical trial for the past 3.5 years.

LC conducted online surveys and interviews of MCL patients and caregivers (as noted in the table below). Links to the surveys were sent via e-mail to patients and caregivers registered on the LC database. The links were also made available via LC Twitter and Facebook accounts as well as through the MCL patient forums and the Lymphoma Research Foundation (USA). The surveys by LC had a combination of multiple choice, rating and open-ended questions. Skipping logic was also built into the surveys so that respondents were asked questions only relevant to them. Interviews were conducted with one caregiver and two patients who had direct experience with ibrutinib.

Overall, the perspectives of 77 respondents are represented in this submission: 16 patients with ibrutinib experience; 40 patients without ibrutinib experience; and 21 caregivers.

Participants by Country	CAN	USA	UK	NLD	AUS	Skipped	N
Patients with Ibrutinib Experience (Survey)	6	5	2	-	-	1	14
Patients with Ibrutinib Experience (Interviews)	3	2	-	-	-	-	5**
Patients without Ibrutinib Experience (Survey)	24	8	4	1	1	2	40
Patients without Ibrutinib Experience (Interviews)	5	2	-	-		-	7*
Caregivers (Survey)	9	10	-	-	1	-	20
Caregivers (Interviews)	2	1	-	-	-	-	3**
* All patients without ibrutinib experience who participated in an interview also completed surveys. **One caregiver and two patients with ibrutinib experience participated in an interview, but did not complete a survey.							

From a patient's perspective, the physical and emotional impact of living with MCL was varied and was dependent on the timing of chemotherapy and other treatments. According to CCSN and LLSC, respondents reported that the symptoms having the most impact were fatigue, loss of appetite and weight loss. Respondents also described a range of experiences with different types of therapy, including autologous stem cell transplants, allogeneic stem cell transplant, ibrutinib, chemotherapy (e.g., bendamustine, rituximab-bendamustine, R- CHOP, VcR-CVAD, Hyper-CVAD) and radiation therapy. Most respondents also reported that they had at least one remission and relapse with their current treatments. Respondents who had no experience with ibrutinib expect the treatment to manage key symptoms that were important to them, including "pain" and "bruising/bleeding". Respondents who have experience with ibrutinib reported that "loss of appetite and/or weight loss" and "fatigue" were symptoms that were managed by ibrutinib. Most of these respondents also indicated that ibrutinib improved their quality of life compared to previous therapies that they have used to treat their MCL. According to LC, respondents seek individualized choice in treatment that will offer disease control and improve quality of life while offering ease of use relative to other treatments. As an oral therapy, LC indicated that it is easier for patients to use, without the necessity to keep track of treatment cycles common to other treatments. As an example, it can be taken in the comfort of a patient's home, which could be a benefit to patients and caregivers.

Please see below for a summary of specific input received from the patient advocacy groups. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that was reported have also been reproduced as is according to the submission, without modification.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Mantle Cell Lymphoma

LC indicated that respondents with indolent MCL reported minimal symptoms associated with their disease, a good quality of life and were under a period of 'watchful waiting' by their doctor. For those with more advanced disease, it was found that their quality of life was impacted more significantly. Respondents reported fatigue, loss of appetite, weight loss, fever, night sweats, nausea, vomiting, indigestion, abdominal pain, bloating, diarrhea, enlarged tonsils, muscle and joint pain. Some respondents with MCL expressed difficulties with vision, concentration, anxiety, depression, insomnia, intimacy and mood swings. Other complications reported included frequent infections (due to compromised immunity), shortness of breath (attributed to anemia), easy bruising (caused by low platelet counts), 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 airway). Many respondents had relapsed from previous treatments. LC noted that all of these symptoms can interfere with a patient's performance, ability to work, travel and day-to-day activities.

CCSN and LLSC indicated that as a result of the small sample size of patient respondents and the wide range of experiences that were expressed, CCSN and LLSC felt that it was more helpful to excerpt some of the key responses that were elucidated by the respondents.

CCSN and LLSC asked respondents to rate their cancer symptoms using a 7 point likert-type scale (where 1= no impact and 7= extremely large impact). According to CCSN and LLSC, out of 24 respondents, 11 respondents reported the symptom as having the most impact was fatigue, (i.e., scores rated between 5-7). Similarly, nine (9) respondents rated loss of appetite and weight loss as also having a large impact (i.e., scores rated between 5-7).

CCSN and LLSC indicated the level of impact varied depending on the timing of chemotherapy and other treatments.

Below were some of the key responses reported by respondents to help illustrate the impacts in regards to their experiences with MCL:

- *"...at different it has been impacted in different manner-- immediately before and after diagnosis-Oct 2013- had no energy and had lost wt (sic)-- but kept on working—after diagnosis and chemotherapy was ok-- first two weeks after chemo were difficult-- but life returned to normal as the chemo worked. Had Stem cell transplant in June 2014-- these were difficult times"*

- *"Now am in what appears to be complete remission, with help of clinical trial."*

- *"At times, MCL has profoundly impacted my daily life. The fear and anxiety with diagnoses and treatments, and with possible and actual relapses has been difficult for me and my family. I have been severely compromised by treatment effects and am very grateful that there have been treatments to take or endure. I had a stem cell transplant and a 3.5.year remission. Now I have periodic relapse and treatment episodes. I am grateful that new drugs are available and hope and pray that I will be able to access them when I need them."*

- *"Being 7 yrs in remission from my first diagnosis of MCL and 2 yrs from my second diagnosis the main impact is the worry every 3 months when I have my scan that the cancer is back. Back when I was going thru the chemo and later BMT there was a lot of fatigue."*

- *"I am in complete remission (5.5 years). The impact to my life is now more a result of my chemo treatments."*

- *"Primary impact has been during and following traditional chemo-therapy and an auto SCT, both of which I have tolerated RELATIVELY well. ...Perhaps most significant impact has been the amount of time devoted to treatments, appointments, travel, etc."*
- *"I went through six and a half months of in-hospital treatment followed by a stem cell transplant. The treatment was a bit of a struggle with loss of weight, loss of taste and a little chemo brain.... Other than recovering from treatment I have led a very full and a new normal life."*

- *"Except during treatment, not much different. Some neuropathy in hands and to a lesser amount, my feet."*

- *"I am in remission (1O+ years) from MCL. I have found that it is to my advantage to keep physically active; full time employed; and carefully control my nutrition. I am very high energy. I am 70 years young."*

- *"More tired but try and keep same routines. Don't sleep well - stress-related. My arthritis has made me feel stiff and sore as my oncologist and hematologist prefer that I not take supplements (was taking glucosamine with chondroitin). Feel anxious, worried, "down" about my future."*

- *"I cannot even do limited manual labour and when I walk my legs shake after 20 minutes"*

- *"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."*

- *"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."*

- *"The tumour had advanced so quickly it was blocking my kidneys and they were not able to function properly. I had renal failure. They had to put a bag with two tubes – a urostomy. I had tubes coming out of both sides of my back for 10 months."*

- *"My husband had to have trach installed for about 7 wks before the chemo treatments began because he had tumor in his throat that cut off his air flow."*

4.1.2 Patients' Experiences with Current Therapy for Mantle Cell Lymphoma

According to CCSN and LLSC, patient respondents described a range of experiences with types of therapy. Of the 24 respondents, it was reported that: 11 were treated with autologous stem cell transplants (ASCT) and one (1) was treated with an allogeneic stem cell transplant; one (1) respondent was preparing for an ASCT; 10 respondents reported being in remission; and seven (7) did not respond to the question about current therapy, as they stated they were not receiving any medication.

While nine (9) respondents did not specify the type of chemotherapy that they had; those who responded listed the following: Bendamustine (n=2), R-Bendamustine (n=1), R-CHOP (n=6), VcR-CVAD (n=1), Hyper-CVAD (n=1), and ibrutinib (n=6). CCSN and LLSC also reported that three (3) people had radiation therapy.

LC reported that while current treatment options can work initially, patients with MCL usually relapse after treatment, and in most cases each period of remission becomes shorter. Thirty-two (32) respondents (8 skipped) indicated they had received the following therapies to treat their MCL: R-CHOP (n=21); Bendamustine (n=14); Rituximab maintenance (n=11); BEAM (n=4); FCR (n=4); Hyper-CVAD (n=2); Bortezomib (n=2); R-Bendamustine (n=4); High dose chemotherapy (n=2); High dose cytarabine (n=1); DHAP (n=1); ICE-R (n=1); Lenalidomide (n=1); BLR -clinical trial (n=1); IVIG (n=1); Steroid therapy (n=7); Stem cell transplant (n=13); Splenectomy (n=2); Radiation (n=7). Four (n=4) patients indicated they were under "watch and wait". The total response count exceeded the total respondents because 23 of the 32 (71.9%) indicated they had used multiple therapies to treat their MCL after relapse.

Similarly, CCSN and LLSC also reported that most of the patient respondents had at least one remission and relapse.

Below were some of the key responses reported to help describe respondents' perspectives regarding their current treatments:

- *Treatment consisted of A-CHOP followed by autologous stem cell transplant in December 2011, which the haematologist guessed would give me a five-year survival prospect, statistically speaking. It did not work out that way, for in 2013 the disease recurred.*
- *Got through first 6 mos. of much chemo, with the usual nausea and weakness. When bendamustine ended, so did weakness and nausea, although fatigue is still around about half the time.*
- *RCHOP: positive that my lymph nodes are responding and decreasing in size. Hopefully my internal affected organs are responding the same way. Negative: the treatment is harsh on my body leaving major side effects.*
- *"No major influence, except one day of restless feelings because of steroid that is part of the treatment."*
- *The chemo lots of nausea and fatigue. So then had to take steroids for fatigue which caused weight gain. A year after the transplant I got shingles so I am now on daily acyclovir. The radiation was no problem. Only had to have 20 treatments for one lymph node of MCL in the breast.*
- *Auto bmt gave me 7 years of happy remission/now after a good clinical trial experience for the first relapse, we are watching it.*
- *Therapy was rough but recovery while slow has resulted in feeling better.*
- *The Rituximab seemed to work wonders - 1 of the other drugs did negatively affect the nerves in my hands and feet. That effect has lessened over the year to wear only my feet (toes) have some residual irritation.*
- *Downside - hate/fear testing (biopsy, bone marrow test, blood work and needle insertion for chemo. My veins are never great and problems cropped up trying to find any for blood work or chemo. Hate being held captive to treatment. Hate having to worry about infection.*
- *Tiredness affects all aspects of my life. Ability to eat & nourish my bod. Hair loss & lower self image.*
- *"No longer working, spending most of the day taking care of myself (undergoing RCHOP chemo), worried for my family, physical limitation due to weakness."*
- *"I am cured. Allogeneic SCT 9 years ago."*

Respondents to LC's survey listed both positive (disease control) and negative side effects (disease progression; adverse events; discontinue treatment due to side effects) of current treatment. One respondent stated "*Could not exercise or get dressed. Trying to maintain a regular routine was impossible. The chemo made it difficult to breath and I had a hard time catching my breath "Could not do a darn thing. I could not concentrate I could not think of anything. It was almost like aphasia. I would say things like 'could you get the laundry out of the pantry'. I could not work at all or travel. People had to drive me. I was shaky. My reflexes and balance were off. I could not do anything*." Another respondent reported "*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*."

CCSN and LLSC noted the following quote from one respondent who had to stop treatment due to the side-effects of chemotherapy, ""*I am well again now, watching one lump that is progressing. It is very stressful to be watching and trying to report changes in a timely way and not over react but get in in time for optimal treatment*."

When respondents were asked how much they agree or disagree with the following statement: "*My current therapy/therapies are able to manage my MCL symptoms*."

The following responses were noted by CCSN and LLSC.

Rating	**1 (strongly agree)**	**2**	**3**	**4 (neutral)**	**5**	**6**	**7**	**Total**
	1	1	0	5	0	2	15	24

CCSN and LLSC reported that there was a high confidence in the ability of therapies in controlling the MCL as seen above. However, they also noted that the comments showed the range of physical and emotional responses to treatment.

Similarly, LC respondents were asked to rate their level of agreement with how much their current therapy(ies) are (or most recent therapy(ies) were able to manage symptoms associated with their MCL with 1 (Strongly Disagree) to 10 (Strongly Agree). Those respondents who received >1 treatment for MCL who answered this question rated lower (rating average 7.1, n= 22) compared to all other patients (rating average 8.7, n = 12). Six respondents skipped this question.

Below were some additional responses reported by respondents in relation to their treatments:

- *My health is better.*
- *My CT scan and PET scan clear.*
- *In remission. -pet scan and ct scans clear for months now.*
- *I've been told by my oncologist that if remission is achieved it will only last approx 2 years and the life span is 5 years. Since there is no confidence in a full recovery and/or no confidence in a long term treatment plan, Ifeel hopeless.*
- *December catscan showed "remission" according to oncologist.*
- *I am currently healthy. I am being monitored.*
- *I am not undergoing any treatment of any kind.*
- *I am in remission and have 6 month checkups.*
- *I have been in remission for either 7 [and then] 2 years*
- *Don't know yet. Am approaching end of 25 radiation oncology treatments which are going well and shrinking the tumor. How this will play out over the next several weeks and months is unknown.*
- *Generally feeling and doing well but some issues linger -no disease to treat -I am not on any current therapy*
- *I agree that my current 11way of life' is helping me stay strong and in remission*
- *My survival term has improved significantly*
- *My 2 year maintenance of Rituxmab therapy after chemo have kept the wolf away*

- *I will add "so far". I hope and pray we can continue to treat relapses.*
- *Not finished yet. I will have SCT and am very worried it's a major hurdle to get through to be told that there is no cure. Remission could end almost as soon as it starts*

CCSN and LLSC asked respondents on a scale of 1 (not at all difficult) to 7 (extremely difficult) how difficult it is to access their current therapy/therapies. CCSN and LLSC reported that out of 24 respondents, 18 respondents stated access to treatment as being "*not difficult at all*." CCSN and LLSC also reported the weighted average for access to therapy on the 7 point likert-type scale was 1.48.

LC respondents were asked how difficult it was to access their current or most recent therapy(ies). Five (5) of the 24 (20.8%) Canadian patient respondents experienced difficulties with access. Difficulties expressed by respondents included the need to: travel great distances to receive treatments in Canada; meet specific provincial drug funding criteria; pay out-of-pocket costs for treatments and associated travel. One respondent stated "*My hematologist is 800KM away and I have to travel there*."

LC respondents were also asked how important is it for them and their physician to have choice in deciding which drug to take based on known side effects and expected outcomes with a rating scale of 1 (Not Important As Long There Is At Least One Treatment Choice) to 10 (Extremely Important To Have Choice of Treatment). Twenty-nine (29) of the 37 (78.4%) respondents who answered this question gave this a rating of 8 or higher. According to LC, the rating average was 8.8, which means a large proportion felt that choice was very important based on known side effects and expected outcomes of a drug. Respondents were also asked if they feel there is currently a need for more choice in drug therapy(ies) for patients with MCL. The vast majority of the 36 respondents (35, 97.2%) who answered this question felt there is a need for more therapies.

4.1.3 Impact of Mantle Cell Lymphoma and Current Therapy on Caregivers

CCSN and LLSC noted that there were seven (7) respondents who responded to the caregiver survey. According to CCSN and LLSC, six (6) caregiver respondents identified caring for patients who had had stem cell transplants. CCSN and LLSC reported that caregiver respondents had much more consistent themes involving high degree of stress and impact in caring for loved ones with MCL. This included taking time off work, loss of income, travel costs, altered social and fitness routines, fear of bringing infection into the home, lack of sleep, stress about whether treatments will work and fear of the death of the patient. According to CCSN and LLSC, the chronicity of MCL is another stress for caregivers.

One caregiver respondent reported, "*Emotionally this has been the greatest struggle I've ever experienced. Having a cancer that is not curable and one that is most likely to come back leaves little hope and that is emotionally draining*."

LC respondents were asked to rate on a scale of 1 (No Impact) to 10 (Very Significant Impact) how caring for the person with MCL has impacted their day-to-day life. Nine (45.0%) respondents were retired at the time of completing the survey and 11 (55.0%) were still working. Two (10.0%) respondents had lost their loved one to MCL For those factors with a rating average of ≥5 there was a greater than neutral impact on day-to-day life.

Impact on Day-to-Day Life of Retired Caregivers (N=5)*	Rating of 7 or Higher n (%)	Rating Average	Impact on Day-to-Day Life of Not Retired Caregivers (N=7)*	Rating of 7 or Higher n (%)	Rating Average
Ability to travel	4 (44.4%)	6.3	Ability to volunteer	6 (54.5%)	6.9
Ability to spend time with family & friends	3 (33.3%)	5.3	Ability to travel	6 (54.5%)	6.8
Ability to concentrate	3 (33.3%)	4.9	Ability to fulfill family obligations	5 (45.5%)	6.5
Ability to fulfill family obligations	2 (22.2%)	4.6	Ability to concentrate	4 (36.4%)	6.5
Ability to volunteer (* 1 skipped)	2 (25.0%)*	4.4*	Ability to spend time with family & friends	4 (36.4%)	6.4
Ability to attend to household chores	3 (33.3%)		Ability to exercise	3 (27.3%)	5.8
Ability to exercise	1 (11.1%)	3.4	Ability to contribute financially to household expenses	4 (36.4%)	5.7
Ability to contribute financially to household expenses	1 (11.1%)	2.4	Ability to Work	4 (36.4%)	5.7
			Ability to attend to household chores	4 (36.4%)	5.5

When asked about challenges caregivers face in caring for patients with this type of cancer, caregivers identified fear, stress, worry, and the desire to be able to take pain away from their loved ones as key factors. CCSN and LLSC also noted that other challenges described by caregivers included coping with physical and emotional changes of the patients and themselves. Caregivers also reported on the duties that they are required undertake in caring for a patient with MCL, including the need to prepare meals, assist with feeding, and provide personal care, especially during chemotherapy treatment and the time around stem cell transplants. One LC respondent reported "*I've had to change jobs where I could work from home and even then it's been tough to have a full time job while going to numerous doctor/hospital appointments. I am the only one financially supporting my family.*" Another respondent stated "*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. Since MCL, he has developed Myasthenia Gravis.*"

When caregivers were asked to describe which treatment side-effects they would be willing to tolerate as a caregiver and the reasons why, the following responses were noted below:

- *For a loved one u start to tolerate any side effects that they may have. It's hard but we try not to show her what bothers us and what doesn't.*
- *We can manage any side effect if the end result is a longer but symptom free remission. However you need to look at the damage that some of these drugs will do and think quality over quantity.*
- *Fatigue is probably one of the easier side effects. It forces the patient to take a nap/rest which in turn helps the caregiver do the same.*
- *Anything to get her through this.*
- *As a caregiver, side-effects such as headaches or tiredness would be okay to handle as long as I knew that it was helping my mom stay healthy.*

- *I would tolerate any side effects in my life if my husband could be healed*
- *Bortezomib was very tough on her. It caused neuropathy and she had to take other drugs to relieve the pain. After that she went on lenalidomide. At that time I think she had too many drugs and she developed leukemia. If a patient could take a more benign drug with less side effects that has decent results compared to what we have available now than that would be fantastic*
- *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, GERD, afib.*

LC caregivers were asked how difficult it was to access the current or most recent treatment(s). Four (4) of the nine (9) Canadian caregivers (44.4%) experienced difficulties with access. Caregivers reported difficulties with "accessibility". The most commonly reported factors were financial burden and distance to drug. Some caregivers had to take time off work to assist in taking care of the patient (loss of income). Other caregivers reported the drug was difficult to access because they had to travel to a cancer centre far from home (travel to United States for a drug not available in Canada; travel long distance from remote community). One respondent stated "*His chemo involved travel to Halifax, more than an hour away. In all kinds of weather, including winter storms. I have upper body issues that make driving tiring. Lots of wait times*."

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with ibrutinib

Expectations of respondents who have no experience with ibrutinib

CCSN and LSCC reported that of the 24 respondents who responded to the survey, 18 respondents had no experience with ibrutinib.

When these respondents were asked how much they know about ibrutinib, the following responses were recorded in the table below.

	1 (nothing)	2	3	4	5	6	7 (extremely knowledgeable)	Total
Knowledge of drug	8	4	1	1	4	0	0	18

Because most respondents were not very familiar with the drug in question, CCSN and LLSC felt it was more important to provide comments that are more general in nature.

CCSN and LLSC reported that 15 respondents who responded to the questionnaire had the following expectations with ibrutinib:

- Nine (9) respondents indicated the symptoms that were most important for ibrutinib to manage included "Pain", which had the highest rating and
- Five (5) respondents indicated that "Bruising/bleeding" was ranked second.

CCSN and LLSC also reported that pain, nausea and vomiting were the side-effects listed of greatest concern.

CCSN and LLSC stated that "loss of appetite" and "fatigue" were identified to be the more tolerable side-effects of unknown therapies, but there was a range of willingness to deal with side- effects. Some key comments from respondents included the following,

> *"I would tend to tolerate a lot to be alive."*
>
> *"I'd be happy to have a drug that would help manage may MCL so I could live."*
>
> *"It would be a matter of degree. If it is the treatment of choice and reduces the severe risks of chemo reactions. The extent or degree of side effect would make a different but it would be worth trying."*

LC respondents were asked on a scale of 1 (Will Not Tolerate Any Side Effects) to 10 (Will Tolerate Significant Side Effects) to rate the extent to which they would be willing to tolerate side effects if they were to consider having treatment with a new drug approved by Health Canada for the treatment of their MCL. Of the 37 respondents who answered this question, 12 (32.4%) respondents gave a rating of 8 or higher (rating average 6.1). Many respondents described they would be willing to tolerate side effects if they could live longer, achieve a remission, have control of their disease and have an improved quality of life. One respondent stated "*I will be willing because I want to live longer and enjoy more time with my loved ones and continue with life's experiences. If however, the side effects of treatment effects my quality of life and makes me a burden to my family and loved ones, I would not want to take the treatment and prolong the agony for everyone.*"

Respondents were asked to rate on a scale of 1 (Not Important) to 10 (Very Important), how important it is for a new drug to be able to control specific aspects associated with their disease. Below were the key responses.

Factors Associated with Long-term Health and Well-being (N=36)	Rating of 10 n (%)	Rating Average
Bring about a remission	34 (94.4)	9.72
Allow me to live longer	33 (91.6)	9.69
Improve Quality of Life	29 (80.6)	9.33
Control disease and symptoms associated with the disease	30 (83.3)	9.28
Improve blood counts	27 (75.0)	9.19

Respondents who have experiences with ibrutinib

CCSN and LLSC reported that, of the 24 respondents who responded to the survey, six (6) respondents have experience with ibrutinib. Among these respondents, two (2) were women and four (4) were men. CCSN and LSCC noted that five (5) respondents were Canadians and the one (1) was an American.

In order to provide further context regarding the duration of treatment with ibrutinib, CCSN and LLSC stated that one respondent had started ibrutinib two weeks prior to the survey but identified immediate response. Another respondent had taken ibrutinib for a month but had sustained an injury from a fall which complicated the ability to discern medication side-effects between the treatment for MCL and the treatment for the injury. Two respondents did not indicate how long they have used ibrutinib, and one respondent has taken ibrutinib for approximately 15 months. One respondent had access through a clinical trial for the past 3.5 years.

These respondents were asked about their knowledge of ibrutinib. CCSN and LLSC reported the following responses in the table below, where most indicated that they had knowledge of ibrutinib.

	1 (nothing)	2	3	4	5	6	7 (extremely knowledgeable)	Total
Knowledge of drug	0	2	0	1	1	2	0	6

LC reported that 16 respondents had experience with ibrutinib; 13 respondents indicated if they are still taking ibrutinib and whether they would recommend ibrutinib to other MCL patients based on their own personal experiences.

Start Date	Still Taking	Recommend Ibrutinib to Other MCL Patients?
Nov 2015	Yes	*Yes. It has worked for me significant improvement in quality of life."(Male; 55-64; USA; Hyper C-VAD; RICE)*
Sept 2015	Yes	*"Yes. To control and elongate their life with minimum side effects." (Male; 55-64; Canada; Previous treatments: Hyper CVAD; Rituximab; Stem Cell Transplant)*
Aug 2015	Yes	*"Yes. Quality of life is 100% better and my disease is shrinking!" (Female; 59; Canada. Previous treatments: Radiation; R-CHOP; Autogenous Stem Cell Transplant; Rituximab; Radiation; Lenalidomide; Steroid)*
July 2015	Yes	*"Yes. Less side effects."(Male; ≥75; UK; No previous treatment)*
June 2015	No (Date not given. Developed infections)	*"Yes. Hope." (Male; 55-64; USA; Previous treatment: Hyper-CVAD)*
Oct 2014	Yes	*"Yes. It brought about a full remission and an excellent quality of life, without any significant side effects."(Male; 71; Previous treatments: R-CHOP, Radiation and Lenalidomide).*
Aug 2014	No (Date and reason not specified)	*"Yes. It has had excellent results for some people." (Female; 55-64; UK; Previous treatments: CHOP; Auto Stem Cell Transplant; PMITCEBO chemo; Radiation)*
May 2014	Yes	"Yes. Overall side effects are minimal."(Male; 55-64; USA; Previous treatments: NORDIC; Auto Stem Cell; Bendamustine-Rituximab; Radiation)
Jan 2014	No (Discontinued In July 2015. Achieved full remission then stem cell transplant)	*"Yes. It's a life saver. Since there are only 6% of us a year affected by this disease. I would say this drug is a miracle and should be able to be given to all MCL patients in need."* (Female; 56; USA; Previous treatments: Bendamustine; Rituximab with RCHOP; was on Ibrutinib 18 months prior to transplant in July 2015)
Jan 2014	Yes	*"Yes. I love the fact that I can take a pill at home. I call it my magic pill." (Female; 77; Canada; Previous treatment: R-CHOP. Taking Ibrutinib with Lenalidomide)*
June 2013	No (Relapsed after 8 or 9	*"Yes. It is an oral pill and from my experience, it was easy to take with minimal side effects. Hopefully it will work well for other MCL patients."* (Female; 55-64; Canada; Treatments: RCHOP;

Start Date	Still Taking	Recommend Ibrutinib to Other MCL Patients?
	months)	Stem Cell Transplant; Bortezomob; Lenalidomide; High Dose Chemo; Stem Cell Transplant; Ibrutinib CAR T Cell Transplant; Nivolumab; Idelalisib; Bendamustine-Rituximab)
June 2013 - Aug 2015	No (Discontinued in Aug 2015. Reason not specified)	*"Yes. I would highly recommend it. Ibrutinib kept my lymphoma stable for 2 years." (Male; 65-74; Canada; Previous treatments: CHOP; Vincristine; Rituximab; Stem Cell Transplant; Radiation; Bendamustine and Rituximab; Gemcitabine and Rituximab; Lenalidomide; Radiation; ICE; Ibrutinib; Cytarabine, Leucovorin, Methotrexate were administered, but I am not sure when)*
March 2011	No (Discontinued after 41 months due to relapse)	*"Yes. Its immense efficacy is astounding! As mentioned, any noted side effects were nonexistent. My strong opinion is, if there is a miracle medication for a targeted cancer treatment for which ibrutinib might be used, this is it."* (Male; 64; USA; Previous treatments: Rituximab + Hyper CVAD; Rituximab + Bortezomib; Lenalidomide; RAD001

When LC respondents were asked about the side effects experienced with ibrutinib, most respondents stated that the side effects were mild with minimal tolerability issues and were far less than chemotherapy or infused/injected drugs. Seven (7) respondents attributed the following negative side effects to ibrutinib: joint/muscle pain (n=3); fatigue (n=2); diarrhea (n=1); dry/cracked fingers (n=1); rash (n=1); light-headedness (n=1). Ten respondents noted positive side effects: lymph node reduction (n=9); increased energy (n=3); tumour reduction (n=1); no nausea (n=1); no loss of appetite (n=1); no neuropathy (n=1); no hair loss (n=1); no back pain (n=1). Respondents were asked how ibrutinib compares in terms of side effects to other treatments they had taken to treat their MCL on a scale of 1 - 10, with 1 being (Fewer Side Effects) and 10 being (Many More Side Effects). Twelve respondents answered this question with 10 (83.3%) of the respondents rating side effects as ≤ 2. One respondent stated "*Freedom to take orally at home. I had leg and arm cramps, but overall my quality of life was mostly normal in comparison.*"

When CCSN and LLSC respondents were asked to select the MCL symptoms that ibrutinib manages or managed better than previous therapies they might have used, respondents reported that "loss of appetite and/or weight loss" and "fatigue" were symptoms that were managed by ibrutinib. The table below outlines the complete responses reported by the six (6) respondents.

Answer Choices	Responses	Total
Loss of appetite and/or weight loss	4	6
Fever and/or night sweats	3	6
Pain	2	6
Fatigue	4	6
Bruising and/or bleeding	2	6
Rashes/skin changes	1	6
Numbness and tingling	2	6
lumps	3	6

According to LC, prior to commencing treatment with ibrutinib, all but three respondents, had switched from therapy to therapy as their disease kept relapsing, which is considered to be

common with MCL. Most respondents reported their symptoms associated with MCL improved dramatically with ibrutinib. Two (2) respondents stated they had a relapse of their disease. One respondent took ibrutinib until she achieved remission and was eligible for a stem cell transplant. One respondent stated "*I had a full remission in less than 6 months after starting ibrutinib treatment (based on CT scan). All my swollen lymph nodes are gone and I have no more stomach pain. I can eat everything and I am now physically and psychologically strong*."

When CCSN and LLSC respondents were asked to rate how much they agree or disagree with the following statement: "*ibrutinib has improved my quality of life compared to previous therapies I have used*." The following were their responses noted.

1 (strongly disagree)	2	3	4	5	6	7 (strongly agree)	Total	Weighted Average
0	0	0	2	0	1	3	6	5.83

LC respondents were asked to rate their Quality of Life while using ibrutinib from 1 (Severely Negatively Impacted) to 10 (Normal Living). Fourteen (14) respondents responded to this question; the rating average was 9.1. One respondent stated "*Once I started the ibrutinib I am not kidding you I was at my 100% best. It was like there was no way aside from not having any hair on my head from previous treatment that anyone would have known I had cancer. That's how good I felt. I did all my own normal things. I grocery shopped. I rode my bike. I went shopping. I went on trips to see family. I did everything I did normally prior to being diagnosed with cancer*." Another respondent reported "*I went from having only 4 out of 14 days of feeling decent to feeling decent daily once I started Ibrutinib. I had quite a large node on the left side of my chin and within 10 days of starting treatment I felt the node shrinking and within 15 days I could no longer feel it. I had energy again because I was no longer taking steroids and I was able to be more productive at home and work. Since I started ibrutinib, my energy levels increased and I've been able to be crazy busy again and feel like I am contributing at work and at home! I am actually going to try to resume my gym membership and start working out again*."

The following quotes were excerpted by CCSN and LLSC to help illustrate respondents' experiences with ibrutinib. These quotes include the responses to the following open-ended question, "*Please describe how ibrutinib has or has not improved your quality of life*."

- *I am very satisfied. This has really improved my life. Before I took these pills I felt weak and depressed. It took about 4 or 5 weeks before I started to feel better again.*
- *With the help of Ibrutinib (Imbruvica), I am living well and enjoying life, with the limitations of having to be near a washroom to pee and having to avoid accidents and viruses.*
- *Has reduced my chills/fever and my visits to washroom-- more energy and interest in life*
- *For first 8 days, I had few, if any, side effects. But I fell on ice on and this has complicated my experience.*
- *Life has returned to virtually normal*
- *Slight loss of peripheral neural sensitivity, which once or twice left me unaware of a cut or bruise (and healing took longer than was normal for me)*

- *Ibrutinib (-3.5 years of remission) was miraculous and very well tolerated. Platelet counts around 100 were most significant impact with little clinical effect. Until recent progression, I was able to live as I wanted, included bicycling 50-100 miles per week*
- *My chills have decreased drastically-- in frequency and intensity. Have more energy and interest in doing things/life. My weight is increasing very slowly--my visits to washroom for passing stool has come back to normal*
- *Am extremely lucky (actually a miracle) that my company group insurance has been able to help me get this medicine--! hope this help continues*
- *I was being treated with the last conventional chemical available. I was not then experiencing any other illness, but the prospects were grim. In October-November 2014, my oncologist was able to secure ibrutinib for me, on compassionate grounds, since when the disease seems to have stabilized then retreated.*
- *Excellent. Within one week of starting, lesions at the top of my head began to shrink noticeably. As noted above, other significant side effect has been compromised platelets, but not enough to prevent, for example, a hernia repair.*
- *It probably saved my life. I take 4 pills a day, with ease. All the tumours have dissolved. I have no swollen nodes. I have clear bone marrow. I am extremely grateful for all this*
- *Fatigue… and compromised left leg function/gait due to pressure of tumor on brain. As tumor shrinks, leg function is improving dramatically.*

4.3 Additional Information

None provided.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could be impact implementation of ibrutinib in the treatment of relapsed or refractory mantle cell lymphoma (MCL):

Clinical factors:

- There is no standard of care; treatment is usually intravenous chemotherapy
- New treatment option that is an oral drug

Economic factors:

- Small number of patients relative to other cancers but potentially large number of prevalent patients
- Unknown treatment duration and number of patients eligible for treatment

Please see below for more details.

5.1 Factors Related to Comparators

Treatments for relapsed or refractory MCL vary across the provinces and there is no standard of care. Treatments include fludarabine-based chemotherapy regimens, rituximab with chemotherapy, bortezomib, bendamustine with rituximab, gemicitabine/dexamethasone/cisplatin or alkylating agents.

The MCL-2001 trial reports on the efficacy and safety of single-agent ibrutinib specifically in patients with MCL who had received a rituximab-containing regimen and had progressed after at least 2 cycles of bortezomib therapy. However, bortezomib is not a funded treatment option for MCL in some provinces.

PAG noted that in the ongoing phase 3 trial, the comparator, temsirolimus, is not used in Canada and the phase 2 trials had short follow-up periods and no comparators. PAG is seeking information on the generalizability of these trial results to Canadian practice.

5.2 Factors Related to Patient Population

The incidence of MCL is low relative to other cancers. However, PAG noted the PCYC-1104 trial included patients with relapsed or refractory MCL who have received one to five prior treatments. Thus, there is a potentially large prevalent number of patients who would be eligible for treatment with ibrutinib.

PAG noted that if funded, ibrutinib may become the treatment of choice for relapsed or refractory MCL and is seeking information on treatment sequence with intravenous chemotherapy, recognizing that data may not be available.

There are ongoing trials for ibrutinib in the treatment of newly diagnosed MCL and other B-cell lymphomas. PAG indicated that there may be pressure from clinicians and patients to use ibrutinib for newly diagnosed MCL and other B-cell lymphomas but recognize these are out of the scope of this review.

5.3 Factors Related to Dosing

PAG noted that the drug's once daily, continuous dosing schedule and the flat dose of 560mg are enablers to implementation. However, barriers to implementation include the need for patients to take four capsules for the dose and the unknown treatment duration as treatment with ibrutinib is until disease progression or unacceptable toxicities.

There is one capsule strength available and dose adjustment is made by adjusting the number of capsules per dose. This reduces wastage and is easier for patients to manage.

5.4 Factors Related to Implementation Costs

As ibrutinib is administered orally, PAG noted that chemotherapy units and chair time would not be required. This is an enabler to implementation.

PAG also noted that additional health care resources may be required to monitor and treat toxicities and monitor drug-drug interactions.

Although the number of patients with relapsed or refractory MCL would be smaller than the number of patients with relapsed or refractory chronic lymphocytic leukemia, there may be a large budget impact in first year given the high cost of ibrutinib and potentially large number of patients who would be eligible for treatment with ibrutinib. PAG noted that uptake would be high given that ibrutinib is an oral drug and provides a new treatment option for relapsed or refractory MCL. PAG is seeking clarification on the number of patients and the duration of treatment.

5.5 Factors Related to Health System

PAG noted that ibrutinib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. PAG identified the oral route of administration is an enabler to implementation.

However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

5.6 Factors Related to Manufacturer

The high cost of ibrutinib is a barrier to implementation.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of ibrutinib compared with standard therapy for the treatment of patients with relapsed or refractory MCL.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 6.1 Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs[†]	Patients with relapsed/ refractory mantle cell lymphoma Subgroups: • Prior therapies (type, line) • Type of treatment indication (relapsed, refractory) • Age • Performance status	Ibrutinib	• fludarabine-based chemotherapy regimens[a] • rituximab with chemotherapy regimens[b] • bortezomib • bendamustine • GDP (gemcitabine + dexamethasone + cisplatin) • gemcitabine • alkylating agents[c] • temsirolimus**	Overall survival Progression-free survival **Quality of life** Response Rate • CR • PR Duration of Response Time to next treatment **Adverse events** Adverse events of special interest: • hospitalization • atrial fibrillation • bleeding • other malignancies

CR = complete response; PR = partial response; RCT = randomized controlled trial.
[†] In the absence of RTC data, fully published clinical trials investigating the efficacy of ibrutinib should be included. Reports of trials with only a dose-escalation design should be excluded. Reports of trials with a mixed design are to be included only if separate data were reported for the cohort of patients who were included in the efficacy-determining phase of the study.
* Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions).
** Identified as agent of interest although not currently used in Canada.
[a] Includes but not limited to FCM (fludarabine + cyclophosphamide + mitoxantrone), FR (fludarabine + rituximab), and FC (fludarabine + cyclophosphamide).
[b] Includes but not limited to R-CHOP (rituximab + cyclophosphamide + doxorubicin +vincristine + prednisone), R-CVP (rituximab + cyclophosphamide + vincristine + prednisone), R-HyperCVAD (rituximab + hyperfractionated cyclophosphamide + vincristine + doxorubicin + dexamethasone), R-GDP (rituximab + gemcitabine + dexamethasone + cisplatin), and rituximab + bendamustine.
[c] Includes but not limited to chlorambucil and cyclophosphamide.

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-present) with in-process records & daily updates via Ovid; Embase (1974 to 2016 February 01) via Ovid; The Cochrane Central Register of Controlled Trials (December 2015) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were ibrutinib, Imbruvica and mantle cell lymphoma.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year. The search is considered up to date as of June 1, 2016.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team made the final selection of studies to be included in the review.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team. A data audit was conducted by another member of the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

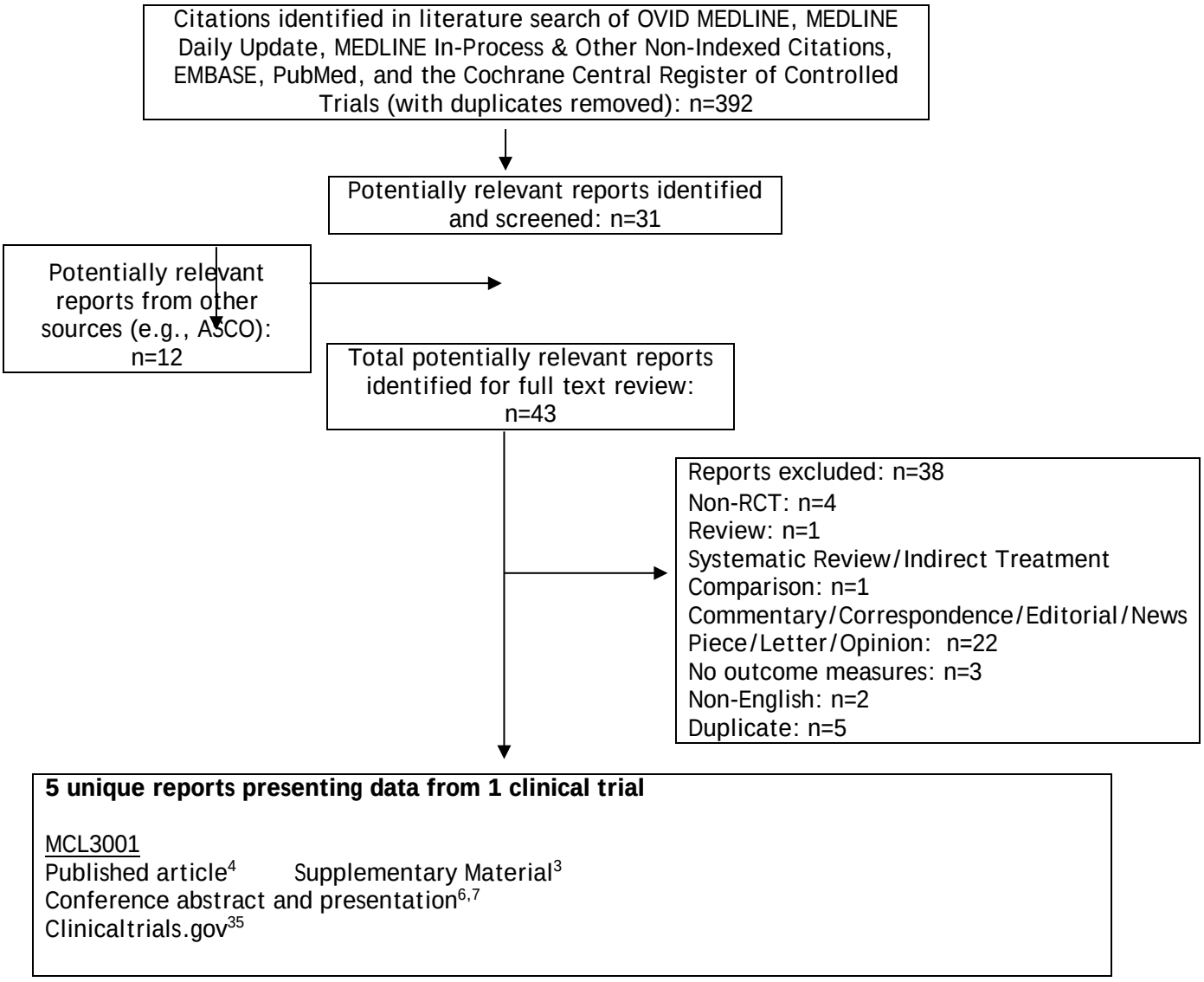
This report was written by the Methods Team, the Clinical Guidance Panel and pCODR:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental issues.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information, the interpretation of the systematic review and wrote guidance and conclusions for the report.
- pCODR wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Figure 6.1 QUOROM Flow Diagram for Inclusion and Exclusion of Studies



Note: Additional data related to MCL3001 were also obtained through requests to the Submitter by pCODR[5]

6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

a) Trials

Trial details are summarized in Table 6.2.

MCL3001 is a randomized, open-label, multicentre, phase 3 clinical trial comparing ibrutinib with temsirolimus in patients with relapsed or refractory MCL who received at least 1 prior rituximab-containing chemotherapy regimen.

MCL3001 was conducted in centres in 21 countries, including Canada, Europe, Latin America and Asia. The study was sponsored by Janssen Research & Development. The study enrolled 337 patients with relapsed or refractory mantle-cell lymphoma confirmed by central pathology. Patients were randomized in a 1:1 ratio to receive oral ibrutinib (560 mg daily) or intravenous temsirolimus (175 mg on days 1, 8, and 15 of cycle 1; 75 mg on days 1, 8, and 15 of subsequent 21-day cycles) until disease progression or unacceptable toxic effects. Randomization was stratified by number of previous lines of therapy (1, 2, or ≥3) and simplified mantle-cell lymphoma international prognostic index (sMIPI) score [low risk (0–3) versus intermediate risk (4–5) versus high risk (6–11)].

Key inclusion criteria were as follows: received at least one prior rituximab-containing chemotherapy regimen; documented relapse or disease progression following the last anti-MCL treatment; ECOG performance status of 0 or 1; haematology and biochemical values within a specified range (see Table 6.2 Summary of Trial Characteristics of the Included Studies for more details).[3]

Key exclusion criteria included: chemotherapy, radiation, or other investigational drugs within 3 weeks, antibody treatment within 4 or immunoconjugates within 10 weeks; central nervous system lymphoma; known history of human immunodeficiency virus, active infection with hepatitis C virus or hepatitis B virus, or any uncontrolled active systemic infection that required IV antibiotics.[3]

The primary endpoint was progression-free survival. Secondary endpoints included: overall response rate, overall survival, 1 year survival rate, duration of response, time to next treatment, safety, patient reported outcomes.

The study design required a minimum of 178 progression-free survival events to ensure a power of 85% to detect a treatment effect at a two-sided significance level of 0.05. No interim analysis was planned. The study protocol was amended on July 30, 2014 to allow for patients who received temsirolimus and had IRC-confirmed disease progression to cross over and receive ibrutinib until disease progression, unacceptable toxicity, or study end. The clinical data cut-off date was April 22, 2015.

Table 6.2 Summary of Trial Characteristics of the Included Studies [3-5,35]

Trial Design	Eligibility Criteria	Intervention & Comparator	Outcomes
MCL3001* Randomized, open-label, multicentre, phase 3 clinical trial Enrolment: Dec 10, 2012 to Nov 26, 2013 N enrolled = 337 No planned interim analysis Median follow-up: 20 months Clinical data cut-off date: April 22, 2015 Crossover date: July 30, 2014 Estimated study completion date: November 2016 Randomized 1:1 ratio, stratified by number of previous lines of therapy (1, 2, or ≥3) and sMIPI (low risk [0-3] vs. intermediate risk [4-5] vs. high risk [6-11]) N randomized = 280 N ibrutinib = 139 N temsirolimus = 141 Funded by Janssen Research & Development	<u>Key Inclusion Criteria</u> • Aged ≥18 years • Diagnosis of MCL reviewed and approved by central pathology laboratory prior to randomisation: o Diagnosis report from local laboratory 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 o If report from local laboratory is not available, diagnosis must be confirmed by central pathology laboratory based on the criteria above • Received at least one prior rituximab-containing chemotherapy regimen • Documented relapse or disease progression following the last anti-MCL treatment • ECOG PS 0 or 1 • Haematology values within: o Absolute neutrophil count ≥1000/mm^3 independent of growth factor support o Platelet count ≥75 000/mm^3 or ≥50 000/mm^3 if bone marrow involvement independent of transfusion support o Haemoglobin level ≥8 g/dL, independent of transfusion support • Biochemical values within: o Alanine aminotransferase and aspartate aminotransferase ≤3 × ULN o Total bilirubin ≤1·5 × ULN o Serum creatinine ≤2 × ULN o Fasting serum cholesterol level ≤350 mg/dL o Fasting serum triglyceride level ≤400 mg/dL • After protocol amendment (July 30, 2014), patients who received temsirolimus and had IRC-confirmed disease progression were eligible to cross over and receive ibrutinib until disease progression, unacceptable toxicity, or study end <u>Exclusion Criteria</u> • Received prior nitrosoureas within 6 weeks, chemotherapy within 3 weeks, therapeutic anticancer antibodies within 4 weeks, radio- or toxin-immunoconjugates within 10 weeks, radiation therapy or other investigational agents within 3 weeks, or major surgery within 4 weeks of randomisation • Received prior treatment with temsirolimus, other mTOR inhibitors, ibrutinib, or other BTK inhibitors • Had central nervous system lymphoma • Had a history of stroke or intracranial haemorrhage within 6 months prior to first dose of study drug • Required anticoagulation with warfarin or equivalent vitamin K antagonists or treatment with a strong CYP3A4/5 inhibitor • Had a known history of human immunodeficiency virus, active infection with hepatitis C virus or hepatitis B virus, or any uncontrolled active systemic infection that required IV antibiotics	<u>Intervention</u> ibrutinib 560 mg orally once per day Continue treatment until disease progression or unacceptable toxic effects. <u>Comparator</u> temsirolimus 175 mg intravenously on days 1, 8, and 15 of the first cycle, followed by 75 mg on days 1, 8, and 15 of each subsequent 21-day cycle. Continue treatment until disease progression or unacceptable toxic effects.	<u>Primary</u> • PFS <u>Secondary</u> • ORR • OS • 1 year survival rate • DOR • TTNT • Safety • Pre-specified PROs • Biomarkers and pharmacokinetics • Medical resource use rate

CT = computed tomography; DOR = duration of response; ECOG PS= Eastern Cooperative Oncology Group performance status; NR = not reported; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PROs = patient reported outcomes; sMIPI = simplified mantle-cell lymphoma international prognostic index; TTNT = time to next treatment; ULN = upper limit of normal; vs. = versus.
*Other Study IDs: NCT01646021; 2012-000601-74, CR100848; PCI-32765MCL3001; U1111-1135-6930

b) Populations

Details of baseline characteristics for MCL3001 are listed in Table 6.3.

A total of 280 patients were randomized to receive ibrutinib (n=139) or temsirolimus (n=141). The median age was 68 years. Most patients were stage IV MCL (83%), relapsed (70%), male (74%), and white (87%). About half of patients had an ECOG performance status of 1. On average, the number of prior lines of therapy received was 2, with 67% of patients having had 1-2 prior lines of therapy and 31% of patient having had 3-5 prior lines of therapy. All except one patient received prior rituximab (<100%), 50 patients received prior bortezomib (18%), and 15 patients received prior lenalidomide (5%).[4,5] Time from initial diagnosis to randomisation and time from end of last previous therapy to randomization were similar between groups.

The two groups appeared balanced; no major imbalances (>10%) in baseline characteristics between arms were noted.

Table 6.3 Baseline Characteristics of Pivotal Trial [4,5]

	Ibrutinib (n=139)	Temsirolimus (n=141)	Total (n=280)
Age			
Median, years	67	68	68
≥65 years	86(62%)	87(62%)	173(62%)
Sex, male	100(72%)	108(77%)	208(74%)
Race			
White	115(83%)	129(91%)	244(87%)
Asian	16(12%)	5(4%)	21(8%)
Other, unknown	8(6%)	7(5%)	15(5%)
ECOG performance status			
0	67(48%)	67(48%)	134(48%)
1	71(51%)	72(51%)	143(51%)
2*	1(1%)	2(1%)	3(1%)
Time from initial diagnosis to randomisation (months)			
Mean (SD)**	50(43)	51(34)	51(38)
Median (IQR)**	39(49)	46(44)	43(46)
<36 months	68(49%)	58(41%)	126(45%)
≥36 months	71(51%)	83(59%)	154(55%)
Time from end of last previous therapy to randomisation (months)			
Mean (SD)**	15(19)	16(20)	16(19)
Median (IQR)**	8(20)	7(22)	7(20)
Stage of MCL at study entry			
I	3(2%)	2(1%)	5(2%)
II	7(5%)	5(4%)	12(4%)
III	17(12%)	14(10%)	31(11%)
IV	112(81%)	120(85%)	232(83%)
Type of histology			
Blastoid	16(12%)	17(12%)	33(12%)
Non-blastoid	123(88%)	124(88%)	247(88%)
sMIPI			
Low risk (1-3)	44(32%)	42(30%)	86(31%)
Intermediate risk (4-5)	65(47%)	69(49%)	134(48%)
High risk (6-11)	30(22%)	30(21%)	60(21%)
Previous lines of therapy			
Mean (SD)**	2(1)	2(1)	2(1)

	Ibrutinib (n=139)	Temsirolimus (n=141)	Total (n=280)
Median (range)	2(1-9)	2(1-9)	2(1-9)
1-2	95(68%)	93(66%)	188(67%)
3-5	41(29%)	45(32%)	86(31%)
>5	3(2%)	3(2%)	6(2%)
Prior Therapy for MCL			
Prior cancer-related surgery	39(28%)	33(23%)	72(26%)
Prior Radiotherapy	26(19%)	26(18%)	52(19%)
Prior Systemic therapy	139(100%)	141(100%)	280(100%)
Bortezomib	30(22%)	20(14%)	50(18%)
Rituximab	138(99%)	141(100%)	279(<100%)
Alkylator	138(99%)	140(99%)	278(99%)
Anthracycline	129(93%)	123(87%)	252(90%)
Vinca alkyloid	128(92%)	127(90%)	255(91%)
Stem cell transplant	33(24%)	33(23%)	66(24%)
Lenalidomide	8(6%)	7(5%)	15(5%)
Cytarabine	67(48%)	75(53%)	142(51%)
Purine analog	23(17%)	26(18%)	49(18%)
Type of treatment indication			
Relapsed disease†	103(74%)	94(67%)	197(70%)
Refractory disease‡	36(26%)	47(33%)	83(30%)

ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; MCL=mantle-cell lymphoma; SD = standard deviation; sMIPI=simplified mantle-cell lymphoma international prognostic index.
*Patients inadvertently enrolled in the study, despite having an ECOG PS of 2.
**Rounded to the nearest whole number.
†Relapsed disease defined as relapse or disease progression after achieving at least a partial response to the last regimen before study entry.
‡Refractory disease defined as failure to achieve at least a partial response to the last regimen before study entry.

c) Interventions

Treatment was self-administered orally for ibrutinib (560 mg once per day) and site visits were conducted on day 1 of the 21-day cycle after 15 months after randomization and every 42 days thereafter until treatment discontinuation.[3] Treatment was administered intravenously for temsirolimus (175 mg on days 1, 8, and 15 of cycle 1; 75 mg on days 1, 8, and 15 of subsequent 21-day cycles) and site visits for study drug administration were conducted on day 1, 8, and 15 of the 21-day cycle until treatment discontinuation.[3] Patients in both groups continued treatment until disease progression or unacceptable toxic effects.

Of the patients treated with the study drug, the median number of cycles was 21.0 (range, 1 to 41) for the ibrutinib group compared with 5.0 (range, 1-40) of the temsirolimus group.[3] The median duration of exposure was 14.4 months for the ibrutinib group versus 3.0 months for the temsirolimus group, with a median relative dose intensity of 99.9% for the ibrutinib group compared with 81.8% for the temsirolimus group.

Dose modifications and delays were permitted for both groups.[5] Of the patients that received study drug, dose reduction due to adverse events was more common in patients treated with temsirolimus compared with patients treated with ibrutinib (43%, 60 of 139 versus 4%, 5 of 139).[4] Similarly, dose interruption/delay was more common in patients treated with temsirolimus compared with patients treated with ibrutinib (86% versus 35%).[5]

Details of subsequent therapy are listed in Table 6.3. More than half (58%) of patients in the temsirolimus group received any subsequent anticancer therapy compared with 32% of patients in

the ibrutinib group who received any subsequent anticancer therapy. The study protocol was amended to allow for patients who received temsirolimus and had IRC-confirmed disease progression to cross over and receive ibrutinib. As a result, a total of 23% of patients (n=32) received subsequent ibrutinib therapy. Patients in the temsirolimus group also received rituximab, bendamustine, and cyclophosphamide as subsequent therapy.

Similarly, patients in the ibrutinib arm received rituximab, bendamustine, and cyclophosphamide as subsequent therapy, and about 3% of patients received temsirolimus as subsequent therapy.

Table 6.4 Subsequent Anticancer Therapy [4]

	Ibrutinib (n=139)	Temsirolimus (n=141)
Any subsequent anticancer therapy	44(32%)	82(58%)
Ibrutinib*	—	32(23%)
Temsirolimus	4(3%)	—
Rituximab	21(15%)	36(26%)
Bendamustine	15(11%)	22(16%)
Cyclophosphamide	12(9%)	19(13%)

* Protocol was amended (July 30, 2014) to include formal crossover of patients on the temsirolimus arm to ibrutinib, who have independent review committee-confirmed progression of disease.

d) Patient Disposition

Details of the patient disposition can be found in Table 6.5. A total of 280 patients were randomized to receive ibrutinib (n=139) or temsirolimus (n=141); two patients did not receive temsirolimus because the patient withdrew consent or had an adverse event unrelated to study drug. At the time of the data cut-off date, 47% of patients in the ibrutinib group were still on treatment and 11% of patients in the temsirolimus group were still on treatment. Disease progression was the most common reason for discontinuing treatment in both arms (40% versus 41%). Adverse events was another reason for treatment discontinuation in 36 (26%) patients in the temsirolimus group and in 9 (6%) patients in the ibrutinib group. The most common adverse events leading to discontinuation were pneumonia, atypical pneumonia, or pneumonitis for patients in the temsirolimus group (4% of patients) and thrombocytopenia for patients in the ibrutinib group (1% pf patients).

Table 6.5 Patient Disposition*[4,5]

Enrolled	337	
Randomized	280	
Allocation	**Ibrutinib**	**Temsirolimus**
Randomized	139	141
Received treatment	139(100%)	139(99%)
Did not receive allocated treated (reasons below):	0	2(1%)
• withdrew consent	0	1(1%)
• adverse event unrelated to study drug	0	1(1%)
Disposition	**Ibrutinib**	**Temsirolimus**
Still on treatment	65(47%)	15(11%)
Discontinued treatment (reasons below):	74(53%)	124(88%)

• disease progression	55(40%)	58(41%)
• adverse events	9(6%)	36(26%)
• deaths	6(4%)	8(6%)
• refused further treatment	4(3%)	16(11%)
• investigator or funder decisions	0	6(4%)
Analysis	**Ibrutinib**	**Temsirolimus**
ITT Population	139	141
Safety Population†	139	139

ITT = intent-to-treat.
*Database locked on April 22, 2015
†patients who received at least 1 dose of study drug.

e) Limitations/Sources of Bias

Despite the open label design, measures to reduce risk of bias were made; complete response, partial response, and progressive disease were assessed by an independent review committee; as well an independent data monitoring committee monitored safety. The open label design may have introduced a risk of bias in patient-reported outcomes. Overall survival results may have been confounded due to the high proportion of cross over, however cross over did not affect the primary endpoint, PFS. The study publication by Dreyling et al. did not report on EQ-5D-5L assessment which was a planned secondary endpoint; this was considered by the Methods team to be selective reporting bias, however, the submitter offered details of the results from the EQ-5D-5L assessment as well, a Poster by Hess et al., 2015[6] reported results on patient reported outcomes including the EQ-5D-5L assessment.

1. Randomization and allocation concealment

As stated in the study publication, central randomisation was used and patients were randomly assigned in a 1:1 fashion to either oral ibrutinib or intravenous temsirolimus based on a computer-generated randomisation schedule. Randomization was balanced using randomly permuted blocks within each stratum [by number of previous lines of therapy (1, 2, or ≥3) and sMIPI score (low risk versus intermediate risk versus high risk).

No major imbalances (>10%) in baseline characteristics between arms were noted.

Risk of randomization and allocation concealment bias was low.

2. Blinding

MCL3001 was an open label study. Patients and investigators were unmasked to treatment assignment.

Measures to reduce the risk of bias with respect to the assessment of primary and secondary endpoints were made. Complete response, partial response, and progressive disease were assessed by an independent review committee; as well an independent data monitoring committee monitored safety. However, the open label design may have introduced moderate-high risk of bias in patient-reported outcomes.

The route of administration differs as well as management of adverse events may different between treatments: ibrutinib is an oral treatment, while temsirolimus is administered intravenously; this difference precluded a blinding strategy.

3. Attrition

At the time of the data cut-off date, 47% of patients in the ibrutinib arm were still on treatment and 11% of patients in the temsirolimus arm were still on treatment. Disease progression was the most common reason for discontinuing treatment in both arms (40% versus 41%). Adverse events was the primary reason for treatment discontinuation in 36 (26%) patients in the temsirolimus arm and 9 (6%) patients in the ibrutinib arm.

The efficacy outcomes were analyzed according to the intention to treat principle. Safety was analysed in patients who received at least one dose of study drug, which included 100% of patients randomized to the ibrutinib group and 99% of patients randomized in the temsirolimus group.

4. Crossover

A high proportion of crossover may confound study results towards the direction of the null hypothesis. It is important to note that 23% of patients in the temsirolimus group crossed over to ibrutinib, and thus, overall survival results may be confounded. Cross over did not however affect the primary endpoint, PFS.

5. Reporting of outcomes

As stated in the study publication, complete response, partial response, and progressive disease were assessed by an independent review committee; as well an independent data monitoring committee monitored safety. The study publication by Dreyling et al. did not report on EQ-5D-5L assessment which was a planned secondary endpoint; this was considered by the Methods team to be selective reporting bias, however, the submitter offered details of the results from the EQ-5D-5L assessment, as well, a Poster by Hess et al., 2015[6] reported results on patient reported outcomes including the EQ-5D-5L assessment.

6. Protocol deviations

Overall, major protocol deviations were reported in 8% of patients (n=21): 5% of patients (n=7) in the ibrutinib arm and in 10% of patients (n=14) in the temsirolimus arm. Major protocol deviations included: developed withdrawal criteria, but not withdrawn; entered trial, but did not satisfy trial entry criteria; received a disallowed concomitant treatment; and safety assessment deviation. The most common major protocol deviation was enrollment criteria deviation.[5] It is important to highlight that major protocol deviations such as developed withdrawal criteria, but not withdrawn could confound the primary outcome; however, in this instance and given the low proportion of major protocol deviations, confounding was not likely a factor.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

a) Efficacy Outcomes

Details of efficacy outcomes are listed in Table 6.6.

Overall Survival

Overall survival (OS) was a secondary endpoint and was defined as the duration (months) from the date of randomization to the date of the subject's death from any cause.[5]

After a median follow-up of 20 months, 42% of patients (n=59) in the ibrutinib group and 45% of patients (n=63) in the temsirolimus group had died. There was no statistically significant difference in OS [hazard ratio for death: 0.76(95%C, 0.53 to 1.09), p=0.1324]. The median OS was not reached for the ibrutinib group, while the median OS for the temsirolimus group was 21.3 months. The 1 year survival rate was 68% in the ibrutinib arm and 61% in the temsirolimus arm.

Progression-Free Survival

The primary endpoint, progression-free survival (PFS), was defined as the interval from date of randomisation to the date of disease progression or date of death, whichever occurred first, irrespective of the use of subsequent antineoplastic therapy. PFS was assessed by an independent review committee. Treatment effect based on progression-free survival PFS was tested with a stratified two-sided log-rank test stratified by sMIPI and previous lines of therapy.

After a median follow-up of 20 months, 53% of patients (n=73) in the ibrutinib group and 79% of patients (n=111) in the temsirolimus group had progressed or died. A statistically significant difference in PFS was found; the hazard ratio for disease progression or death was 0.43 (95%CI, 0.32 to 0.58), p<0.0001. The median PFS was 14.6 months for the ibrutinib group compared with 6.2 months for the temsirolimus group. The PFS rate at 2 years was 41% in the ibrutinib group compared with 7% in the temsirolimus group.

Results from subgroup analysis of special interest for PFS (prior therapies, type of treatment indication, age, and performance status) were consistent with the overall PFS results (Table 6.7).

Results from various sensitivity analyses (e.g., using Investigator-assessed date of progression, unstratified log-rank test, censored at last disease assessment date prior to subsequent therapy) were consistent with independent review committee-assessed PFS.[3] As well, investigator-assessed PFS and PFS2 (defined as 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) showed similar trends in PFS over time.[3]

Patient Reported Outcomes

The secondary endpoints relating to patient-reported outcomes (PROs) were defined as follows: time to worsening in the LYM subscale of the FACT-LYM and the mean change from baseline in EQ-5D-5L scores.[5,35] FACT-LYM was performed until disease progression, death, or clinical cut-off, whichever came first and the EQ-5D-5L was performed until death or study end. FACT-LYM is a cancer specific measure part of the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System; this 15-item FACT-LYM is constructed to complement the 27-item complement Functional Assessment of Cancer Therapy General (FACT-G).[36] According to the literature, FACT-LYM has shown to be reliable and valid.[8,36-38]

The proportions of patients improving and declining were calculated, and the median time to clinically meaningful improvement (defined as a 5-point or greater increase from baseline) and time to worsening (defined as a 5-point or greater decrease from baseline) were estimated.[8] According to the literature provided by the submitter, evidence suggests that a likely minimal important difference range for the LYM subscale is approximately 3–5 points,[8] and based on this, the submitter used a more conservative minimal important difference of 5 points; this appears to be reasonable.

According to Hess et al.,2015, patient reported outcome compliance rates were generally acceptable, with <20% missing at most time points.[6] Hess et al., 2015 noted that higher PRO score indicated better outcomes. FACT-LYM scores could range from 0-60. The mean baseline lymphoma symptom score was 43.3 (±10.4) for patient in the ibrutinib group and 45.3 (±8.9) patients in the temsirolimus group. EQ-5D-5L utility values (using UK time trade-off value set) could range from -1 to 1; VAS scores could range from 0-100. The mean baseline scores for utility values and VAS scores were 0.7(±0.2), 66.6(±19.3) for patient in the ibrutinib group and 0.7 (±0.2), 64.5 (±21.9) patients in the temsirolimus group.[6]

Time to worsening in the LYM subscale of the FACT-LYM (defined as a 5-point or greater decrease from baseline

Of patients treated with ibrutinib, 27% had a clinically meaningful worsening in lymphoma symptoms compared with 52% of patients treated with temsirolimus. The median time to clinically meaningful worsening was 9.7 weeks in the temsirolimus arm and was not reached in the ibrutinib arm, with a hazard ratio 0.27 (95% CI, 0.18 to 0.41, p<0.0001).[6]

Time to clinically meaningful improvement in the LYM subscale of the FACT-LYM (defined as a 5-point or greater increase from baseline)
Post-hoc analysis was reported by the Dreyling et al. and Hess et al., 2015 to highlight time to clinically meaningful improvement.[4-6] With a median time to follow-up of 20 months,[7] 62% of patients treated with ibrutinib had a clinically meaningful improvement in lymphoma symptoms compared with 35% of patients treated with temsirolimus. The median time to clinically meaningful improvement was 6.3 weeks compared with 57.3 weeks, with a hazard ratio 2.19 (95% CI, 1.52 to 3.14, p<0.0001).[6]

Mean change from baseline in FACT-LYM (FACT-G and LYM subscale)
Additional exploratory analyses were conducted by the submitter to highlight the mean change from baseline in FACT-LYM (FACT-G and LYM subscale) over time. No MID for FACT-G subscale scores within FACT-LYM were reported. As a result, assessment of FACT-G subscale scores within FACT-LYM (physical, social/family, emotional, and functional well-being) was limited and therefore, results were not reported.

Mean change from baseline in EQ-5D-5L scores
Hess et al., 2015 noted that with the ibrutinib group, changes from baseline for EQ-5D-5L utility values were positive at all time points up to Week 40, and statistically different from temsirolimus at all time points up to Week 49. Hess et al., 2015 also noted that with the ibrutinib group, changes from baseline for VAS values were positive and statistically different from temsirolimus at all time points. With the temsirolimus group, patients had consistently lower utility and VAS scores from baseline, and EQ-5D-5L values did not return to baseline at any time point, up to Week 106.[6]

Overall Response Rate

Independent review committee-assessed overall response rate (complete response and partial response) was greater in the ibrutinib group compared with the temsirolimus group (72% versus 40%, with an odds ratio of 3.98 (95%CI, 2.38 to 6.65), p-value not reported). The complete response rate was 19% group compared with 1%. More than half of patients (53%) in the ibrutinib arm achieved a partial response, while 39% of patients in the temsirolimus arm achieved a partial response.

Investigator-assessed overall response rates fairly similar to independent review committee-assessed overall response rates (77% versus 46%).

Duration of Response

The median duration of response was 7.0 months in the temsirolimus group and was not reached in the ibrutinib group. At 18 months, the estimated rate of duration of response was 58% in the ibrutinib group and 20% in the temsirolimus group; in other words, at 18 months it was estimated that 58% versus 20% of responders would be alive without progression.

Time to Next Treatment

The median time to next treatment was 11.6 months in the temsirolimus group and was not reached in the ibrutinib group. At 18 months, the estimated rate of time to next treatment was 66% in the ibrutinib group and 26% in the temsirolimus group; in other words, at 18 months it was estimated that 66% versus 26% of patients would be without subsequent therapy.[5]

Table 6.6 Summary of Efficacy Outcomes [4,5]

	Ibrutinib (n=139)	Temsirolimus (n=141)
Profession-Free Survival, Primary Outcome (IRC-assessed)		
PFS† median	**14.6 months**	**6.2 months**
HR* (95%CI), p-value	0.43 (95%CI:0.32-0.58), p<0.0001	
PFS rate at 2 years	41%	7%
Overall Survival, Secondary Outcome		
OS median	**Not reached**	**21.3 months**
HR*(95%CI), p-value	0.76 (95%CI:0.53-1.09), p=0.1324	
OS rate at 1 year	68%	61%
Patient Reported Outcomes, Secondary Outcome (using the FACT-Lym Lymphoma Subscale)		
Clinically meaningful improvement in lymphoma symptoms, n (%)	86(62%)	50(35%)
Median time to clinically meaningful improvement	**6.3 weeks**	**57.3 weeks**
HR (95%CI), p-value	2.19 (95%CI:1.52-3.14), p<0.0001	
Clinically meaningful worsening of lymphoma symptoms, n (%)	37 (27%)	73 (52%)
Median time to clinically meaningful worsening	**Not reached**	**9.7 weeks**
HR* (95%CI), p-value	0.27 (95%CI:0.18-0.41), p<0.0001	
Overall Response Rate, Secondary Outcome (IRC assessed)		
ORR	**100(72%)**	**57(40%)**
Difference in ORR (95%CI), p-value	31.5% (95%CI:20.5-42.5), p<0.0001	
OR (95%CI) p-value	3.98 (2.38-6.65), p=NR	
Complete response, n (%)	26 (19%)	2(1%)
Duration of Response, Secondary Outcome		
Median DOR	**Not reached**	**7.0 months**
p-value	p=NR	
Estimated rate of DOR at 18 months	58%	20%
Time to Next Treatment, Secondary Outcome		
Median TTNT	**Not reached**	**11.6 months**
p-value	p<0.0001	
Estimated rate of TTNT at 18 months	66%	26%

CI = confidence interval; DOR = duration of response; HR = hazard ratio; IRC = independent review committee; NR = not reported; OR = odds ratio; ORR = overall response rate; TTNT = time to next treatment.
*HR < 1 favours Ibrutinib
†PFS defined as the interval from date of randomisation to the date of disease progression (as assessed by the independent review committee) or date of death, whichever occurred first, irrespective of the use of subsequent antineoplastic therapy. Median follow-up of 20 months.
[a]defined as a 5-point or greater increase from baseline.
[b]defined as a 5-point or greater decrease from baseline.

Table 6.7 Subgroup Analysis of Special Interest for Progression-Free Survival*[4]

Subgroup	Hazard Ratio**(95%CI)	Ibrutinib (n=139)		Temsirolimus (n=141)	
		EVT/N	Median	EVT/N	Median
All patients	**0.43 (0.32-0·58)**	**73/139**	**14.6**	**111/141**	**6.2**
Previous lines of therapy					
1 or 2	0.39 (0.26-0.59)	36/85	NE	62/85	6.2
≥3	0.50 (0.32-0.77)	37/54	10.5	49/56	4.4
Previous bortezomib					

Subgroup	Hazard Ratio**(95%CI)	Ibrutinib (n=139)		Temsirolimus (n=141)	
		EVT/N	Median	EVT/N	Median
Yes	0.68 (0.36-1.30)	20/30	7.9	18/20	8.0
No	0.39 (0.27-0.54)	53/109	18.5	93/121	6.0
Refractory disease					
Yes	0·45 (0·26-0·76)	21/36	12.5	40/47	4.1
No	0·44 (0·31-0·63)	52/103	15.6	71/94	6.5
Age					
<65 years	0.41 (0.24-0.70)	24/53	20.7	40/54	8.5
≥65 years	0.43 (0.30-0.62)	49/86	12.1	71/87	4.8
ECOG performance status					
0	0.33 (0.21-0.53)	28/67	NE	51/67	8.2
1	0.50 (0.33-0.74)	44/71	9.3	58/72	4.2

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; EVT = event (progressed or died); NE = not estimable.
* Progression-free survival assessed by independent review committee
** Hazard ratio less than 1 favours ibrutinib.

b) Harms Outcomes

Details of harms outcomes reported are listed in Table 6.8.

Treatment-Emergent Adverse Events

TEAEs of any grade were reported in almost all patients treated with either ibrutinib or temsirolimus. Grade ≥3 TEAEs were less frequent in the ibrutinib group compared with the temsirolimus group (68% versus 87%). TEAEs leading to discontinuation was also less frequent in the ibrutinib group compared with the temsirolimus group (6% versus 26%), with the most common adverse events leading to discontinuing being thrombocytopenia in two patients treated with ibrutinib and pneumonia, atypical pneumonia, or pneumonitis in five patients treated with temsirolimus. Death during treatment or within 30 days of the last dose of study drug was reported in 17% (n=24) patients in the ibrutinib group and 11% (n=15) in the temsirolimus group. TEAEs leading to death was similar between arms (6% versus 8%).

The most frequently reported TEAEs of any grade (≥20% of patients) in the ibrutinib group were diarrhoea, cough, and fatigue. In the temsirolimus arm, the most frequently reported TEAEs of any grade (≥20% of patients) were thrombocytopenia, anaemia, diarrhoea, fatigue, neutropenia, epistaxis, cough, peripheral oedema, nausea, pyrexia, and stomatitis.

Adverse Events of Special Interest

Adverse events leading to hospitalization were not reported in the study publication, however, the number and days of hospitalization per treatment group were similar between groups.[5] Atrial fibrillation (of any grade) was reported in 6 (4%) patients in the ibrutinib group and in 3 (2%) patients in the temsirolimus group.[3] Major bleeding (of any grade was reported in 14 (10%) patients in the ibrutinib group and in 9 (6%) patients in the temsirolimus group. Other malignancies were reported in 5 (4%) patients in the ibrutinib arm and in 4 (3%) patients in the temsirolimus arm; according to Dreyling et al., most of which were non-melanomatous skin cancers.[4]

Table 6.8 Summary of Treatment-emergent adverse events†[4]

	Ibrutinib (n=139)		Temsirolimus (n=139)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Treatment-emergent adverse events	138(99%)	94(68%)	138(99%)	121(87%)
Treatment-emergent adverse events leading to discontinuation	9(6%)	NR	36(26%)	NR
Treatment-emergent adverse events leading to death*	NA	8(6%)	NA	11(8%)
Haematological				
Thrombocytopenia	25(18%)	13(9%)	78(56%)	59(42%)
Anaemia	25(18%)	11(8%)	60(43%)	28(20%)
Neutropenia	22(16%)	18(13%)	36(26%)	23(17%)
Non-haematological				
Diarrhoea	40(29%)	4(3%)	43(31%)	6(4%)
Fatigue	31(22%)	6(4%)	40(29%)	10(7%)
Cough	31(22%)	0	31(22%)	0
Pyrexia	23(17%)	1(1%)	29(21%)	3(2%)
Nausea	20(14%)	0	30(22%)	0
Peripheral oedema	18(13%)	0	31(22%)	3(2%)
Epistaxis	12(9%)	1(1%)	33(24%)	2(1%)
Stomatitis	4(3%)	0	29(21%)	5(4%)
Adverse Events of Special Interest				
Hospitalization	NR	NR	NR	NR
Atrial Fibrillation	6(4%)	5(4%)	3(2%)	2(1%)
Major bleeding^	14(10%)	11(8%)	9(6%)	7(5%)
Other Malignancies	5(4%)	-	4(3%)	-

NA= not applicable; NR = not reported
† Safety population included patients who received at least 1 dose of study drug.
^Major bleeding was defined as any grade 3 or higher haemorrhage, any haemorrhage reported as a serious adverse event, and all grades of central nervous system haemorrhage
* During the first 6 months of treatment. Death during treatment or within 30 days of the last dose of study drug was reported in 17% (n=24) patients in the ibrutinib group and 11% (n=15) in the temsirolimus group.

6.4 Ongoing Trials

Other than the MCL3001 described above, no ongoing trial that met our inclusion criteria was identified by our search.

7 SUPPLEMENTAL QUESTIONS

The following supplemental issue was identified as relevant to the pCODR review of ibrutinib for the treatment of patients with relapsed or refractory MCL:

- Critical appraisal of the manufacturer-submitted indirect treatment comparison (ITC) of ibrutinib with other therapies for relapsed or refractory MCL.

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

A matching adjusted indirect comparison (MAIC) in abstract form was identified by the Methods Team.[39] The objective was to compare the efficacy of ibrutinib to available treatments (i.e., bortezomib, fludarabine + cyclophosphamide + mitoxantrone, fludarabine + cyclophosphamide + mitoxantrone + rituximab) for relapsed or refractory MCL patients. Based on the conclusions of the abstract, the MAIC was not based on the phase III MCL3001 study, and for this reason, a critical appraisal of the MAIC was not made.

7.1 Critical Appraisal of Indirect Treatment Comparison of Ibrutinib versus Investigator's Choice of Single-Agent Treatment

7.1.1 Objective

The objective of this section is to summarize and critically appraise the methods and findings of the manufacturer-submitted ITC of ibrutinib with other therapies for relapsed or refractory MCL.

There is no standard of care for relapsed or refractory MC and therapies vary across provinces. The following are reasons for which this critical appraisal was necessary:

- A single randomized controlled trial was identified in the systematic review which compared ibrutinib to temsirolimus, therefore, there is currently no available direct comparison of ibrutinib to other therapies for the treatment of relapsed or refractory MCL (such as fludarabine-based chemotherapy regimens, rituximab with chemotherapy, bortezomib, bendamustine with rituximab, gemicitabine/dexamethasone/cisplatin or alkylating agents),
- The manufacturer submitted an economic evaluation which included Investigator's Choice of single-agent treatment (IC) as a proxy for standard of care. The ITC included a comparison between ibrutinib and IC.

7.1.2 Findings

The manufacturer submitted an ITC with the objective of estimating the comparative efficacy [measured by progression-free survival (PFS) and overall survival (OS)] for ibrutinib versus other therapies among patients with relapsed or refractory MCL.

A systematic review was conducted. Eligibility criteria were summarized in Table 7.1.

Table 7.1 Summary of PICOS Criteria for the Systematic Review and ITC

Item	Description
Population	Relapsed or refractory MCL patients
Intervention/ Index Node	• Ibrutinib
Comparators	• Ibrutinib monotherapy • Ibrutinib combination therapy • Bendamustine + rituximab • R-CHOP (rituximab + cyclophosphamide + doxorubicin +vincristine + prednisone) • FC ± M (fludarabine + cyclophosphamide ± 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 (rituximab + dexamethasone + cytarabine + cisplatin) ± low dose aracytine • Lenalidomide monotherapy
Outcomes	• Progression-free survival • Overall survival
Study design	ITC of published RCTs

ITC = indirect treatment comparison; MCL = mantle cell lymphoma; RCT = randomized controlled trial
* Table adapted from manufacturer's submitted indirect treatment comparison[40]

Other exclusion criteria included:

- Studies without at least 85% of patients with relapsed or refractory MCL (e.g., studies involving treatment-naïve MCL patients, other lymphoma subtypes, or patients receiving first-/front-line therapies)
- Articles reporting only select outcomes (e.g., not PFS or OS) for the relapsed or refractory MCL population
- No treatment of interest (e.g., radioimmunotherapy, "watch and wait"/no treatment, prophylactic or palliative care alone)
- Non-randomized comparative clinical efficacy and safety studies reporting only one treatment of interest
- Publications that do not report safety, efficacy, or patient-reported outcomes for relapsed or refractory MCL specifically.
- Articles investigating in vitro, animal, fetal, molecular, genetic, pathologic, or pharmacokinetic/pharmacodynamic outcomes without outcomes of interest reported
- Narrative publications, non-systematic reviews, case studies, case reports, and editorials
- Non-English full text articles or articles without an English abstract
- Less than 10 patients per treatment group in at least two treatments

The literature search for studies on clinical efficacy and safety were conducted on May 7, 2014 and updated on June 4, 2015. Multiple databases (e.g., MEDLINE, EMBASE, and Cochrane Central Registry of Trials) were searched. Additional steps (e.g., bibliographies of relevant systematic reviews, conference meetings) to identify studies were made.

Two independent investigator screened abstracts using the criteria specified above; any discrepancies between the two investigators were resolved by a third investigator before proceeding to full-text screening. A single investigator screened full text articles and all rejected full text articles were validated by a second investigator. A modified PRISMA flow diagram was presented which included the reasons for exclusion [diagram not presented here].

Data were extracted by one investigator and validated by a second investigator and discrepancies between the two investigators were resolved by a third investigator.

The submitter stated that the search and study selection described above were performed by a consultancy and a risk of bias assessment of eligible studies was performed by another consultancy. A graphical representation of the evidence network can be found in Figure 7.1.

The ITC Report included a table summarizing the study design and patient characteristics of the trials that were included in the network [Table not presented here]. Differences in eligibility criteria, for instance ECOG Performance Status 0 or 1 versus Karnofsky ≥ 60, were comparable. In the OPTIMAL trial, patients must have had a prior alkylating agent, anthracycline and rituximab. In MCL3001, patients must have had at least 1 prior rituximab-containing chemotherapy; most patients had prior alkylating agent (99%) and prior anthracycline (90%) without having prior alkylating agent and anthracycline as an eligibility criteria.[5] Dosages of temsirolimus in both trials were also comparable (refer to Table 7.2 Therapies used in OPTIMAL Trial and in MCL3001 Trial for comparison).

Table 7.2 Therapies Used in OPTIMAL Trial and in MCL3001 Trial

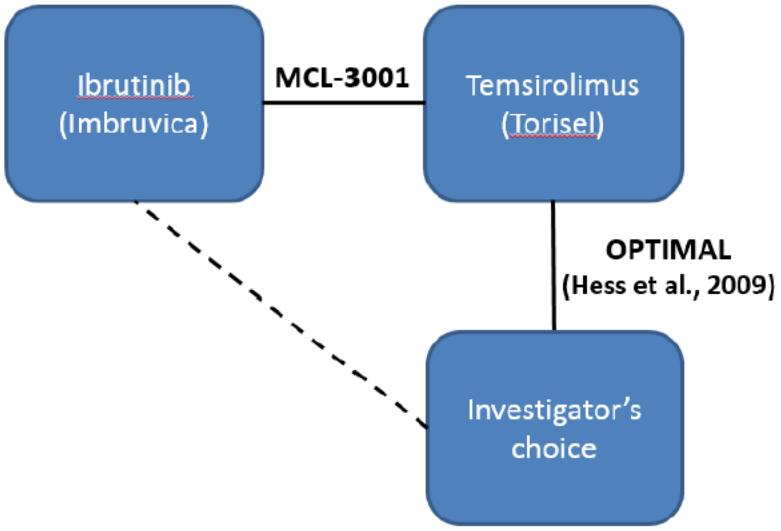
MCL3001 TRIAL[4]		
Therapy	**Dose Description**	
Ibrutinib	560 mg orally once per day	
Temsirolimus IV	175 mg intravenously on days 1, 8, and 15 of the first cycle, followed by 75 mg on days 1, 8, and 15 of each subsequent 21-day cycle.	
OPTIMAL TRIAL [28]		
Therapy	**Dose Description**	
Temsirolimus IV	175 mg/week for 3 weeks followed by weekly doses of 75mg	
Temsirolimus IV*	175 mg/week for 3 weeks followed by weekly doses of 25mg	
Investigator's Choice Group	For therapy and dose description see below.	
OPTIMAL TRIAL - Therapies Used in the Investigator's Choice Group [28]		
Therapy	**Dose Description**	**No. of Patients (%) [N=53]**
Gemcitabine IV	a) 1 g/m2 as 30-minute infusion on days 1, 8, and 15 every 28 days, or (b) 1 g/m^2 as 30-minute infusion on days 1 and 8 every 21 days	22 (42%)
Fludarabine IV	25 mg/m^2 as 30-minute infusion daily for 5 consecutive days every 28 days	12 (23%)
Fludarabine oral	40 mg/m^2 daily for 5 consecutive days every 28 days	2(4%)
Chlorambucil oral	0.1 to 0.2 mg/kg daily for 3 to 6 weeks	3(6%)
Cladribine IV	5 mg/m^2 daily for 5 consecutive days every 28 days (1 cycle) for 2 to 6 cycles	3(6%)
Etoposide IV	50 to 150 mg/m^2 daily for 3 to 5 days every 21 to 28 days	3(6%)
Cyclophosphamide oral	200 to 450 mg/m2 daily for 5 consecutive days every 21 to 28 days	2(4%)
Thalidomide oral	200 mg daily	2(4%)
Vinblastine IV	10 mg weekly	2(4%)
Alemtuzumab IV	30 mg/d for 3 times a week on alternate days for 12 weeks	1(2%)

MCL3001 TRIAL[4]		
Therapy	**Dose Description**	
Lenalidomide oral	25 mg daily for 28 days	1(2%)

IV = intravenous.
*Results of temsirolimus 175/25mg group were not considered since it was a different dose than the temsirolimus group included in the MCL3001 trial.

Bayesian ITC was performed. Sensitivity analysis using frequentist approach was also performed. Outcomes included in the analysis were PFS and OS. A fixed effects model was used as the primary model and a random effects model was used as a sensitivity analysis. The authors stated that the use of a random-effects model with a vague prior on the between study variance exerts a large degree of influence on the credible interval because there are insufficient studies to reign in the prior and provide an accurate estimate of the between study variance. As a result, results often appear unrealistic. Results from the sensitivity analysis using the random effects model support this statement. Thus, the authors opted for a fixed effects model recognizing that it may not address heterogeneity, and therefore conducted sensitivity analyses to account for this.

Figure 7.1 Indirect Treament Comparison Network to Compare Ibrutinib with Investigator's Choice of Single-Agent Treatment[40]



The ITC was performed using WinBUGS (version 1.4.3) based on burn-in samples of 40 0000 iterations or more and subsequent sampling iterations of 40 000 iterations or more; WinBUGS code was provided. The manufacturer stated that Trace plots and Gelman-Rubin plots were reviewed to assess model convergence. Hazard ratios used in the indirect treatment comparison analyses can be found in Table 7.3.

Table 7.3 Hazard ratios used in the indirect treatment comparison analysis*

	MCL3001 Ibrutinib versus Temsirolimus[4]		OPTIMAL Temsirolimus versus IC[†28]		
Outcome	IRC-PFS HR(95%CI)	OS HR(95%CI)	IRC-PFS HR(95%CI)	OS HR(95%CI) July 19, 2007[‡]	OS HR(95%CI) February 1, 2008[‡]
ITC Input	0.43 (0.32-0.58)	0.76(0.53-1.09)	0.44(0.25-0.78)	0.77(0.46-1.28)	0.80(0.50-1.28)

	MCL3001 Ibrutinib versus Temsirolimus[4]	OPTIMAL Temsirolimus versus IC†[28]
CI = confidence interval; IC = Investigator's Choice of single-agent treatment; IRC = independent review committee; HR = hazard ratio; PFS= progression-free survival; OS = overall survival * Table adapted from manufacturer's submitted indirect treatment comparison[40] † investigator's choice of single agent therapy consisted 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 Hess et al., 2009 publication reported OS data at two separate study dates.[28]		

Approaches for addressing identified heterogeneity/uncertainty across trials were reported. Sensitivity analyses were performed to address the following:

- statistical approach - Additional analysis using frequentist approach using the CADTH ITC Calculator was performed;
- prior lines of therapy - Assumed the efficacy of subgroup of patients in MCL3001 who received ≥3 prior treatments had a hazard ratio of 0.50 (95%CI, 0.32 to 0.72);
- rates of cross over - Adjusted for cross-over among the studies;
- and generalizability of IC node in the OPTIMAL study - Assumed the hazard ratio for PFS and OS was 1 (95% CI, 0.5 to 2.0) for the OPTIMAL trial to represent the worst case scenario of an effect estimate of ibrutinib compared to IC.[28]

A summary of results from the primary analysis and sensitivity analyses comparison of ibrutinib to IC can be found in Table 7.4.

Table 7.4 Pairwise Comparison Ibrutinib versus IC† from ITC*

Outcome	PFS‡ HR(95%CrI)	OS HR(95%CrI)
Primary Analysis		
Fixed Effect Model	0.19(0.10-0.36)	0.61(0.34-1.10)
Sensitivity Analysis		
Random Effects	0.19 (0.00 to 1436.55)	0.61 (0.00 to 4125.74)
CADTH ITC calculator, FE effects	0.19 (0.1 to 0.36)	0.61 (.34 to 1.10)
Prior Lines of Therapy	0.22 (0.11 to 0.45)	-
Generalizability of IC	0.43 (0.32 to 0.58)	0.76 (0.53 to 1.09)
Cross-over (IPCW adjusted)	-	0.62 (0.34 to 1.13)
Cross-over (RPSFT adjusted)	-	0.59 (0.32 to 1.09)
CrI = credible interval; FE = fixed-effects; HR = hazard ratio; IC = Investigator's Choice of single-agent treatment; IPCW = Inverse Probability of Censoring Weighting; NA = not applicable; OS = overall survival; PFS= progression-free survival; RPSFT = Rank Preserving Structural Failure Time. * Table adapted from manufacturer's submitted indirect treatment comparison[40]† investigator's choice of single agent therapy consisted 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%). ‡ PFS assessed by an independent review committee		

The ITC report also included a summary of ranks and probabilities for PFS and OS (which included mean rank with 95% credible intervals, and probability of best, second best, and so forth, as well as the Surface Under the Cumulative RAnking curve as an additional measure to reflect ranking and uncertainty). However, the treatment rankings are subject to uncertainty given the small number of trials in the network. When only a small number of trials are available, the addition of a single trial to the network may have a profound impact on the treatment rankings. As a result, inferences on the ranking of treatments were not made and the summary of ranks and probabilities for PFS and OS were not reported in this critical appraisal.

The credibility of the submitted ITC/MNA was assessed in accordance with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparison.[9] Details and commentary with respect to the submitted ITC/MNA for each item identified by the ISPOR Task Force are provided in Table 7.5.

Table 7.5 ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison†

ISPOR Questions	Details and Comments‡
1. Is the population relevant?	Yes. The population considered was patients with relapsed or refractory MCL. This was consistent with the population in the funding request. Although relapsed or refractory were not defined in the ITC report, the Methods team assumed the following definition: relapsed disease defined as relapse or disease progression after achieving at least a partial response to the last regimen and refractory disease defined as failure to achieve at least a partial response to the last regimen.
2. Are any critical interventions missing?	Yes. The CGP identified the following relevant interventions: fludarabine-based chemotherapy regimens, rituximab with chemotherapy regimens, bortezomib, bendamustine, GDP (gemcitabine + dexamethasone + cisplatin), gemcitabine, alkylating agents, and temsirolimus. Although the manufacturer's PICOS criteria of the systematic review for the ITC included monotherapies and combination therapies, GDP was not included. Moreover, results of the ITC are limited to the comparison of ibrutinib to investigator's choice single agent chemotherapy, and therefore, combination therapies or other relevant monotherapies were not included in the network. The CGP felt that although the doses in the investigator's choice single agent seemed reasonable and reflect current clinical practice, bortezomib and bendamustine (if not given first line) were not listed. Bortezomib and bendamustine (if not given first line) may be given either as single agents or in combination with rituximab for second-line mantle cell lymphoma. Further, despite having specified several comparators there was a lack of literature and, as such, no direct or indirect comparisons could be made for key regimens. It is important to highlight that the latter is a limitation of the paucity of RCTs comparing active combination therapies to single agent therapies, rather than a limitation of the manufacturer's PICOS criteria.
3. Are any relevant outcomes missing?	Yes, in part. Progression-free survival and overall survival are relevant outcomes reported in the ITC. Response rate, quality of life, duration of treatment, time to next

ISPOR Questions	Details and Comments‡
	treatment and safety are other relevant outcomes identified by the CGP but were not considered in the ITC.
4. Is the context (e.g., settings and circumstances) applicable to your population?	Results of the ITC compare the treatment effect of ibrutinib to investigator's choice single agent therapy (of which 42% is gemcitabine). Currently treatments for relapsed or refractory MCL vary across the provinces and there is no standard of care. In the absence of standard of care for MCL, it is of the opinion of the CGP that the comparison of ibrutinib to investigator's choice single agent therapy is relevant.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	Yes. The search strategy was provided. Multiple databases (e.g., MEDLINE, EMBASE, and Cochrane Central Registry of Trials) were searched. Additional steps (e.g., bibliographies of relevant systematic reviews, conference meetings) to identify studies were made. Selection criteria were listed.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	Yes. Refer to Figure 7.1. Anchored indirect treatment comparison.
7. Is it apparent that poor quality studies were included thereby leading to bias?	The manufacturer noted that the risk of bias assessment of eligible studies was performed using the Cochrane Risk of Bias Tool. An overview of the assessment was provided. The manufacturer stated that there was insufficient evidence to critically assess the overall quality of the RCT's methodology and implementation. According to the manufacturer, details regarding randomization method, concealment procedures, and estimates for patient prognostic factor variation were not available from the OPTIMAL study publication. As a result, the manufacturer reviewed the clinicaltrials.gov site for details and noted that the OPTIMAL study was open label and in the attempt to reduce bias, the sponsor used an independent review committee to assess trial outcomes (e.g., progression-free survival) in addition to investigator reporting. The manufacturer highlighted a variation between the investigator and independent outcome assessments and acknowledged this to be a potential source of bias. Nonetheless, progression-free survival assessed by the independent review committee rather than the investigator's assessment was used in the manufacturer's model.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	The Methods team performed a "check" to identify whether any of the selected studies did not report some of the outcomes of interest and were therefore not included in some of the ITCs of the different end points. Selected studies did report outcomes of interest. Possible risk of publication bias. The Methods team performed a "check" on the reasons studies were excluded and it appeared that 1 RCT (on NHL with a MCL sub-population) was excluded only because the outcome of interest. The stated reason for exclusion was the following: "No Kaplan Meier for PFS or OS".
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the	Yes. The manufacturer noted the following: there were slight differences in number of prior lines of therapy between trials; differences were observed across trials with respect to the proportion of patients that crossed over to the alternative therapy. Sensitivity analyses around prior

ISPOR Questions	Details and Comments‡
treatment effects) across the different treatment comparisons in the network?	lines of therapy and cross over were performed to determine the potential effect.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	Yes. The manufacturer sought input from "key opinion leaders" which identified the following factors: age, statistical approach, percentage of patients relapsed or refractory, prior lines of therapy, stage of MCL at baseline, cross over and blinding. Additional effect modifiers identified by CGP were not considered: distribution of classical versus blastic variant mantle cell, distribution of MIPI scores at diagnosis and/or relapse, gene expression profile and whether allogeneic transplant is offered to a substantial number of patients at relapse, whether patients received an aggressive approach with first line autologous stem cell transplantation or not.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	Yes. Bayesian ITC was performed. Sensitivity analysis using frequentist approach was also performed.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	Not applicable. This was not a closed loop network.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Not applicable. This was not a closed loop network.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	Sensitivity analyses (when possible) were performed. The manufacturer noted that the structure of the evidence network (i.e., the presence of several single-study connections between interventions) precluded the performance of a meta-regression analysis or sub-group/sensitivity analyses related to certain characteristics of interest.
15. Was a valid rationale provided for the use of random-effects or fixed-effects model?	The focus of the report was the findings from the fixed-effects model and findings from the random-effects model were also reported (as a sensitivity analysis). A valid rationale was provided for the use and focus of the fixed-effects model.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	As noted above, a fixed effects model was used as the primary model and a random effects model was used as a sensitivity analysis. With respect to the random effects model, exploration or discussion of choice between random-effects variants was not reported, rather the manufacturer stated that a similar approach in the CADTH atrial fibrillation Therapeutic Review,[41] focusing on findings from the fixed-effects model but also reporting findings from the random-effects model was used.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	The manufacturer noted that the structure of the evidence network (i.e., the presence of several single-study connections between interventions) precluded the performance of a meta-regression analysis or sub-group/sensitivity analyses related to certain characteristics of interest. Meta-regression analysis could not be performed due to the small number of studies, rather sensitivity analyses were performed to address heterogeneity/uncertainty across trials.

ISPOR Questions	Details and Comments‡
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes. Refer to Figure 7.1. One RCT per direct comparison.
19. Are the individual study results reported?	Yes. A table reporting the PICOS results for each individual study was provided. Refer to Table 7.2.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	Yes. The results of the direct comparisons were reported separately from results of the indirect comparisons. Refer to Table 7.3.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Yes. Pairwise comparisons from the fixed-effects model were reported in terms of summary hazard ratios and 95% credible interval. As part of the sensitivity analysis, pairwise comparisons from the random effects model were also reported in terms of summary hazard ratios and 95% credible interval.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	Yes. Summary of ranks and probability of each rank along with the surface under the cumulative ranking curve were provided. However, when only a small number of trials are available, the addition of a single trial to the network may have a profound impact on the treatment rankings. As a result, inferences on the ranking of treatments were not made and the summary of ranks and probabilities for PFS and OS were not reported in this critical appraisal.
23. Is the impact of important patient characteristics on treatment effects reported?	Yes. The impact of prior lines of therapy and crossover on treatment effects were reported as sub group analyses.
24. Are the conclusions fair and balanced?	Overall, the submitted ITC was well conducted and transparent. The submitted ITC adhered best practices for the conduct of ITC, as well as the CADTH Guidelines for Reporting Indirect Comparisons. In brief, the Methods team would agree based on the evidence provided in the ITC Report that there is reason to believe that ibrutinib was associated with statistically significant improvement in PFS compared with investigator's choice for the treatment of relapsed or refractory MCL and there were no statistically significant difference in overall survival between treatments.
25. Were there any potential conflicts of interest?	The ITC Report was prepared from the submitter of this pCODR review.
26. If yes, were steps taken to address these?	Yes. As stated in the ITC report, an independent ITC was conducted to support the pCODR submission. The search and study selection were performed by a consultancy on behalf of the submitter. The risk of bias assessment of eligible studies was performed by another consultancy on behalf of the submitter.

CADTH = Canadian Agency for Drugs and Technologies in Health; CGP = clinical guidance panel; ITC = indirect treatment comparison; MCL = mantle cell lymphoma; NHL = non-Hodgkin lymphoma; pCODR = pan-Canadian Oncology Drug Review; PFS = progression-free survival; PICOS = population, intervention, comparator, outcome, setting; OS = overall survival; RCT = randomized controlled trial.
† Adapted from Janssen et al [9].

7.1.3 Summary and Interpretation

Overall, the submitted ITC was well conducted and transparent. For instance, details of the underlying systematic review methodology (searches, study selection, data extraction, critical

appraisal, etc.) were provided. The submitted ITC adhered to best practices for the conduct of ITC,[9] as well as the CADTH Guidelines for Reporting Indirect Comparisons.[10]

The validity of a ITC are based on three assumptions: homogeneity, similarity, and consistency (i.e., were the results from trials on the same comparison homogeneous or heterogeneous; were these trials similar across comparisons enough to consider together; and were the results from direct and indirect comparisons consistent).[42]

Here, heterogeneity was explored in the form of sensitivity analyses. Meta-regression analysis could not be performed due to the small number of studies. Results from these sensitivity analyses were consistent with the results from the primary analysis for PFS and OS.

Furthermore, similarity was explored in submitted ITC in the form of collection of information (i.e., study design and patient characteristics) and consideration of whether the studies appeared similar enough to be compared. The submitted ITC included details on study design and patient characteristics. Upon review, the Methods team and CGP agreed that the studies appeared similar enough to be compared.

Lastly, consistency was not applicable because the network was not a closed loop; therefore, among the pairwise comparison, no direct evidence was available to compare with indirect evidence.

The population considered was patients with relapsed or refractory MCL. This was consistent with the population in the funding request.

However to reiterate, although the manufacturer's PICOS criteria of the systematic review for the ITC included monotherapies and combination therapies, GDP was not included. Moreover, results of the ITC are limited to the comparison of ibrutinib to investigator's choice single agent chemotherapy, and therefore, combination therapies or other relevant monotherapies were not included in the network. The CGP felt that although the doses in the investigator's choice single agent seemed reasonable and reflect current clinical practice, bortezomib and bendamustine (if not given first line) were not listed as an option for investigator's choice single agent chemotherapy. Bortezomib and bendamustine (if not given first line) may be given either as single agents or in combination with rituximab for second-line mantle cell. Further, despite having specified several comparators there was a lack of literature and, as such, no direct or indirect comparisons could be made for key regimens noted above.

Additional effect modifiers (i.e., MIPI scores, type of histology, gene expression, allogeneic transplant) identified by the CGP were not considered in the submitted NMA. However, the Methods Team recognized that limited reporting of baseline characteristics (i.e., distribution of classical versus blastic variant mantle cell, distribution of MIPI scores at diagnosis and/or relapse, gene expression profile and whether allogeneic transplant is offered to a substantial number of patients at relapse, and whether patients received an aggressive approach with first line autologous stem cell transplantation or not) in the study publications may have precluded the submitter for analyzing the additional effect modifiers identified by the CGP.

In brief, the Methods team agreed that based on the evidence provided in the ITC Report that there is reason to believe that ibrutinib was associated with statistically significant improvements in PFS compared investigator's choice single agent therapy for the treatment of relapsed or refractory MCL and there were no statistically significant differences in overall survival between treatments.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lymphoma & Myeloma Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on ibrutinib (Imbruvica) for relapsed or refractory mantle cell lymphoma. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Lymphoma & Myeloma Clinical Guidance Panel is comprised of three haematologists .The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** December 2015**, Embase** 1974 to 2016 February 01**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

line #	Searches	Results
1	(Imbruvica* or ibrutinib* or CRA032765 or "CRA 032765" or "JNJ 02" or PC32765 or PC 32765 or PCI32765 or PCI 32765 or 1X70OSD4VX or 936563-96-1).ti,ab,ot,kf,hw,rn,nm.	1992
2	Lymphoma, Mantle-Cell/ or ((mantle or diffuse or lymphocytic or small cell or centrocytic) adj3 lymphoma*).ti,ab,kf.	25819
3	1 and 2	503
4	3 use pmez	126
5	3 use cctr	7
6	*ibrutinib/ or (Imbruvica* or ibrutinib* or CRA032765 or "CRA 032765" or "JNJ 02" or PC32765 or PC 32765 or PCI32765 or PCI 32765 or 1X70OSD4VX).ti,ab,kw.	1410
7	Mantle cell lymphoma/ or ((mantle or diffuse or lymphocytic or small cell or centrocytic) adj3 lymphoma*).ti,ab,kw.	27124
8	6 and 7	464
9	8 use oemezd	339
10	4 or 5 or 9	472
11	limit 10 to English language	458
12	remove duplicates from 11	344

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#5	Search **#3 AND publisher[sb]** Filters: **English**	16
#4	Search **#3 AND publisher[sb]**	17
#3	Search **#1 AND #2**	178
#2	Search **Lymphoma, Mantle-Cell[mh] OR ((mantle[tiab] OR diffuse[tiab] OR lymphocytic[tiab] OR small cell[tiab] OR centrocytic[tiab]) AND lymphoma*[tiab])**	26436
#1	Search **PCI 32765 [Supplementary Concept] OR Imbruvica*[tiab] OR ibrutinib*[tiab] OR CRA032765[tiab] OR CRA 032765[tiab] OR JNJ 02[tiab] OR PC32765[tiab] OR PC 32765[tiab] OR PCI32765[tiab] OR PCI 32765[tiab] OR 1X70OSD4VX[tiab] OR 936563-96-1[rn]**	525

3. **Cochrane Central Register of Controlled Trials (Central)**
   Searched via Ovid

4. **Grey Literature search via:**

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search terms: Imbruvica/ibrutinib, mantle cell lymphoma

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search terms: Imbruvica/ibrutinib, mantle cell lymphoma

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

American Society of Hematology
http://www.hematology.org/

Search terms: Imbruvica/ibrutinib, mantle cell lymphoma - last 5 years

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