CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Ibrutinib (Imbruvica) for Waldenström's Macroglobulinemia

November 3, 2016

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

TABLE OF CONTENTS

1 GUIDANCE IN BRIEF

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 (Imbruvica) for Waldenström's macroglobulinemia. 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 Report is includes: a systematic review of the literature on ibrutinib (Imbruvica) for Waldenström's macroglobulinemia 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; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review is reported in Section 6. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on ibrutinib (Imbruvica) for Waldenström's macroglobulinemia, and a summary of submitted Provincial Advisory Group Input on ibrutinib (Imbruvica) for Waldenström's macroglobulinemia, on ibrutinib (Imbruvica) for Waldenström's macroglobulinemia, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

Ibrutinib has Health Canada approval for the treatment of patients with Waldenström's macroglobulinemia (WM) and the treatment of patients with chronic lymphocytic leukemia.[1] Ibrutinib was also issued marketing authorization with conditions by Health Canada for the treatment of patients with relapsed or refractory mantle cell lymphoma.[1]

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 WM, as it appears in the Health Canada Product Monograph, is 420 mg (three 140 mg capsules) once daily until disease progression or unacceptable toxicity.[1]

The following severe warnings and precautions were noted in the Health Canada Product Monograph:[1]

- 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.

The objective of the current review was to evaluate the efficacy and safety of ibrutinib for the treatment of patients with Waldenström's macroglobulinemia (WM).

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included two open-label, non-randomized, single arm studies, PCYC-1118E and treatment arm C of study PCYC-1127 (study PCYC-1127 had randomized groups but the results were not available; see Figure 2 for PCYC-1127 study design). PCYC-1118E[2] was published recently and PCYC-1127[3] was available only in abstract format as an interim analysis. These studies enrolled adult patients with Waldenström's macroglobulinemia who required treatment

according to recent guidelines, had ECOG≤2 and median ages of patients in studies PCYC1118E and PCYC-1127 were 63 and 67 years, respectively. Patients in both studies received oral ibrutinib 420mg daily until disease progression or unacceptable toxicity. The baseline characteristics were similar between the two trials with a few notable exceptions. Study PCYC-1118E enrolled patients with better performance scores (ECOG) and a lower number of previous therapies for WM. Study PCYC-1127 enrolled patients with disease refractory to the last prior rituximab-containing therapy.

- PCYC-1118E included 63 patients at three sites in the United States who had used at least one prior therapy for WM. Dose lowering was permitted in the event of toxicity. The data analysis was performed after a median 19.1 months of follow up with 60 patients alive and 43 patients (68%) continuing to receive therapy.
- PCYC-1127 included three treatment arms, but results were only available for arm C. Arm C included 31 patients from North America, Western Europe and Australia. The data analysis was performed after a median 17.1 months follow up with all patients alive and 26 patients (84%) continuing on ibrutinib therapy.

Efficacy
Progression free survival was 69.1% (95%CI: 53.2-80.5) at 24 months in study PCYC-1118E. In study PCYC-1118E, after a median 19.1 months of follow up, there were 10 (16%) patients with very good partial response, 36 (58%) with partial response, 11 (17%) with minor response, 5(8%) with stable disease and 1(2%) with progressive disease. No patients had complete response. This resulted in an overall response (the primary endpoint of the study) of 90.5% (95%CI: 80.4-96.4) and a major response of 73.0% (95%CI: 60.3-83.4). The main analyses for response were performed using investigators' assessments.

Progression free survival (the primary endpoint for study PCYC-1127) was 93% at one year in study PCYC-1127. In study PCYC-1127, after median 17.1 months of follow up there were 4 (13%) patients with very good partial response (> 90% reduction in serum IgM levels), 18 (58%) with partial response, 6 (19%) with minor response and 2 (6%) with stable disease. No patients had complete response. This resulted in an overall response of 90% and a major response of 71%. The response data reported are from the investigators' assessments and are best response. Some quality of life data were provided by the manufacturer, but it was not possible to assess the statistical or clinical significance of these data.

Harms
Serious adverse events occurring in study PCYC-1118E more than once included: thrombocytopenia (n=2), pyrexia (n=3), pneumonia (n=5). Serious adverse events that occurred once included: febrile neutropenia, neutropenia, atrial fibrillation, sinus tachycardia, chills, malaise, cholecystitis, cellulitis, herpes zoster, influenza, pleural infection, streptococcal endocarditis, upper respiratory tract infection, post-procedure hematoma, dehydration, B-cell lymphoma, myelodysplastic syndrome, syncope, pleural effusion.[4] There was one death in study PCYC-1118E due to worsening of pleural effusion 22 days after the last dose of study drug, attributed to disease progression.[4] Half (n=32) of the patients in study PCYC-1118E experienced an adverse event rated grade 3 or higher. In study PCYC-1118E, 44.4% of the patients experienced a haemorrhagic adverse event of any grade. At a median treatment duration of 19.1 months, there was one report of grade 3 hematoma (post procedural bleeding event), but no grade 4 bleeding events. In study PCYC-1118E, adverse events leading to ibrutinib discontinuation (each occurred once) included: atrial fibrillation, B-cell lymphoma, myelodysplastic syndrome, pleural effusion, post procedural haematoma, and thrombocytopenia.

In study PCYC-1127, serious adverse events occurred in 10 patients (32%) as summarized below.
Patient 1: neutropenia, thrombocytopenia

Patient 2: upper respiratory tract infection
Patient 3: gastrointestinal amyloidosis
Patient 4: diarrhea, pneumonia, faecalith
Patient 5: femoral fracture, renal cell carcinoma
Patient 6: acute cholecystitis, ileus
Patient 7: disease transformation to high grade DLBCL
Patient 8: cellulites (legs), prostatic abscess
Patient 9: orchitis
Patient 10: dehydration, syncope

Twenty patients (65%) experienced a grade ≥3 adverse event in study PCYC-1127. Any-grade adverse events occurring at an incidence greater than 15% included diarrhea (42%); upper respiratory tract infections, hypertension, increased tendency to bruise (23% each); nausea, thrombocytopenia, neutropenia (19% each); and pyrexia, arthralgia, back pain (16% each). Common adverse events (≥ grade 3) included neutropenia (13%), hypertension (10%), anemia and diarrhea (6% each). There were no events of IgM flare or atrial fibrillation. There were no grade 3 or 4 bleeding events reported. In study PCYC-1127, one patient discontinued ibrutinib because of gastrointestinal amyloidosis and another patient discontinued ibrutinib because of diarrhea.[3]

Table 1 Select efficacy and safety outcomes for PCYC-1118E and PCYC-1127 (Arm C)

	PCYC-1118E N=63[2,4]	PCYC-1127 (Arm C) N=31[5]
Median time on ibrutinib (range) at time of data analysis, months	19.1 (0.5 to 29.7)	17.1 (6.3 to 20.0)
OS (95%CI)	95.2%(86.0,98.4) at 24 months	NR
PFS(95%CI)	69.1%(53.2,80.5) at 24 months	**93% (95%CI NR) at one year***
Median PFS	Not reached	Not reached
Response		
Complete response, n(%)	0	0
Very good partial response, n(%)	10(16)	4(13)
Partial response, n(%)	36(57)	18(58)
Minor response, n(%)	11(17)	6(19)
Stable disease, n(%)	5(8)	2(6)
Progressive disease, n(%)	1(2)	0
Overall response	**57 (90.5%, 95%CI:80.4-96.4)***	90% (NR)
Major response	46 (73.0%, 95%CI:60.3-83.4)	71% (NR)
Serious adverse event, n(%)	24(38%)	10(32%)
Treatment discontinuation due to adverse events, n(%)	6(10%)	2(6%)

OS=overall survival; PFS=progression free survival; NR=not reported; *Primary outcome of the study
Note: PCYC-1118E is ongoing and the data presented here were analyzed from the December 2014 data lock after a median of 19.1 months on study.
Study PCYC-1127 also included randomized groups, but no results were available for these groups.

Limitations

The main limitations of the included studies are related to their non-randomized, open-label study designs. While PCYC-1127 was a randomized controlled trial with three arms (see Figure 2), data are only available for Arm C (ibrutinib monotherapy). For both studies, making inferences from the results of non-comparative study or the single arm of an RCT is challenging and the efficacy and harms of ibrutinib in WM relative to other agents is uncertain. Results for study PCYC-1127 were presented only in abstract form and were from an interim analysis; the data will need to be reviewed as full results become available in the future.

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

From a patient's perspective, the physical and emotional impact of living with WM was varied. According to LC and CORD, most respondents reported that the impact of WM on their quality of life was moderate; however, there was a sizeable minority who reported that their quality of life was significantly impacted due to symptoms of WM. Respondents reported that the symptoms having the most impact were tiredness/lack of energy, tingling or numbness in feet or legs, weakness, shortness of breath, joint or muscle pain, swollen lymph nodes, heavy night sweats, and frequent infections.

Respondents also described a range of experiences with different types of therapy, including rituximab alone/maintenance, bendamustine, fludarabine, intravenous immunoglobulin (IVIG), velcade, cyclophosphamide vincristine prednisone (CVP), and cyclophosphamide hydroxy doxorubicin vincristine prednisone (CHOP).

Most respondents also reported that they feel there is a need for the availability of additional therapies because they feel that their symptoms and the disease will return even if they are responding to the therapy or they are in remission. Respondents reported the following desired outcomes for a "new drug": (1) bring about a remission, (2) control their disease symptoms, (3) allow them to live longer, (4) improve their quality of life, and (5) improve blood counts. Respondents who have experience with ibrutinib reported fewer side effects with ibrutinib than other drug therapies. Some of the side effects reported with using ibrutinib included: diarrhea/nausea, bruising/bleeding, rash or skin irritation, joint/muscle pain, fatigue/decreased energy, changes to heart rhythm, elevated blood pressure, brittle nails, dizziness, hair thinning, edema, pneumonia, mouth sores, indigestion, blurred vision, confusion, incontinence, insomnia, headache, weight gain, neuropathy, new curly hair, hoarseness, loss of hearing, cough, and shortness of breath. Most respondents reported that the reported side effects were manageable. Respondents indicated that there was a significant improvement in symptoms management with using ibrutinib. The top symptoms that most respondents felt were managed by ibrutinib included weakness, tiredness or lack of energy and shortness of breath. This in turn has markedly improved their self-reported quality of life.

Please see Section 3 for more details.

Provincial Advisory Group (PAG) Input

Input was obtained from the 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 Waldenström's macroglobulinemia (WM):

Clinical factors:

- Standard of care is intravenous chemotherapy
- New treatment option that is an oral drug

Economic factors:

- Very small number of patients relative to other cancers
- Long duration of treatment

Please see Section 4 for more details.

Registered Clinician Input

Registered clinician input was not received for the review.

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

Comparison with Other Literature

We performed a literature search for systematic reviews and network meta-analyses of ibrutinib in WM.

Section 8 of this report summarizes some relevant comparator data to give context to the ibrutinib results.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2 Assessment of generalizability of evidence for ibrutinib (Imbruvica) for WM.

Domain	Factor	Evidence from studies PCYC-1118E and PCYC-1127	Generalizability Question	CGP Assessment of Generalizability
Population	Organ dysfunction	Patient with hepatic or renal dysfunction were excluded from the trials. The Health Canada product Monograph for ibrutinib indicates the following serious warnings and precautions: 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.	Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	The CGP agree that it would be reasonable to give ibrutinib to patients with hepatic or renal dysfunction. However, it should be prescribed by hematologists or oncologists familiar with its toxicity and who recognize the potential for significant increases in toxicity from concomitant use of moderate or strong CYP3A inhibitors (such as ketoconazole, itraconazole, voriconazole, clarithromycin, antiretroviral agents [ritonavir, indinavir], grapefruit juice) and potential decreased efficacy when administered with CYP3A inducers (rifampin, St John's wart, phenytoin, carbamazepine).
Intervention	Prior therapy	The Clinical Guidance Panel noted that the trial had greater usage of bortezomib in patients entered into the trial. This was more than is expected for use in Canadian patients.	Given that a greater proportion of patients received bortezomib in the first line treatment setting, are the results of the trial generalizable to the Canadian setting?	The CGP noted that the proportion of patients who received bortezomib in earlier line within the two trials is not representative of clinical practice in Canada. The CGP do not anticipate that this will have an impact on the magnitude of treatment effect and agreed,the results of the trial are generalizable to the Canadian practice.
Comparator	Appropriateness of Primary and Secondary Outcomes	The primary outcome of the trials evaluating ibrutinib in WM was overall response rate in Study 1118 and PFS in Study 1127. Secondary outcomes included PFS and OS in study 1118 and ORR and OS in Study 1127.	Are the primary outcomes used in the two trial accepted surrogates for OS?	The CGP agreed that the outcomes used in the trial are similar to those used in the evaluation of other agents in lymphoma are evaluated. Response rates are therefore appropriate and provide a clinically meaningful outcome in the setting. The CGP also noted that iNHL is an indolent disease and it would be difficult to demonstrate OS benefit. Therefore, PFS is

Domain	Factor	Evidence from studies PCYC-1118E and PCYC-1127	Generalizability Question	CGP Assessment of Generalizability
				considered to be a reasonable endpoint to report.
Outcomes	Assessment of Key Outcomes	Mutation status was assessed in the trial. Response criteria were taken from recent consensus meetings (Third and Sixth International Workshop on WM)	Is mutation status used to determine treatment selection in Canada?	While response to treatment with ibrutinib according to the presence of MYD88 mutation, together with mutations in CXCR4, may provide some insight into patients more or less likely to respond to therapy, at the moment data on mutation status is exploratory and would not be used to select for patients.
Setting	Supportive medications, procedures, or care	Antiemetics and growth factors (e.g. G-CSF, erythropoietin) were permitted.	Are the results of the trial generalizable to a setting where different supportive medications, procedures, or care are used?	The CGP discussed that clinicians would likely use dose reduction to manage toxicities before use of anti-emetics. If used, the proportion of patients receiving antiemetics and growth factors would be similar to what was done within the trial. Therefore the results of the trial is generalizable to the Canadian population.

1.2.4 Interpretation

Burden of Illness and Need

Waldenstrom's Macroglobulinemia is an uncommon indolent B cell lymphoma, characterized by bone marrow infiltration, anemia and the presence of an IgM paraprotein, which is variably responsible for symptoms of hyperviscosity (fatigue, congestive heart failure, easy bruising) and peripheral sensory neuropathy. The average age at diagnosis is 65 years, and median survival after diagnosis is approximately 10 years, with a disease course that consists of multiple episodes of treatment, following by ever shortening periods of symptom and biochemical remission. Current initial therapy for patients with anemia and hyperviscosity—the most common indications for initiation of therapy—consists of bendamustine and rituximab (R) given monthly for 6 months, followed by maintenance of response with single agent rituximab every 3 months for 2 years. Prior to the approval of bendamustine in Canada in 2012,[6] most patients in Canada would have received cyclophosphamide, vincristine and prednisone (CVP) with rituximab; occasionally oral chlorambucil, or intravenous or oral fludarabine would also be used in combination with R. Indications for resumption of therapy is the presence of worsening fatique, anemia, or organomegaly (lymphadenopathy or splenomegaly), and treatment choice is largely guided by data from uncontrolled phase II studies and prior treatment history, making comparisons between currently available agents and with new therapies challenging. Patients with WM generally have a high symptom burden, which may include neuropathy related to the IgM paraprotein or from previous treatment with vincristine. In addition, second-line treatment is frequently given intravenously, is of relatively limited effectiveness in terms of progression-free survival and may have significant toxicity, especially myelosuppression. New treatments with high response and progression free survival rates, especially oral therapies, are highly desirable.

Effectiveness

Ibrutinib is a specific inhibitor of Bruton's Tyrosine Kinase (BTK), which has significant activity in other indolent B cell neoplasms including chronic lymphocytic leukemia and mantle cell lymphoma. Nearly all patients with WM have mutations in myd88 in the malignant cell population, which triggers activation of nuclear factor κB (NF-κB) through BTK signaling. Responses to ibrutinib were observed in patients with WM during phase I clinical testing.

Ibrutinib has been tested in relapsed and refractory (R/R) WM in one phase II trial and one non-randomized companion sub-study within the randomised phase 3 trial (PCYC-1127). Patients enrolled in the PCYC-1118E trial (n=63) had clinical indications for therapy (most frequently anemia, fatique and organomegaly), and received ibrutinib 420mg daily for up to twenty six 4 week cycles, disease progression or unacceptable toxicity. The median number of prior regimens was 2, 80% had intermediate or high risk disease according to the International WM prognostic index, and 40% were refractory to their prior therapy; 90% had received rituximab, 50% bortezomib, 50% an alkylator and 25% bendamustine. A major response (partial or very good partial response; no complete responses) was seen in 73% of patients, with time to partial response of 8 weeks. At a median duration of follow up of 14.8 months[27], 43 patients remained on ibrutinib and 20 had discontinued therapy (10 for treatment failure, 2 for bleeding and 8 for other reasons). Two year PFS was 69% and overall survival 95%, representing excellent disease control in a heavily pre-treated patient population. Given the indolent nature of the disease, it is difficult to demonstrate OS benefit in this patient population. The CGP agreed that PFS is a meaningful and appropriate endpoint. Median time to progression on those with treatment failure was 9.5 months (3-17). Response and PFS from the PCYC-1127 study, reported in abstract form, are consistent with

these data: in 31 patients with similar pre-treatment characteristics to those enrolled in the 1118E trial, major response rate (partial or very good partial response) was 71% and PFS at 1 year was 95%.

Response to treatment with ibrutinib according to the presence of MYD88 mutation (89%, 60/64 patients in PCYC-1118 study), together with mutations in CXCR4 (34%, 21/64 patients in PCYC-1118 study), may provide some insight into patients more or less likely to respond to therapy: those with mutation L265P and germline CXCR4 had significantly improved IgM responses and improvement in hemoglobin compared to those with $CXCR4^{WHIM}$ mutation alone or those without the l265P mutation. Lower rates of PFS were seen in patients with high IPSS scores, more than 3 prior therapies and a $MYD88^{WT}$ $CXCR4^{WT}$ genotype. The data on mutation status is however exploratory and would not be used to select for patients.

In their feedback on the Initial Recommendation, the submitter and the patient advocacy groups noted that complete responses in patients with relapsed or refractory WM are rare. The CGP agreed that complete responses to therapy would be uncommon in this patient population.

Quality of life was measured using the FACT-An Total Score, FACT-An Anemia Subscale, and the EQ-5D-5L Visual Analogue Scale in study PCYC 1127. Although limited data were available for analysis in this review, results indicated that there is no decline in quality of life. No statistical comparisons were provided. There were changes from baseline but they appeared to be small in the data provided and the clinical significance of the changes is uncertain.

After considering feedback on the initial recommendation provided by the submitter and patient advocacy groups, the CGP noted that treatment options for patients with relapsed or refractory WM include alklyators, such as chlorambucil; purine analogues, such as fludarabine; cladribine; or bortezomib (see Table 13). These agents could be given with or without rituximab, which is commonly used in the relapsed setting. However, if a patient progresses to the point of needing treatment within 12 months of the last dose of rituximab, retreatment with rituximab would be less common. The CGP also noted that without a randomized clinical trial, it is not possible to determine the comparative efficacy and effectiveness of ibrutinib with these treatment options. Based on the available evidence, all of these treatment options have activity in relapsed or refractory WM; however, it is not possible to determine whether one is more effective than another.

Safety

In this patient population, ibrutinib is well tolerated, with manageable hematologic and non-hematologic toxicities. Grade 2-4 neutropenia and thrombocytopenia occurred in 22% and 14% of patients respectively. Grade 2 atrial fibrillation occurred in 2 patients and grade 3 in one patient (overall rate 5%) and was manageable without discontinuation of the drug. Four patients experienced grade 2-4 bleeding (2 epistaxis, 2 post-procedural), necessitating discontinuation of therapy in 2 patients. Because ibrutinib is metabolized through the CYP3A hepatic enzyme pathway, co-administration with strong CYP3A inhibitors is to be avoided; short dosage interruptions may be undertaken if medications that are known strong inhibitors of this pathway are necessary.

In its feedback on the Initial Recommendation, the submitter stated that the toxicity profile of ibrutinib is favourable compared to available treatment options, and that, specifically, treatment-related IgM flare, neurotoxicity or infusion reactions were not reported with ibrutinib. The CGP noted that rituximab is a well-tolerated treatment, with a manageable side effect profile. While it can be associated with IgM flare and infusion reactions, these

events are rare. The CGP agrees that these complications have not been observed with ibrutinib; however, ibrutinib does have other side effects and toxicities. In addition to rituximab, there exist other well-tolerated treatment options for patients with relapsed or refactory WM, such as chlorambucil and fludarabine. Futhermore, the CGP noted that, without a randomized controlled trial to directly compare these agents, it is not possible to clearly conclude that one agent is better than the other with respect to safety and tolerability.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net clinical benefit to treatment with ibrutinib in patients with relapsed or refractory WM. This conclusion is based on the high response rate and long progression –free survival reported in a phase II study, supported by preliminary results from a three-arm trial reported in abstract form. The toxicity profile of ibrutinib in this patient population is favourable and side effects are manageable.

The Clinical Guidance Panel also considered that from a clinical perspective:

- The response rates and durations of response with ibrutinib were considered to be clinically meaningful. The activity in this heavily pre-treated patient population suggests that its unique mechanism of action translates into a true addition to the treatment armamentarium.
- The CGP agreed that PFS is an appropriate endpoint in this setting; WM is an indolent NHL with a long natural history and patients will receive multiple lines of therapy in varying orders sequence. Therefore it will be hard to demonstrate OS improvement with therapy in a clinical trial.
- The high rate of disease control, manageable toxicity and preservation of quality of life is in line with goals of therapy outlined by the patient advocacy groups.
- Current data in support of ibrutinib in the setting of relapsed WM are only from relatively small phase II trial reports with short follow-up; nonetheless the response rate and PFS with ibrutinib compare favourably with previous reports of monoclonal antibodies or single agent chemotherapy drugs including alkylating agents, proteasome inhibitors and purine analogues. Information is lacking on the optimum timing of administration of ibrutinib (eg second vs third-line) or in sequencing of active agents in WM. The CGP agree that the use of ibrutinib should be in patients who have had at least one prior therapy. While the CGP agreed that a number of other treatment options are available to patients with WM in this setting and the comparative efficacy of ibrutinib is unknown, it would be reasonable to provide ibrutinib as an alternative treatment option. Additionally, there is no evidence to inform the optimal sequencing of therapies in this setting and choice of therapy should be left to the treating oncologist.
- The CGP noted that there is currently no evidence to comment on the efficacy and safety of using ibrutinib plus rituximab in the front line or previously treated patients. There results of arms A and B from the randomised portion of study PCYC-1127, currently ongoing, will answer this question. The CGP also agreed that there is no role for dose escalation outside of clinical trials.
- The CGP expressed some reservation due to the lack of phase III data however the number of patients with WM is small, and phase III trials comparing currently available drugs to new agents such as ibrutinib in the multiply relapsed setting are unlikely to be carried out.
- Ibrutinib should be prescribed by hematologists or oncologists familiar with its toxicity and who recognize the potential for significant increases in toxicity from concomitant use of moderate or strong CYP3A inhibitors (such as ketoconazole, itraconazole, voriconazole, clarithromycin, antiretroviral agents [ritonavir, indinavir], grapefruit juice) and potential

decreased efficacy when administered with CYP3A inducers (rifampin, St John's wart, phenytoin, carbamazepine).

2 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.

2.1 Description of the Condition

Waldenström's Macroglobulinemia (WM)/lymphoplasmacytic lymphoma (LPL) is an indolent lymphoma comprised of small B lymphocytes, plasmacytoid lymphocytes (those with some of the cytologic characteristics of plasma cells) and mature plasma cells infiltrating the bone marrow, spleen and lymph nodes. According to the 2008 World Health Organization classification, LPL with any detectable IgM paraprotein is classified as Waldenström's macroglobulinemia.[7] Symptoms typically arise from the consequences of extensive BM infiltration, resulting in anemia, or due to high levels of IgM paraprotein, which can cause increased blood viscosity, resulting in neurological symptoms such as blurred vision, headache, confusion, focal deficits and even stroke, as well as bleeding and pulmonary symptoms (shortness of breath, chest pain). WM/LPL is a rare disease with an incidence of 3-5 per million in the US (WM and LPL combined). Some patients are identified by identification of an IgM paraprotein, in the absence of other laboratory findings, similar to other benign monoclonal gammopathies.

Distinction of LPL/WM from other low grade B cell lymphomas may be difficult, since marginal zone lymphoma can show evidence of plasmacytoid differentiation and may present with an elevated IgM paraprotein. The immunophenotype of WM shows expression of CD19, CD20, CD22, FMC7, BCL2, CD38, and CD79a with monotypic surface light chain, without expression of markers of other indolent lymphomas such as CD5, CD10 and CD23.[7] Recent molecular studies have demonstrated the presence of a somatic mutation in myeloid differentiation primary response gene 88 (MYD88), L265P, in approximately 90% of patients with WM. Presence of the L265P mutation is associated with anemia, elevated IgM and bone marrow infiltration.[8] More than one half of individuals with IgM secreting monoclonal gammopathy of unknown significance harbor the MYD88L265P mutation, suggesting its role in development of WM. Additional mutations in CXCR4 have been identified in approximately 2/3 of patients with WM and have been associated with bone marrow disease burden and symptomatic hyperviscosity; their relationship to response to therapy are discussed below.

2.2 Accepted Clinical Practice

Approximately one-third of patients with WM/LPL are asymptomatic at presentation, and the median time to initiation of therapy after diagnosis is 5 years. Predictors of need for early therapy include M spike, elevated serum β2microglobulin, lower hemoglobin and extensive marrow involvement. Indications for therapy include complications related to IgM paraproteinemia (symptomatic cryoglobulinemia; cold agglutinin hemolytic anemia, nephropathy, amyloidosis) and constitutional symptoms from anemia, hyperviscosity, adenopathy or hepatosplenomegaly and neuropathy.[9,10] Plasma exchange is typically used to lower IgM levels in symptomatic patients with hyperviscosity prior to initiation of chemoimmunotherapy. First line therapy consists of rituximab combined with cyclophosphamide and dexamethasone,[11] bendamustine,[12] or cyclophosphamide, vincristine and prednisone; first line therapy with bortezomib is common practice in the US and other countries.[13] There are few randomized trials addressing choice of first-line therapy. The addition of rituximab to cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) improved response rate and PFS[14] but this combination has significantly more toxicities than other regimens[12] and is rarely used as initial therapy . Fludarabine has been shown to be superior to chlorambucil in patients with WM or LPL for response rate and PFS, but this trial was conducted prior to the use of rituximab, and fludarabine is now not considered to be appropriate for initial therapy due to myelosuppression

and concerns about late secondary MDS and AML. Following induction treatment, maintenance therapy with rituximab monotherapy is given in most provinces in Canada, in the same dose and schedule as for other indolent lymphomas (375mg/m^2 every 3 months for 2 years).

Survival in patients with WM/LPL is variable (median 5 years),[15] and depends on prognostic factors present at initial diagnosis. The WM International Prognosis Scoring System (IPSS) identifies 5 factors that have an impact on overall survival: age >65, hemoglobin < 11.6g/l, platelets <100 x 10^9/L, B2M > 3.0 g/L, IgM paraprotein > 70 g/L.[16] Increasing numbers of these factors is associated with shorter overall survival:[16]

- Low risk (0-1) (except age): median survival 143 months
- Intermediate (2 risk factors or age >65): median survival 99 months
- High risk (>3 factors): median 44 months

Current treatment of WM at relapse or progression depends on agents used in initial treatment, and whether re-treatment with rituximab is considered appropriate (generally, for those with progression more than 12 months following last rituximab administration). In a randomized trial that included patients with WM/LPL, the combination of bendamustine + rituximab was superior to fludarabine rituximab, and would be appropriate for patients with rituximab-sensitive WM not previously treated with bendamustine.[17] If initial treatment consisted of an alkylating agent and rituximab, then second-line therapy could reasonably include rituximab in combination with nucleoside analogues, rituximab/bendamustine or bortezomib.[18] Response rates of 60-80% may be expected with combination therapies and 30-80% with single agents, with PFS duration of approximately 12-16 months.[4]

2.3 Evidence-Based Considerations for a Funding Population

Based on the inclusion criteria of the PCYC-1118[2] and PCYC-1127 (arm C)[3] trials, patients with WM or lymphoplasmacytic lymphoma who have had at least one prior treatment would be eligible for treatment with ibrutinib. The patient population with WM/LPL and who have had at least one prior treatment is small. Although the PCYC-1118 trial provided response rates according to the presence of MYD88 mutation (89%, 60/64 patients in PCYC-1118 study) and the CXCR4 mutation (34%, 21/64 patients in PCYC-1118 study), these data are exploratory and would not be used to select for patients for treatment with ibrutinib. The CGP agree that eligibility of patients should follow the trial inclusion criteria of PCYC-1118 and arm C of the PCYC-1127 study. There is currently no evidence available to make a conclusion on the use of ibrutinib combination therapy with rituximab in either front line or relapsed/refractory settings. Arms A and B of the PCYC-1127 study, currently ongoing, will provide further clarity on this combination treatment.

2.4 Other Patient Populations in Whom the Drug May Be Used

Ibrutinib is currently being used or under investigation in indolent lymphomas in a number of indications including CLL/SLL, MCL and WM.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following patient advocacy group(s) provided input on ibrutinib (Imbruvica) for the treatment of patients with Waldenström's macroglobulinemia and their input is summarized below: [Lymphoma Canada (LC) and Canadian Organization for Rare Disorders (CORD)].

LC and CORD conducted online surveys and interviews directed to patients with WM and caregivers about the impact of WM on their lives and the effects of treatment. Links to the surveys were sent via e-mail to WM patients and caregivers registered on LC and CORD databases. The links were also made available via LC social media, International Waldenström's macroglobulinemia Foundation of Canada (IWMF), and several online patient forums and blogs. The surveys had a combination of multiple choice, rating and open-ended questions. Skipping logic questions was built into the surveys so that respondents were only asked questions relevant to them.

LC and CORD indicated that open-ended responses and quotes obtained from the surveys have been included verbatim to provide a deeper understanding of patient and caregiver perspectives.

Please see the table below for a list of total respondents and the breakdown by country.

Participants by Country	CAN	USA	EU	AUS	Other	Skipped	Total
Patients **with** Ibrutinib Experience (Survey)	11	92	-	3	-	9	**115**
Patients **with** Ibrutinib Experience (Interview)	3	4	-	1	-	-	**8***
Patients without Ibrutinib Experience(Survey)	94	131	28	9	7	52	**321**
Caregivers (Survey)	23	15	3	1	1	2	**45**
The perspectives of a **total of 481 patient and caregiver participants** are represented in this submission. ***All patients who participated in an interview also completed a survey.							

It is important to note that telephone interviews were also conducted with eight patients who had direct experience with ibrutinib as monotherapy for relapsed/refractory WM, in order to provide meaningful patient perspectives.

From a patient's perspective, the physical and emotional impact of living with WM was varied. According to LC and CORD, most respondents reported that the impact of WM on their quality of life was moderate; however, there was a sizeable minority who reported that their quality of life was significantly impacted due to symptoms of WM. Respondents reported that the symptoms having the most impact were tiredness/lack of energy, tingling or numbness in feet or legs, weakness, shortness of breath, joint or muscle pain, swollen lymph nodes, heavy night sweats, and frequent infections.

Respondents also described a range of experiences with different types of therapy, including rituximab alone/maintenance, bendamustine, fludarabine, intravenous immunoglobulin (IVIG), velcade, cyclophosphamide vincristine prednisone (CVP), and cyclophosphamide hydroxy doxorubicin vincristine prednisone (CHOP).

Most respondents also reported that they feel there is a need for the availability of additional therapies because they feel that their symptoms and the disease will return even if they are responding to the therapy or they are in remission. Respondents reported the following desired outcomes for a "new drug": (1) bring about a remission, (2) control their disease symptoms, (3) allow them to live longer, (4) improve their quality of life, and (5) improve blood counts. Respondents who have experience with ibrutinib reported fewer side effects with ibrutinib than other drug therapies. Some of the side effects reported with using ibrutinib included: diarrhea/nausea, bruising/bleeding, rash or skin irritation, joint/muscle pain, fatigue/decreased energy, changes to heart rhythm, elevated blood pressure, brittle nails, dizziness, hair thinning,

edema, pneumonia, mouth sores, indigestion, blurred vision, confusion, incontinence, insomnia, headache, weight gain, neuropathy, new curly hair, hoarseness, loss of hearing, cough, and shortness of breath. Most respondents reported that the reported side effects were manageable. Respondents indicated that there was a significant improvement in symptoms management with using ibrutinib. The top symptoms that most respondents felt were managed by ibrutinib included weakness, tiredness or lack of energy and shortness of breath. This in turn has markedly improved their quality of life.

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.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Waldenström's Macroglobulinemia

LC and CORD reported that 321 patients living with Waldenström's macroglobulinemia (WM) who had no experience with ibrutinib responded to the survey. On an average, respondents were diagnosed three years ago; with 33% of respondents diagnosed less than four years ago and 20% diagnosed more than 12 years ago. According to LC and CORD, more than half (~57%) were over the age of 65 and 42% were between 45 and 65 years old.

When LC and CORD asked respondents about their quality of life, most respondents reported that the impact of WM on their quality of life was moderate. However, there was a sizeable minority whose quality of life was significantly impacted due to symptoms of WM.

LC and CORD stated that tiredness/lack of energy was commonly reported among respondents with an average rating of 7.15 on a 10-point scale. There were 126 patient respondents (42.9%) who rated this symptom as having a significant impact (rating ≥ 8) on their quality of life. Other symptoms reported that significantly impacted on their quality of life were tingling or numbness in feet or legs (26.9%), weakness (23.3%), shortness of breath (19.9%), joint or muscle pain (15.8%), swollen lymph nodes (15.0%), heavy night sweats (14.8%), and frequent infections (14.4%). According to LC and CORD all of these symptoms interfered with a patient's performance and their day-to-day activities.

As can be seen in the table below, LC and CORD noted that one-fourth to one-third of respondents reported that their symptoms had a significant impact on their ability to work (34.6%), travel (28.0%), exercise (27.9%), and volunteer (25.9%). This was ranked with a rating ≥ 8 on a 10-point scale.

Please see the table below for further details on respondents' impact on daily life and their corresponding ratings.

Impact on Daily Life (n = 299)	Rating ≥ 8 n (%)	Average Rating	Impact on Daily Life (n = 299)	Rating ≥ 8 n (%)	Average Rating
Ability to work	101 (34.6)	4.83	Ability to attend to household chores	53 (18.0)	4.24
Ability to travel	83 (28.0)	4.72	Ability to fulfill family obligations	41 (14.1)	3.63
Ability to exercise	82 (27.9)	4.98	Ability to spend time with family and friends	40 (13.5)	3.66

Impact on Daily Life (n = 299)	Rating ≥ 8 n (%)	Average Rating	Impact on Daily Life (n = 299)	Rating ≥ 8 n (%)	Average Rating
Ability to volunteer	76 (25.9)	4.29	Ability to concentrate	38 (13.0)	3.79
Ability to contribute financially to household	63 (22.0)	3.64			

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

- *"The neuropathy in my hands and feet make many tasks difficult. When the pain (discomfort) is high it is painful and hard to walk and it is frustrating to try to do simple tasks such as buttoning a blouse or doing up a zipper or feeling in a pocket for keys." (Female, 65-74; Canada)*
- *"Retired early as a result of WM and due to the lack of energy, have found it very difficult to commit to part time work or volunteering my time…This has had a tremendous impact on our ability to generate income over the past 5 years and will have ongoing consequences. I have frequent naps during the day and the ability to exercise on a regular basis…has been compromised due to my lack of energy." (Male, 55-64; Canada)*
- *"I have become dependent [on] family members to take me wherever I need to go, because I am afraid that I will fall (as I have on several occasions). I can't do most of the house, and have to depend on my husband and daughter to do it. I am unable to work, and my husband is working three jobs to try to keep up with the bills." (Female, 55-64; USA)*
- *"I am very cautious of putting myself at risk for picking up infections. This means I sometimes avoid activities with family/friends. We also do not travel even though we are retired. I tire quickly when being physically active. Trips to my hospital for blood tests, doctor's appointments and treatments take one and a half hours each way, so at those times our normal activities and routines are completely interrupted."(Female, 65-74; Canada)*

3.1.2 Patients' Experiences with Current Therapy for Waldenström's Macroglobulinemia

According to LC and CORD, while current treatment options for WM can work initially, patients with WM usually relapse after treatment, and in most cases each period of remission becomes shorter.

LC and CORD asked respondents on a scale of 1 (strongly disagree) to 10 (strongly agree), how much current therapies are able to manage their WM symptoms. LC and CORD reported that of the 240 respondents who answered this question, most felt that their current therapy was able to adequately manage their disease symptoms (rating average = 7.1; rating ≥7 = 63.4%). However, many respondents (at least 36.3%) stated that they had relapsed after previous treatments (15% of respondents did not know whether they had relapsed).
Eighty-five percent (85%) of respondents stated they had received drug therapy to treat their WIM and 79% had received more than one drug therapy. Sixty four (64%) of respondents had received three or more types of drugs while 18% had received 5 or more types of drugs.

Please see the table below for details on current therapies and number of respondents that received them.

Current therapies (n=279)	Number of patients, n (%)	Current therapies (n=279)	Number of patients, n (%)
Rituximab alone/maintenance	94 (33.7)	Plasmapheresis	19 (6.8)
Bendamustine or BR	62 (22.2)	Stem cell transplant	13 (4.7)
Fludarabine, FCR or FR	46 (16.5)	Blood transfusion	12 (4.3)
IVIG	45 (16.13	Chlorambucil	12 (4.3)
Velcade + other(s) regimen	38 (13.6)	Radiation	9 (3.2)
CVP or R-CVP or R-CP	24 (8.6)	Neupogen	7 (2.5)
CHOP or R-CHOP	19 (6.8)	Thalidomide	4 (1.3)

LC and CORD indicated that other WM therapies reported by respondents included: cladribine and melphalan.

When LC and CORD asked respondents about the side effects of current therapies, respondents listed both positive side effects including disease control, improved energy, return to regular routines and negative side effects including disease progression, toxicities, and dose interruptions due to side effects of current therapies.

Below were some of the key responses reported by three respondents to help illustrate the impacts of side effects with their current therapies:

- *"During the chemotherapy treatment program I did not feel well for the first couple of days afterwards. For the entire 6-month chemo program my quality of life was affected in that I didn't go out in public unless I had to in order to avoid compromising my immune system, and I avoided any social gatherings for the same reason. I felt that I had to put my life on hold until my therapy was completed." (Female, 65-74; Canada)*
- *"…breathlessness, rapid onset tachycardia and moderate to severe chest pains following the slightest physical exertion, loss of dexterity, unsteadiness of balance, dizziness, minor headaches, diminished visual acuity, slightly garbled hearing, loss of ability to concentrate for any length of time, numbness in hands and feet…" (Male, ≥ 75; Canada)*
- *"…have nausea, vomiting, tiredness, chemo brain, prone to infections. Hemoglobin went to 78. Beginning with the 2nd treatment I was unable to receive treatments every 21 days as prescribed due to neutropenia." (Female, 55-64; Canada)*

LC and CORD also asked respondents about access issues. According to LC and CORD, respondents were asked how difficult it was to access their current therapy (ies). Nineteen (19) of the 86 Canadian patient respondents (22.1%) who answered this question experienced difficulties. Access issues expressed by respondents included the need to: travel great distances to receive treatment; meet specific provincial drug funding criteria; pay out-of-pocket costs for treatments and associated travel.

Below were some of the key responses as described by three respondents:

- *"We live in a rural area and the hospital is over 100 km from our home. As each monthly treatment was over the course of 2 days we decided to stay over in the city rather than go home and travel back early the next day." (Female, 65-74; Ontario, Canada)*
- *"Initial cancer therapies were completely covered from 2009 through 2011. We have been told that subsequent therapies will be at our expense…my wife's supplementary medical provider does not cover most cancer therapies." (Male, 45-54; Ontario, Canada)*

- *"Because I live in a rural community 3 hours from my primary care physician in Toronto, my health expenses are high. I pay hotel bills, travel costs, meals and parking." (Male, 55-64; Ontario, Canada)*

Regarding choice of treatment, LC and CORD asked respondents on a scale of 1 (not important as long as there is at least one treatment choice) to 10 (Extremely important to have choice of treatment), how important it is for them and their physician to have choices when deciding what treatment is best for them. LC and CORD reported that of the 261 respondents who answered this question, 210 (80.9%) respondents gave a rating of 8 or higher. According to LC and CORD, a rating average of 8.7 indicated a large majority feel that choice is 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 drug therapy options for patients with WM. LC and CORD stated that almost all respondents (98.5%) who answered this question feel there is a need for the availability of additional therapies.

3.1.3 Impact of Waldenström's Macroglobulinemia and Current Therapy on Caregivers

LC and CORD received responses from 45 caregivers. They noted that 93% of the caregiver respondents identified themselves as a spouse and the remaining 7% as a child or other relative. Most caregiver respondents were female (71%) and the majority of respondents were less than 65 years of age (60%).

When respondents were asked on a scale from 1 (no impact) to 10 (very significant impact), how caring for the person with WM has impacted their "day-to-day" life, the following responses were noted in the table below. LC and CORD indicated that differences in ratings were reported based on a caregiver's retirement status, and for those factors with an average rating ≥ 5, it was deemed to be a greater than neutral impact on day-to-day life.

Impact on Retired Caregivers (n = 27)	Rating ≥ 5 n (%)	Average Rating	Impact on NOT retired Caregivers (n = 18)	Rating ≥ 5 n (%)	Average Rating
Ability to travel	20 (74.1)	7.1	Ability to travel	16 (88.9)	7.7
Ability to volunteer	14 (53.8)	4.6	Ability to spend time with family and friends	13 (72.2)	6.8
Ability to spend time with family and friends	13 (50.0)	5.0	Ability to concentrate	12 (66.7)	6.2
Ability to exercise	12 (44.4)	4.1	Ability to work	12 (66.7)	5.6
Ability to fulfill family obligations	10 (37.0)	3.9	Ability to contribute financially to household expenses	11 (61.1)	5.9
Ability to concentrate	10 (37.0)	4.3	Ability to volunteer	11 (61.1)	6.2
Ability to attend to household chores	9 (33.3)	3.6	Ability to attend to household chores	10 (55.6)	4.8
Ability to contribute financially to household expenses	5 (18.5)	3.0	Ability to fulfill family obligations	10 (55.6)	5.6

When caregiver respondents were asked to describe their experience, the following responses were noted:

- *"…as a caregiver for the past 20+ years we have been riding a rollercoaster. Family plans, trips, just sleeping together are stopped or delayed. Sometimes it's visit to the hospital over several days…Other times it's staying home to watch and care for her after a treatment or just because she is tired, asking friends and family for support. It's watching young children grow up while their mom is undergoing a treatment or just feeling tired and 'not now son/daughter'. It's going for a walk and turning back because "I can't, lets go back and rest"." (Male spouse, 55-64; not retired; USA)*
- *"While having chemo my role was solely to look after my husband 24/7. I needed to take him to emergency, chemo, and appointments. I needed to follow up on any additional appointments that needed to be booked as well as passing info back to the doctor/office. I helped him finish the contract work he was involved in, set up meetings including phone calls, meeting space, etc. Worry and fatigue were constant…I was solely responsible for asking questions, checking on his medications and insuring he was looked after. I attended almost all of his chemo appointments…and all his doctor appointments." (Female spouse, 65-74; retired; Canada)*

When asked about side effects, LC and CORD noted that caregivers reported difficulties managing "side effects" of treatment. The most commonly reported challenges were related to fatigue, weakness and infections.

Below were some key responses as reported by two caregiver respondents:

- *"I must take care of all the chores and running the household. My husband was very active from sun up til sundown. Now, fatigue has him laying down as soon as his work day is finished. No energy for yard work, housework, or anything like fun." (Female spouse, 55-64; USA)*
- *"At times full support, as weakness etc. left him unable to do much at all...I have spent countless nights at his bedside in the hospital and rushed to Emerg. several times. Meals, driving, housekeeping - one couldn't have managed alone of this I am certain." (Female spouse, 55-64; Canada)*

Similar to patient respondents, LC and CORD indicated that caregivers reported difficulties with "access" to treatments, including financial burden and distance to treatment. Some caregivers had to take time of 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 (e.g., travelling to United States for a drug not available in Canada; travelling to another province to receive drug; travelling long distance from remote community).

Below were some key responses as described by two Canadian caregiver respondents:

- *"Parking costs really started to add up during chemo, so friends and family offered to drop us off and pick us up each day. After the first round of chemo, my husband had to work extra hours to cover the time he missed when he was getting treatment." (Female spouse, 45-54; Canada)*
- *"My husband hasn't been able to work as his past job required long intense days and a lot of travel. The flights/travel was too hard on his body. We live outside the city. Travel costs and hotel costs to the hospital have really added up for us." (Female spouse, 45-54; Canada)*

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Ibrutinib

LC and CORD stated that when respondents were asked to rate the "desired outcomes" if there was a "new drug", which outcomes were important. As can be seen in the table below, most respondents assigned a rating of '10' (on a 10-point scale) on all outcomes that were considered.

Desired outcome of a new therapy	Rating of '10', n (%)	Average Rating	Response Count
Bring about a remission	213 (80.7)	9.4	264
Control disease symptoms	215 (81.4)	9.4	264
Allow me to live longer	218 (82.6)	9.4	264
Improve blood counts	192 (73.9)	9.2	260
Improve quality of life	218 (82.3)	9.5	265

LC and CORD reported that respondents seek access to new therapies that produce quick, favourable outcomes with relatively mild side effects compared to existing treatments.

In terms of long-term health and well-being, LC and CORD reported that although the majority of respondents said their therapy was working to manage their symptoms, most respondents feel that their symptoms and the disease will return even if they are responding to the therapy or in remission.

To help illustrate the above, two respondents stated the following:

- *"We all know that we will eventually need future treatments as there is no cure at this time. It would be nice to know that when I need treatment in the future that there is a "sure thing" I can be treated with." (Female, 55-64; USA)*
- *"I am running out of options, as I have already used many treatments. I keep hoping that there will be something new when I need it." (Female, 65-74; Canada)*

LC and CORD is of the view that there is an unmet need and stated that patients seek individualized choice in treatment that will offer disease control and improve quality of life while offering ease of use relative to other treatments.

LC and CORD submit that as an oral therapy, ibrutinib is not administered in a hospital or cancer care setting which could lower the risk of patients developing hospital acquired infections. Moreover, LC and CORD indicated that ibrutinib can be taken in the comfort of a patient's home, which could be seen as a true benefit to patients and caregivers. For example, patients and caregivers who live far from cancer treatment facilities and the elderly would particularly benefit from an oral medication. According to LC and CORD, an oral drug with mild side effects for most and proven efficacy will permit patients to regain a good quality of life, have fewer hospital visits and contribute to society.

LC and CORD indicated that WM patients want to transition from an era of chemotherapy to an era of targeted therapy with proven efficacy in treating a broad range of patients, including those who are of advanced age with existing co-morbidities. LC and CORD believe new targeted therapies will change the management of WM for many patients for the better.

Respondents who have experiences with ibrutinib

LC and CORD reported that they received responses from 115 patient respondents who had experience with ibrutinib. Specifically, 18.5% of respondents were between the ages of 55-64; 10.7% were age 45-54; 39.8% of respondents were between the ages of 65-74; and 31.0% of respondents were age 75 years and over. There was an almost even split between males (48%) and females (52%) respondents.

LC and CORD noted that 101 respondents (88.6%) had received at least one prior therapy before receiving ibrutinib. Out of the 90 respondents who identified their previous treatments, 36 (40%) had one (1) prior therapy; 21 (23%) had two (2) prior therapies; 16 (18%) had three prior therapies; 17 (19%) had four (4) or more prior therapies.

In order to provide further context regarding the duration of treatment with ibrutinib, LC and CORD asked respondents the following questions:

1) When they began taking ibrutinib - Of the 96 respondents who responded, 4 (4.2%) started to take ibrutinib in 2012, 11 (11.5%) in 2013, 20 (20.8%) in 2014, 43 in 2015 (44.8%), 18 (18.8%) in 2016.

2) Are they still taking ibrutinib - 98 respondents (90.7%) continue to take ibrutinib, 10 respondents have stopped. Nine (9) respondents reported why they stopped ibrutinib treatment: three (3) reported that they did not respond to the treatment, one (1) had an initial response then relapsed, three (3) stopped due to side effects but one is targeted to restart once the side effect is controlled, one (1) was in a time-limited trial, one (1) achieved remission and then progressed to a stem cell transplant.

3) If they would recommend ibrutinib to other patients with WM based on their own personal experiences. Of the 107 respondents who answered this question, 106 (99.1%) respondents said they would recommend ibrutinib.

When respondents were asked about side effects, they reported comparatively fewer side effects with ibrutinib than other medications, with an average rating of 2.3 (where "1" = far less and "10" = far more). Four-fifths (82.6% or 76/92 respondents) rated side-effects as "3" or less, with only 3% reporting "much more".

When respondents were asked to name the side effects experienced with ibrutinib, 19 of 99 respondents (19.2%) reported no side effects. According to LC and CORD, side effects reported included diarrhea/nausea (n=30), bruising/bleeding (n=26), rash or skin irritation (n=21), joint/muscle pain (n=20), fatigue/decreased energy (n=19), changes to heart rhythm (n=11), elevated blood pressure (n=10), brittle nails (n=9), dizziness (n=5), hair thinning (n=4), edema (n=4), pneumonia (n=4), mouth sores (n=3), indigestion (n=3), blurred vision (n=3), confusion (n=3), urinating difficulties (n=3), insomnia (n=2), headache (n=2), weight gain (n=1), neuropathy (n=1), new curly hair (n=1), hoarseness (n=1), loss of hearing (n=1), cough/shortness of breath (n=1).

When respondents were probed further about the "acceptability" of side effects associated with ibrutinib, 65.9% reported they were nonexistent or entirely acceptable, while 30.6% cited specific side effects that were being managed like bruising, fatigue, nail issues, diarrhea and rashes, sometimes with other medications or lowered dosage, and only very few respondents (4.7%) stated that the side effects were not acceptable.

The following quotes were excerpted by LC and CORD to help illustrate three respondents' experiences relating to side effects with ibrutinib.

- *"All of them are more manageable than the side-effects from other more toxic treatments. None of the side-effects are anywhere near serious enough for me to consider stopping ibrutinib, given the benefit I derive from it. (Female; 65-74; Canada - on ibrutinib since May 2015)*
- *"All of the above effects are acceptable to me. They are minor problems compared to the problems of active and progressing WM." (Female; 65-74; United States – on ibrutinib since March 2015)*
- *"Didn't enjoy any of them. Was able to deal with all of them in that they have been temporary. (Male; 65-74; Canada; completed short-term ibrutinib trial)*

When LC and CORD asked respondents about their improvement in symptoms, respondents indicated that there was a significant improvement in symptoms management with ibrutinib therapy. This question was rated on a scale of 1 (no Improvement) to 10 (very Significant Improvement).

Please see the table below for further details on respondents' ratings regarding symptom improvement.

Improvement in WM Symptoms Since Taking Ibrutinib	Rating ≥8 n (%)	N/A	Rating Average	Improvement in WM Symptoms Since Taking Ibrutinib	Rating ≥8 n (%)	N/A	Rating Average
Tiredness or lack of energy N=99	43 (43.4.0%)	9 (9.1%)	9.0	Swollen lymph nodes N=96	24 (25.0%)	55 (57.3%)	4.3
Weakness N=98	47 (48.0%)	19 (19.4%)	8.0	Bleeding N=98	17 (17.3%)	58 (59.2%)	4.1
Tingling or numbness in feet and legs N=97	14 (4.4%)	36 (37.1%)	6.3	Vision problems N=98	9 (9.2%)	58 (59.2%)	4.1
Joint or muscle pain N=97	13 (13.4%)	37 (38.1%)	6.2	Unexplained weight loss N=98	18 (18.4%)	67 (68.4%)	3.2
Frequent infections N=98	22 (22.4%)	39 (39.8%)	6.0	Headaches N=98	10 (10.2%)	68 (69.4%)	3.1
Heavy Night Sweats N=98	30 (30.6%)	39 (39.8%)	6.0	Swollen abdomen N=97	7 (7.2%)	68 (70.1%)	3.0
Shortness of breath N=97	25 (25.8%)	42 (43.3%)	5.7	Fevers N=97	15 (15.5%)	69 (71.1%)	2.9
Confusion, loss of coordination, dizziness N=97	15 (15.5%)	44 (45.4%)	5.5				
Not all patients experienced all symptoms. The number of patients who did not experience a symptom is listed under N/A. The number of patients who responded to each symptom is shown in the table as indicated by "N".							

LC and CORD also asked respondents how ibrutinib changed or is expected to change their long-term health and well-being. Please see the table below for key responses relating to respondents expectations for ibrutinib.

Long-Term Health or Well-Being (N=100)	N (%)
Control my WM and symptoms associated with WM	91 (91%)
Improve my blood counts	82 (82%)
Improve my quality of life	81 (81%)
Allow me to live longer	68 (68%)
Bring about a remission	35 (35%)

In terms of quality of life, LC and CORD asked respondents to rate their quality of life while on treatment with ibrutinib based on a scale from 1 (severely negatively impacted) to 10 (normal living).

LC and CORD reported that ninety-nine (99) respondents answered this question. Seventy-five (75) respondents (75.8%) gave a rating between 8 & 10. According to LC and CORD, ibrutinib brought the majority of the symptoms under control and allowed them to have an improved quality of life.

Below were some key responses relating to quality of life as reported by three respondents:

- *"I LIVE because of Imbruvica. For this I am eternally grateful - so is my family, I might add. I have returned to normal activities and feel productive and useful again. I feel that I effectively manage the side effects I have experienced while taking Ibrutinib and can cope with these."(Female; 55-64; Canada – on ibrutinib since September 2014)*

- *"I have gone from a depressed, transfusion-dependent husk of a man to a positive, energetic, relatively fit 65-year old who carries his grandchildren on his shoulders for blocks, and swims and walks 3-5 miles a day. Priceless! (Male; 55-64; Canada – on ibrutinib since December 2014)*

  "The improvement cannot be overstated. At my worst, I went from passing out on the floor to walking up to 10,000 steps a day."(Female; 65-74; USA – on ibrutinib since March 2015)

3.3 Additional Information

None provided.

4 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 the 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 Waldenström's macroglobulinemia (WM):

Clinical factors:

- Standard of care is intravenous chemotherapy
- New treatment option that is an oral drug

Economic factors:

- Very small number of patients relative to other cancers
- Long duration of treatment

Please see below for more details.

4.1 Factors Related to Comparators

The standard treatment in Canada is rituximab in combination with chemotherapy.

For newly diagnosed WM, treatment is combination chemotherapy such as bendamustine/rituximab, rituximab/cyclophosphamide/dexamethasone, or cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab.

For previously treated WM, treatment options include fludarabine, bendamustine/rituximab, rituximab/cyclophosphamide/dexamethasone, cyclophosphamide/vincristine/prednisone/rituximab or cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab.

PAG noted that mature results in the ongoing phase 3 trial (PCYC-1127) are not available until 2019 and there is presently a lack of long-term comparative data. In addition, the comparator in this phase 3 trial is rituximab monotherapy, which is not a funded treatment option in all the provinces.

PAG noted that ibrutinib monotherapy is a treatment option for previously treated WM and ibrutinib in combination with rituximab is a treatment option for both newly diagnosed and previously treated patients in the PCYC-1127 trial. PAG is seeking information on ibrutinib monotherapy compared to ibrutinib in combination with rituximab for both newly diagnosed and previously treated WM, if available.

4.2 Factors Related to Patient Population

PAG indicated that the number of patients would be very small relative to other cancers. In addition, PAG noted that not all patients require treatment immediately upon diagnosis.

The phase 2 single-arm, open-label prospective study addresses patients with previously treated WM. However, PAG noted that this study had a small number of patients and is seeking

information on the generalizability of this data to Canadian patients. PAG is also seeking data comparing ibrutinib to rituximab combination chemotherapy.

PAG noted that if funded, ibrutinib may become the treatment of choice for WM given that it is an oral treatment. PAG is seeking information on treatment sequence with intravenous chemotherapy.

PAG noted in some patients with high IgM levels, rituximab is not administered until disease burden is controlled by chemotherapy in order to prevent disease flare. PAG is seeking information on whether this clinical practice would apply to ibrutinib with rituximab combination therapy.

4.3 Factors Related to Dosing

PAG noted that the drug's once daily, continuous dosing schedule and the flat dose of 420mg are enablers to implementation. However, barriers to implementation include the need for patients to take three capsules for the dose and the unknown treatment duration as treatment with ibrutinib is until disease progression.

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.

PAG noted that higher doses are used for treatment of mantle cell lymphoma and chronic lymphocytic leukemia. As such, there is the potential for upward dose escalation in the treatment of WM.

4.4 Factors Related to Implementation Costs

As ibrutinib is administered orally, PAG noted that chemotherapy units and chair time would not be required for ibrutinib monotherapy. This is an enabler to implementation.
However, for ibrutinib in combination with rituximab, chemotherapy units and chair time would still be required for the rituximab portion of the treatment.

PAG also noted that additional health care resources may be required to monitor and treat toxicities and monitor drug-drug interactions. Ibrutinib is a new oral agent for this group of patients, although there is familiarity with its use in other diseases.

4.5 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.

4.6 Factors Related to Manufacturer

The high cost of ibrutinib is a barrier to implementation.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Registered clinician input was not received for this review.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the safety and efficacy of ibrutinib on patient outcomes in the treatment of adults with Waldenström's macroglobulinemia who have received at least one prior therapy.

Supplemental question: Relevant literature was sought to provide data on the efficacy of relevant comparators for the treatment of adults with Waldenström's macroglobulinemia. These data are summarized in section 7.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP 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 3. Selection Criteria

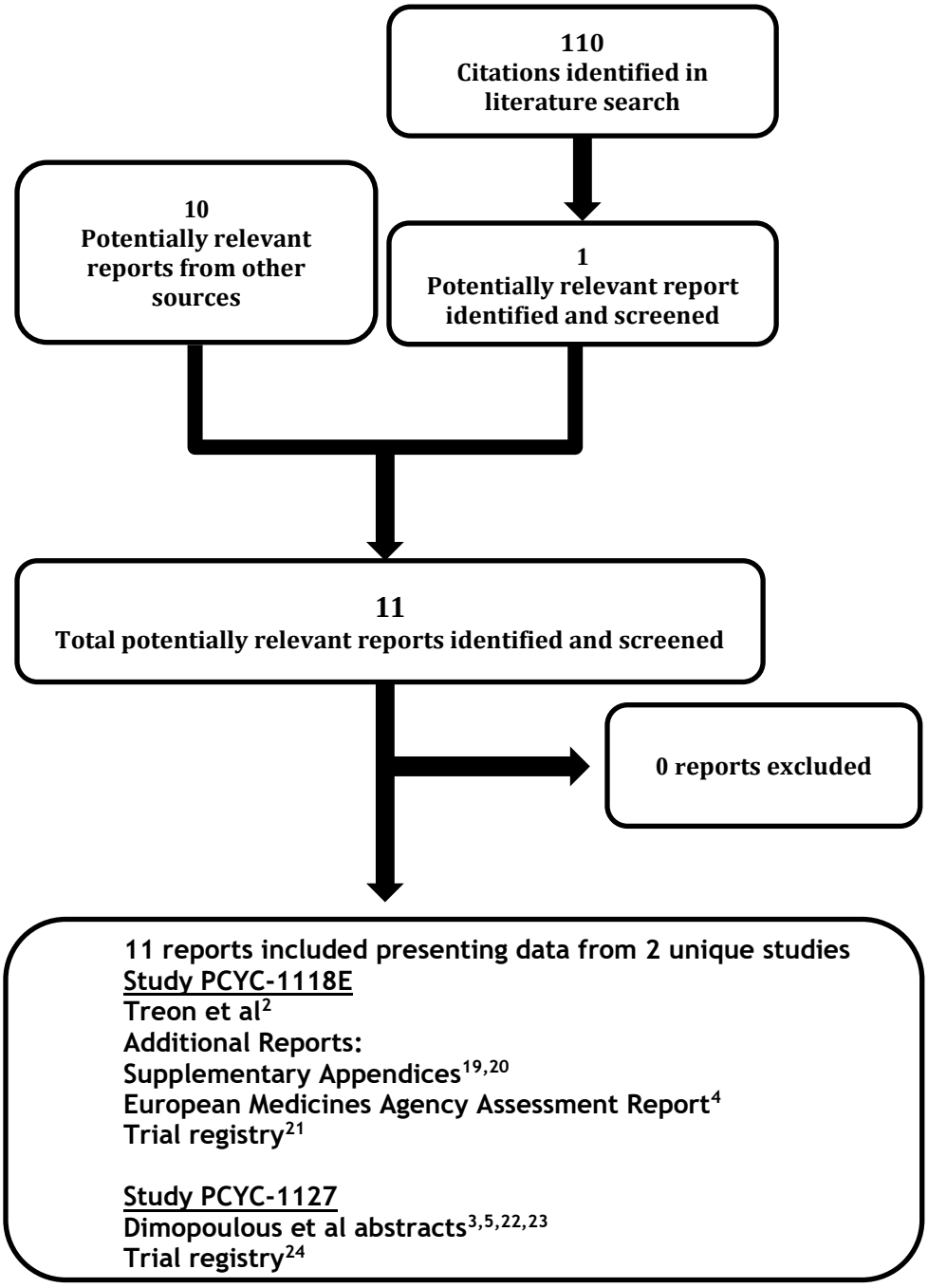
Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs or non RCTs. In the absence of RCT data, fully published clinical trials investigating the efficacy of ibrutinib should be included. Reports of trials with a mixed design are to be included if separate data were reported for the cohort of patients who were included in the efficacy-determining phase of the study.	Adult patients with Waldenström's macroglobulinemia who have received at least one prior therapy. Subgroups of interest: Symptomatic versus asymptomatic patients	Ibrutinib monotherapy	All appropriate multi-agent chemotherapy regimens including but not limited to: • Cyclophosphamide, vincristine, prednisone with/without rituximab • Cyclophosphamide dexamethasone, rituximab, • Bendamustine, rituximab • Regimens including cladribine or fludarabine • Chlorambucil alone • Rituximab alone	• **OS** • **PFS** • Response • Duration of Response • Time to next therapy • **Quality of Life** • **Disease symptoms including neuropathy headache, confusion, shortness of breath** • Hb levels • **SAEs** • **AEs** • WDAEs • Adverse events of interest include major bleeding, atrial fibrillation, diarrhea, skin rash,
Notes: AE= adverse event; Hb= hemoglobin; PFS= progression free survival; OS= overall survival; SAE=serious adverse event; WDAE= withdrawal due to adverse event; WM: Waldenström's macroglobulinemia; **Standard and/or relevant therapies available in Canada* *Note: outcomes indicated as important to patients in Section 3 are in bold*				

6.3 Results

6.3.1 Literature Search Results

Of the 11 potentially relevant reports identified, 2 studies were included in the pCODR systematic review.

Figure 1: QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to study PCYC-1127 were also obtained through requests to the Submitter by pCODR[25]

6.3.2 Summary of Included Studies

Two non-randomized interventional trials were identified that met the eligibility criteria of this systematic review (see Table 4).[2-5,19-24]

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary of Trial Characteristics of the Included Studies

PCYC-1118E[2,4,19-21]			
Trial Design	**Key Inclusion Criteria**	**Intervention**	**Trial Outcomes**
Phase II, open-label, multicenter, single arm study Non randomized Enrollment: 63 Study start date: May 2012 Enrollment closed: June 2013 Final data collection for NEJM publication: December 2014 Estimated study completion date: August 2018[21] Funded by Pharmacyclics, Janssen and several other grants.	• Adults with diagnosis of WM and need for treatment according to consensus guidelines[26] • At least one prior therapy for WM • IgM>2x ULN • ECOG ≤2 • ANC ≥ 1,000/mm^3 • Platelets ≥ 50000/mm^3 • Hemoglobin ≥ 8 g/dL • Total bilirubin ≤ 1.5 mg/dL or < 2 mg/dL if attributable to hepatic infiltration by neoplastic disease • AST and ALT ≤ 2.5x ULN • Creatinine ≤ 2 mg/dL Excluded if had CNS lymphoma or clinically significant CVD, taking warfarin or drugs that prolong QT interval	Oral ibrutinib 420 mg daily for twenty-six 4-week cycles until disease progression or unacceptable toxic effects; patients without disease progression could continue therapy beyond 26 cycles	<u>Primary:</u> Overall response rate, which included minor response (≥25% reduction in serum IgM levels), partial response (≥50% reduction), very good partial response (≥90% reduction), and complete response; Major response (a complete response or responses with a ≥50% reduction in serum IgM levels) <u>Secondary:</u> Major response rate (including >50% reduction in serum IgM levels), PFS, OS, , Time to next treatment, Adverse events, Hemoglobin improvement <u>Other:</u> Tumour involvement, change in serum IgM levels

PCYC-1127/iNNOVATE[3,5,22-24]			
Trial Design	**Key Inclusion Criteria**	**Intervention**	**Trial Outcomes**
Study had 3 treatment arms (A, B and C). Data in this report come solely from Arm C, an open label, non-randomized group of patients with WM Enrollment in arm C: 31 Study start date: July 2014 Recruitment completed for arm C: April 2015	Arm C: • Adults with symptomatic WM meeting at least 1 of the recommendations from consensus guidelines • IgM ≥0.5 g/dL • Hemoglobin ≥ 8 g/dL • Platelets > 50000/mm^3 • ANC > 750 /mm3 • AST and ALT < 3x ULN • bilirubin ≤ 1.5 mg/dL • ECOG ≤2	Arm C: Oral ibrutinib 420 mg daily until disease progression Arm A Oral ibrutinib 420 mg daily until disease progression + rituximab 375 mg/m^2	<u>Primary:</u> PFS <u>Secondary:</u> Overall response rate OS Hematologic improvement (hemoglobin levels)

PCYC-1127/iNNOVATE[3,5,22-24]			
Trial Design	**Key Inclusion Criteria**	**Intervention**	**Trial Outcomes**
Study is ongoing but recruitment has stopped. Estimated study completion date: January 2019[24] Note: There was also a randomized group of patients (n=150; "arm A" and "arm B"), but no analyses are available on these arms as they are still blinded. Funded by Pharmacyclics and Janssen	• Disease that is refractory to the last prior rituximab-containing therapy defined as relapse after <12 months since last rituximab dose OR Failure to achieve at least a minor response after the last rituximab-containing therapy Excluded if CNS involvement Arms A and B included patients with untreated or previously treated WM. If previously treated must have documented PD or no response to last treatment. Patients were excluded if disease was refractory to the last rituximab-containing therapy (e.g. relapse after <12 months since last rituximab dose or failure to achieve at least a minior response after the last rituximab containing therapy	IV on day 1 of weeks 1-4 and weeks 17-20 Arm B Placebo until disease progression + rituximab 375 mg/m^2 IV on day 1 of weeks 1-4 and weeks 17-20	Time to next treatment Adverse events Other:[22] FACT-An EQ-5D-5L Mutation status (MYD88, CXCR4)

ANC= absolute neutrophil count; ALT= alanine aminotransferase; AST=aspartate aminotransferase; CNS=central nervous system; CVD=cardiovascular disease; EQ-5D-5L= Euro QoL questionnaire; FACT-An= functional assessment of cancer therapy-anemia; IgM=immunoglobulin M; ECOG=eastern cooperative oncology group; PD=progressive disease; PFS=progression free survival; PS=performance status; ULN=upper limit of normal; WM= Waldenström's macroglobulinemia;

Figure 2 Study Design of PCYC-1127

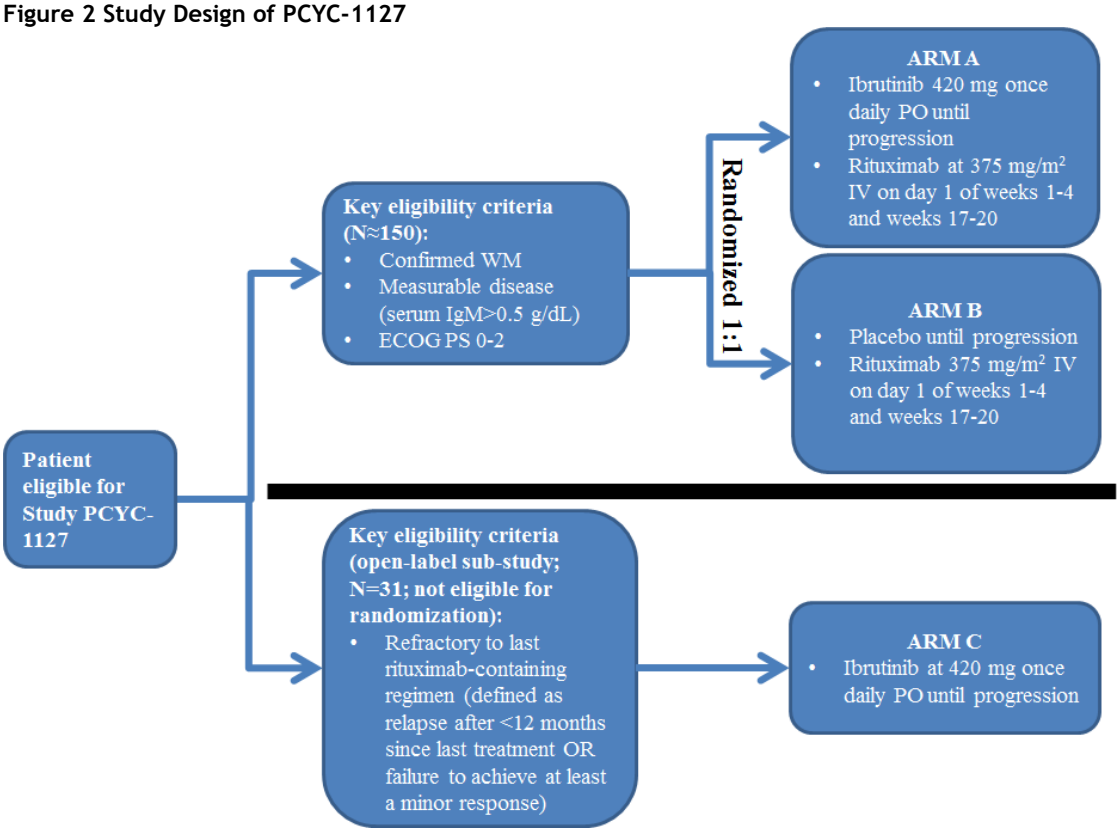


Table 5: Select quality characteristics of included studies of ibrutinib in patients with Waldenström's macroglobulinemia

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
PCYC-1118E	n/a	ORR	60*	63	n/a	n/a	n/a	Yes	n/a	n/a	Yes
PCYC-1127	n/a	PFS	NR	31	n/a	n/a	n/a	NR	n/a	n/a	NR

ITT= intent to treat; NR=not reported; ORR= overall response rate; PFS=progression free survival; n/a= not applicable;

*The required sample size was estimated to be 33 and later changed to 60.

a) Trials

PCYC-1118E

PCYC-1118E is an open-label single arm study that enrolled adults with WM who had a need for treatment according to consensus guidelines. The primary endpoint of the study was the overall response rate, defined as a minor response or better. Responses were defined according to criteria adopted from the Third International Workshop on Waldenström's Macroglobulinemia (IWWM) as described in Table 6 below.[4]

Subjects were evaluated for response and tolerance to ibrutinib on the first day of each cycle (4 weeks ±2 days) at Cycle 2, Cycle 3, and thereafter every 3 cycles (12 ±1 week) for a maximum of 40 four-week cycles (ie, approximately 3 years), or until disease progression. Participants were to be followed for up to two years after removal from or completion of the study, until the initiation of new treatment or death, whichever occurs first.[4]

Progression free survival was defined as the time between the initiation of therapy and the date of disease progression, death, or last follow-up.

Three sites in the United States enrolled 63 patients and the study is ongoing. Serum IgM and complete blood counts were obtained at the beginning of each cycle for 3 cycles and thereafter every 3 cycles. Bone marrow biopsies and computed tomography (if extramedullary disease was present at baseline) were repeated at cycles 6, 12, and 24, and annually thereafter.

A Simon two-stage MinMax design with alpha set at 0.05 and beta at 0.20 assuming a null response rate of 20% and a successful response rate of 40% was used and needed 18 patients in the first stage. If at least 5 participants respond in this first stage another 15 participants would be enrolled (total sample size = 33 participants). If at least 11 participants are found to have a response (>25% reduction in disease burden) the trial will be deemed a success and ibrutinib will warrant further testing in symptomatic participants with relapsed/refractory WM. The protocol was amended to enroll a total of 60 participants, with at least 10 participants at each institution. Assuming the ORR for ibrutinib was 50% in the study population, with 60 evaluable participants, the study would have slightly greater than 80% power to declare that the lower bound of the two sided 95% CI for ORR will exceed 32%.[20]

PCYC-1127

Study PCYC-1127 is an ongoing study with three treatment arms. The only results available for this study come from an interim analysis of data from the ibrutinib open-label treatment arm ("arm C"). There are no data available for arms A and B, which are still blinded. It is notable that more than half of patients in the randomised portion of the PCYC-1127 study, Arms A and B, were previously treated. The estimated primary completion date is January 2019. The interim results for the open label portion of the study, Arm C, are available only in abstract form. The primary endpoint of the study is progression free survival as defined by the modified Consensus Response Criteria from the Sixth International Workshop on WM.[27] Response was assessed using the modified consensus criteria adapted from the 6th International Workshop on WM and these criteria are listed in the Table 6 below.[3]

Table 6. Modified Response and Progression Criteria per the 3rd and 6th IWWM for Investigator Assessment[4,25]

Category	PCYC-1118E Response Criteria based on 3rd IWWM	PCYC-1127 Response Criteria based on 6th IWWM
Complete response (CR)	Resolution of all symptoms, normalization of serum IgM levels with complete disappearance of IgM paraprotein by immunofixation, and resolution of any adenopathy or splenomegaly.	Normal serum IgM values Disappearance of monoclonal protein by immunofixation No histological evidence of bone marrow involvement Complete resolution of lymphadenopathy/ splenomegaly if present at baseline
Very good partial response (VGPR)	> 90% reduction in serum IgM levels.	≥90% reduction of serum IgM from baseline or normal IgM values Reduction in lymphadenopathy/splenomegaly if present at baseline
Partial response (PR)	> 50% reduction in serum IgM levels.	≥50% reduction of serum IgM from baseline Reduction in lymphadenopathy/splenomegaly if present at baseline
Minor response (MR)	25-49% reduction in serum IgM levels.	At least 25% but <50% reduction of serum IgM from baseline
Stable disease (SD)	< 25% change in serum IgM levels, in the absence of new or increasing adenopathy or splenomegaly and/or other progressive signs or symptoms of WM	Not meeting criteria for CR, VGPR, PR, MR, or progressive disease
Progressive disease (PD)	> 25% increase in serum IgM level with an absolute increase of at least 500 mg/dL occurs from the lowest attained response value, or progression of clinically significant disease related symptom(s). Reconfirmation of the initial IgM increase is required when IgM is the sole criterion for progressive disease confirmation.	At least one of the following: A ≥25% increase in serum IgM with a total increase of ≥500 mg/dL from nadir** – Confirmation of the initial IgM increase is required when IgM is sole criterion for PD New lymph nodes >1.5 cm in any axis, ≥50% increase from nadir in SPD of >1 node, or ≥50%

Category	PCYC-1118E Response Criteria based on 3rd IWWM	PCYC-1127 Response Criteria based on 6th IWWM
	Death from any cause or initiation of a new anti-neoplastic therapy will also be considered a progression event.	increase in longest diameter of a previously identified node >1 cm in short axis New splenomegaly or ≥50% increase from nadir in enlargement of the spleen New extranodal disease New or recurrent involvement in bone marrow New symptomatic disease (based on presence of malignant pleural effusion, Bing Neel syndrome, amyloidosis or light chain deposition disease, or other paraprotein-mediated disorder)

SPD, sum of the products of the greatest perpendicular diameters.

***Nadir from serum IgM is defined as the lowest serum IgM value obtained at any time from baseline with the exception that serum IgM levels post-plasmapheresis will not be considered for up to 35 days.*

b) Populations

Table 7. Baseline patient characteristics in the included studies of ibrutinib in patients with previously treated Waldenström's macroglobulinemia[2-5,19-25]

	PCYC-1118E N=63	PCYC-1127 N=31
Median age (range), years	63(44-86)	67(47-90)
Male sex, n(%)	48(76)	NR
ECOG PS	0: 47(75) 1-2: 16(25)	0-1: 25(81) 2: 6(19)
Median time from WM diagnosis(range), months	76(6-340)	NR
IPSS, n(%)		
Low	14(22)	7(23)
Intermediate	27(43)	11(35)
High	22(35)	13(42)
Median Serum IgM(range), mg/dL	3520(724-8390)	3830(740-10700)
Median Hemoglobin level (range), g/dl	10.5(8.2-13.8)	10.3(6.4-14.6)
Median platelet count/mm^3 (range)	214 (24-459)	218(51-896)
Median absolute neutrophil count/mm^3 (range)	3.19(1.14-10.97)	2.9(0.7-15.4)
Median B2 microglobulin (range), mg/L	3.9(1.3-14.2)	3.6(1.7-24)
Median number of previous therapies for WM (range)	2(1-9)	4(1-8)
Type of previous therapy, n(%)		
Rituximab	NR	31(100)
Monoclonal antibody	57(90)	NR
Glucocorticoid	42(67)	25(81)
Puring analog	NR	13(42)
Proteasome inhibitor	33(52)	14(45)
Alkylator	32(51)	25(81)
Nucleoside analogue	15(24)	2(6)
MTOR inhibitor	13(21)	NR
Immunomodulator	7(11)	2(6)
Anthracycline	7(11)	8(26)
Autologous transplantation	4(6)	2(6)
Bendamustine[25]	17(27)	7(23)
Other	13(21)	8(26)
Most recent treatment, n(%)		
Monotherapy		32%
Combination therapy without antibody		29%
Combination therapy with antibody		39%
Disease refractory to most recent regimen	25(40)	NR
Adenopathy ≥ 1.5cm, n(%)	37(59)	NR
Splenomegaly ≥15 cm, n(%)	7(11)	NR
Median bone marrow involvement(range), %	60(3-95)	NR
$MYD88^{L265P}$, n/N(%)	56/63(89)	NR
$CXCR4^{WHIM}$, n/N(%)	21/62(34)	NR

Abbreviations: IgM=immunoglobulin M; ECOG=eastern cooperative oncology group; IPSS=international prognostic scoring system; MTOR= mammalian target of rapamycin; PS=performance status; WM= Waldenstrom's macroglobulinemia;

A total of 63 and 31 patients were enrolled in studies PCYC-1118E and PCYC-1127, respectively. As summarized in Table 7, baseline characteristics were similar between the two studies for most prognostic factors reported at baseline with a few exceptions. Study PCYC-1118E enrolled patients with slightly better ECOG status at baseline, relative to PCYC-1127. Patients in the PCYC-1127 study had more previous treatments for WM (median 4) compared to patients in study PCYC-1118E (median 2). While the exact figures were not disclosable, approximately a quarter of patients used bendamustine prior to study enrollment

in PCYC-1118E and in Arm C of study PCYC-1127. Age distribution of the study populations were similar, but gender distribution was not reported for study PCYC-1127. In study PCYC-1127, 29% of patients had progression on or within 60 days of their last therapy; an additional 29% had no response (stable disease or disease progression) to their most recent therapy.[3]

Study PCYC-1127 was performed at 19 sites located in Australia, Canada, France, Greece, Italy, Spain and the United States. Three patients were enrolled at two Canadian sites (Montreal, Halifax).[25]

Reasons for initiating treatment are summarized in Tables 8 and 9 below.

Table 8. Reasons for Initiating WM Treatment by Investigator at Study Entry in study PCYC-1118E (All-Treated Population)[25]

Reasons for Initiating WM Treatment (PCYC-1118E)	Ibrutinib N=63, n (%)
Anemia	47 (74.6)
Fatigue	35 (55.6)
Extramedullary Disease	18 (28.6)
Peripheral Neuropathy	9 (14.3)
Night Sweats	6 (9.5)
Thrombocytopenia	5 (7.9)
Hyperviscosity	4 (6.3)

Multiple reasons may be selected for each subject. There are other reasons including IgM, involved bone marrow, epistaxis, amyloidosis, leg cramps, burning sensation of skin, cytopenia, pancytopenia, von Willebrand's disease and lymphoplasmacytic lymphoma.

Table 9. Reasons for Initiating WM Treatment in study PCYC-1127 [25]

Reasons for Initiating WM Treatment (PCYC-1127)	Arm C open label (N=31), n (%)
Any symptomatic disease criteria met	31 (100)
Constitutional symptoms	13 (42)
Weight loss [1]	8 (26)
Fever [2]	0
Night sweats [3]	10 (32)
Fatigue [4]	22 (71)
Hyperviscosity [5]	5 (16)
Lymphadenopathy [6]	7 (23)
Symptomatic hepatomegaly and/or splenomegaly and/or organ tissue infiltration	3 (10)
Peripheral neuropathy due to WM	4 (13)
Symptomatic cryoglobulinemia	0
Cold agglutinin anemia	0
IgM related immune hemolytic anemia and/or thrombocytopenia	0
Nephropathy related to WM	0
Amyloidosis related to WM	0
Hemoglobin <=10g/dL	13 (42)
Platelet count <100x10^9/L	2 (6)

Reasons for Initiating WM Treatment (PCYC-1127)	Arm C open label (N=31), n (%)
Serum monoclonal protein >5g/dL, with or without overt clinical symptoms	4 (13)

Note: For the open-label ibrutinib arm, safety population is used

[1] Unintentional weight loss >= 10% within the previous 6 months prior to Screening.

[2] Fevers higher than 100.5 degrees F or 38.0 degrees C for 2 or more weeks prior to Screening without evidence of infection.

[3] Night sweats for more than 1 month prior to Screening without evidence of infection.

[4] Clinically relevant fatigue which is not relieved by rest due to WM.

[5] Symptomatic hyperviscosity or serum viscosity levels greater than 4.0 centipoises.

[6] Lymphadenopathy which is either symptomatic or bulky (>=5 cm in maximum diameter)

c) Interventions

In Study PCYC-1118E, ibrutinib 420 mg daily was given to all patients and was withheld in the event of hematologic toxicity defined as: neutrophil count of less than 500/mm^3 or a platelet count of less than 25,000/mm^3 or less than 50,000/mm^3 with bleeding. Ibrutinib was withheld if the patient had nausea of grade 3 or higher, vomiting or diarrhea, or nonhematologic toxic effects of grade 3 or higher. After ibrutinib was withheld the first time, full-dose retreatment was permitted after the patient recovered from toxic effects. Thereafter, reductions in the dose to 280 mg and then to 140 mg and, finally, discontinuation of the study drug if subsequent events occurred. No anticancer agents other than ibrutinib were permitted during the study.[20] Filgrastim therapy or transfusions were permitted and filgrastim was used in 4 patients (6%).

Patients in Study PCYC-1127 are taking ibrutinib 420 mg daily until disease progression occurs. Five patients received concomitant growth factors including neutrophil growth factors (n=3) and erythropoietin stimulating agents (n=2).[5] Filgrastim was used in 1 patient (3%) in arm C.

d) Patient Disposition

In study PCYC-1118E, 60 of 63 patients were alive at the time of the data analysis. The median duration of treatment was 19.1 months (range, 0.5 to 29.7); 43 patients (68%) continued to receive therapy after the database was locked (in December 2014). Reasons for discontinuation of treatment included nonresponse (1 patient), progressive disease (7 patients), treatment-aggravated thrombocytopenia (1 patient), hematoma after bone marrow biopsy (1 patient), prolonged withholding of the drug because of infection unrelated to ibrutinib (1 patient), myelodysplasia and acute myeloid leukemia associated with baseline 5q deletion related to prior therapies (1 patient), disease transformation possibly related to prior nucleoside analogue therapy (2 patients), antineoplastic therapy for rectal carcinoma (1 patient), ibrutinib-incompatible medication (1 patient), the patient's decision to use commercially sourced ibrutinib (2 patients), travel difficulties (1 patient), and alternative therapy (1 patient).[2]

In study PCYC-1127, no deaths were reported in the most recent abstract.[5] Five patients discontinued ibrutinib (three due to progressive disease and two due to adverse events). Overall, 26 patients (84%) were continuing on ibrutinib therapy at the time of the interim analysis, with a median follow-up of 17.1 months. Dose reductions occurred in 4 patients (13%), with no dose reductions for hematologic toxicity.[3]

e) Limitations/Sources of Bias

Both trials:

- Non-randomized open-label trials that lack blinding of participants and investigators are at risk for a number of different biases that can affect the internal validity. Interpretation of the study results also needs to take into account the potential biases inherent in open label study designs such as unblinded response assessment (Study PCYC-1118E), patient selection and assessment of adverse events. The direction and magnitude of bias on these factors are unknown.
- Neither study used a comparator treatment arm and therefore the efficacy and harms of ibrutinib relative to other treatments is uncertain.
- WM is an indolent disease with a chronic course. While the trials provide some information regarding the risk of harm in WM patients taking ibrutinib, the median follow-up is short relative to the anticipated duration of ibrutinib therapy in clinical practice. Long term risk of harm cannot be adequately estimated from the two studies in patients with WM.

PCYC-1127:

- Interim results for study PCYC-1127 were presented in conference abstracts that may not have undergone peer review and there were many important details that will need to be assessed when the peer-reviewed publications and final analyses become available.
- Data were incomplete and derived mostly from abstracts. Overall survival was not reported for this study and the variance around the estimate for progression free survival was not reported.
- Quality of Life data were collected in this trial but very few results were available for inclusion in this report. The variance around the changes in quality of life scores is large and the clinical significance of the changes in this small patient cohort is uncertain.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Table 10. Summary of efficacy[2-5,19-24]

	PCYC-1118E N=63[2]	PCYC-1127 N=31[5]
Median time on ibrutinib (range) at time of data analysis, months	19.1 (0.5 to 29.7)	17.1 (6.3 to 20.0)
OS (95%CI)	95.2%(86.0,98.4) at 24 months	NR
PFS(95%CI)	69.1%(53.2,80.5) at 24 months	**93% (95%CI NR) at one year***
Median PFS	Not reached	Not reached
Response		
Complete response, n(%)	0	0
Very good partial response, n(%)	10(16)	4(13)
Partial response, n(%)	36(57)	18(58)
Minor response, n(%)	11(17)	6(19)
Stable disease, n(%)	5(8)	2(6)
Overall response (95%CI)	**90.5% (80.4-96.4)***	90% (NR)
Major response (95%CI)	73.0% (60.3-83.4)	71% (NR)

	PCYC-1118E N=63[2]	PCYC-1127 N=31[5]
Median duration of overall response at 18 months (95%CI), months	Not reached (95%CI:0.03-29.0) n=57	NR
Median hemoglobin, mg/dL	10.5 at baseline 13.8 at time of best response, (p<0.001 vs baseline)	10.3 11.4 after cycle 1 12.7 at week 49 (p-value NR)

OS=overall survival; PFS=progression free survival; NR=not reported;
*Primary outcome of the study
In study PCYC-1118E, overall response rate was > 25% reduction in disease burden and major response rates was >50% reduction in disease burden.[20] Overall and major response definitions were not defined in study PCYC-1127.

Overall Survival
Median overall survival was not reached in study PCYC-1118E. Overall survival was reported to be 95.2%(95%CI: 86.0-98.4) at 24 months.[2] Median OS was not reached for the PCYC-1127 study.

Progression Free Survival
Median progression free survival was not reached in study PCYC-1118. Progression free survival was 69.1%(95%CI: 53.2-80.5) at 24 months.[2] Progression free survival (the primary endpoint for study PCYC-1127) was 93% at one year in study PCYC-1127 (after median follow up 17.1 months).[25]

Response
In study PCYC-1118E, after a median 19.1 months of follow up, there were 10(16%) patients with very good partial response, 36(58%) with partial response, 11(17%) with minor response, and 5(8%) with stable disease. No patients had complete response. This resulted in an overall response (the primary endpoint of the study) of 90.5% (95%CI: 80.4-96.4). The main analyses for response were performed using investigator assessments. The European Medicines Agency reported that the investigator assessed response rates were slightly higher than the response ratings performed by an independent review committee.[4]

In response to a request for additional information, the manufacturer provided data on overall response by patients <70 and ≥70 years of age in study PCYC-1118E, summarized in figure 3 below.[25]

Figure 3. Overall response by patients <70 and ≥70 years of age in study PCYC-1118E by investigator (data cutoff February 28, 2014)

In study PCYC-1127, after median 17.1 months of follow up there were 4(13%) patients with very good partial response, 18(58%) with partial response, 6(19%) with minor response and 2(6%) with stable disease. No patients had complete response. This resulted in an overall response of 90%. The response data reported are from the investigators' assessments and are best response. There was an Independent Review Committee that assessed the primary

endpoint (PFS), but the specific response assessments from this committee were not available in the abstracts for this study.

Subgroups of interest for this pCODR report included symptomatic (versus asymptomatic) patients but there were no analyses performed on these subgroups in either included study.

Duration of Response
Median duration of overall response was not reached (95%CI: 0.03-29.0) in study PCYC-1118E at 18 months.[4] Duration of response was not reported for study PCYC-1127.

Time to Next Therapy
Time to next therapy was an outcome described in the protocol for the PCYC-1118E study and in the PCYC-1127 abstract. Data on this outcome were requested from the manufacturer but the results were not available for either study.[20,25]

Quality of Life
Study PCYC-1118E:
Quality of life was not a planned outcome for study PCYC-1118E.

Study PCYC-1127:
Interim Quality of Life data were provided for study PCYC-1127 for FACT-An Total Score, FACT-An Anemia Subscale, and the EQ-5D-5L Visual Analogue Scale. Arm C data for these three scales were provided by the manufacturer in graphical format and are presented in the figures below. The changes from baseline appeared to be small in the graphs and the clinical significance of the changes is uncertain.

The pCODR review team requested data on completion rates and minimally important differences for these data. At the time of this review, the manufacturer informed pCODR that a manuscript was underway on the full results for patient reported outcomes from study PCYC-1127. These data were requested but not made non-disclosable until publication of the data.

Figure 3. FACT-An Total Score. PCYC-1127 (Arm C) [25]

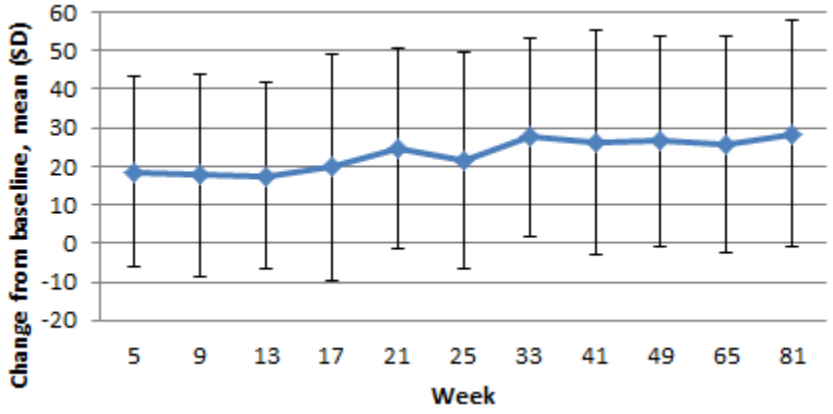


Figure 4. FACT-An Anemia Subscale. PCYC-1127 (Arm C) [25]

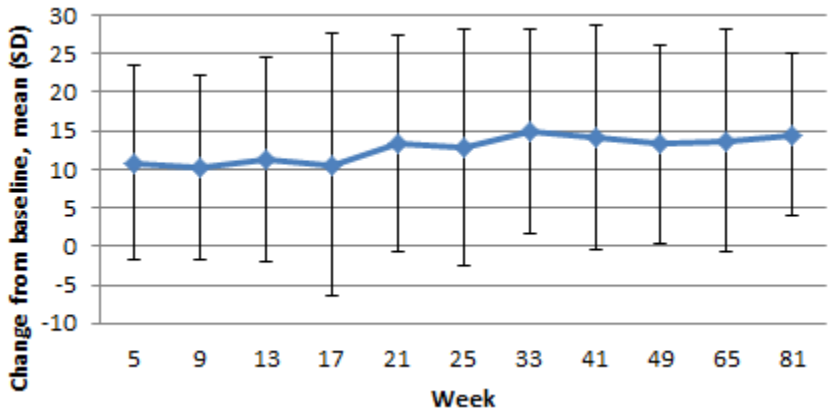
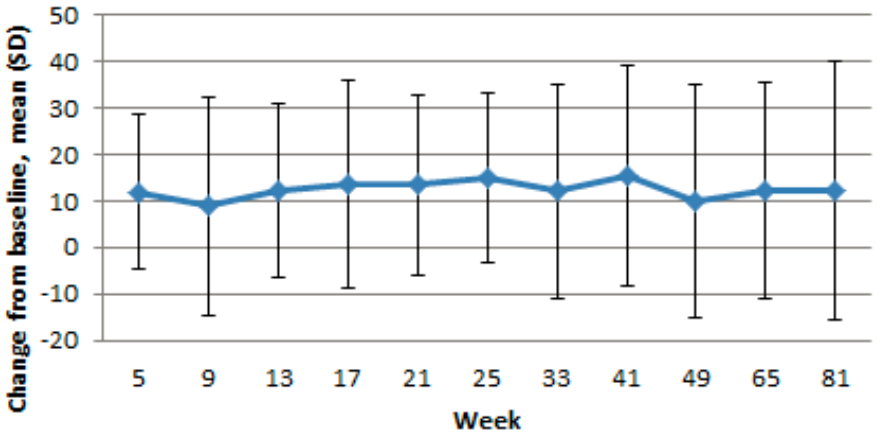


Figure 5. EQ-5D-5L - Visual Analogue Scale. PCYC-1127 (Arm C) [25]



Disease Symptoms

In study PCYC-1118E, CT-identified adenopathy (≥1.5 cm) was present in 37 patients at baseline. Serial imaging in 35 patients showed decreased or resolved adenopathy in 25 patients (68%), stable adenopathy in 9 patients (24%), and increased adenopathy in 1 patient (3%). Two patients discontinued the study before repeat imaging was required. Among 7 patients with CT-identified splenomegaly (≥15 cm), spleen size was decreased in 4 patients (57%), stable in 2 patients (29%), and could not be evaluated in 1 patient (14%) after elective splenectomy. Nine patients (14%), 3 of whom had anti-myelin-associated glycoprotein antibodies, received ibrutinib for progressive IgM-related peripheral sensory neuropathy. All 9 patients had a response, and subjective improvements in peripheral sensory neuropathy occurred in 5 patients and remained stable in 4 patients during the treatment course.[2]

Symptomatic hyperviscosity related to progressive disease that necessitated plasmapheresis prompted the initiation of ibrutinib in 4 patients. All had a response, and none required additional plasmapheresis by the end of cycle 2. One patient required plasmapheresis for acquired factor VIII deficiency. He had a response and did not require further plasmapheresis. The spontaneous bleeding events that prompted therapy also resolved, and he continued to receive ibrutinib.[2]

There were no data reported for disease symptoms for study PCYC-1127. There was no information reported in either trial on symptoms of headache, confusion, or shortness of breath.

Hemoglobin Levels
In study PCYC-1118E, median hemoglobin levels increased from 10.5 g/dL to 13.8 g/dL ($p<0.001$). In study PCYC-1127, median hemoglobin levels increased from 10.3 g/dL to 12.7 g/dL at week 49 (p value not reported).

Harms Outcomes

Serious Adverse Events
For study PCYC-1118E, serious adverse events were not reported in the main publication which included data with median treatment duration of 19.1 months.[2] Serious adverse events data were reported in the European Medicines Agency Assessment Report, which used data from an earlier data cutoff point (median treatment duration 11.7 months).[4] Twenty four patients (38%) experienced a serious adverse event.[4]

Serious adverse events occurring in study PCYC-1118E more than once included: thrombocytopenia (n=2), pyrexia (n=3), pneumonia (n=5). Serious adverse events that occurred once included: febrile neutropenia, neutropenia, atrial fibrillation, sinus tachycardia, chills, malaise, cholecystitis, cellulitis, herpes zoster, influenza, pleural infection, streptococcal endocarditis, upper respiratory tract infection, post-procedure hematoma, dehydration, B-cell lymphoma, myelodysplastic syndrome, syncope, pleural effusion.[4]

There was one death in study PCYC-1118E due to worsening of pleural effusion 22 days after the last dose of study drug, attributed to disease progression.[4]

In study PCYC-1127, serious adverse events occurred in 10 patients (32%) as summarized below.[5]

- Patient 1: neutropenia, thrombocytopenia
- Patient 2: upper respiratory tract infection
- Patient 3: gastrointestinal amyloidosis
- Patient 4: diarrhea, pneumonia, faecalith
- Patient 5: femoral fracture, renal cell carcinoma
- Patient 6: acute cholecystitis, ileus
- Patient 7: disease transformation to high grade DLBCL
- Patient 8: cellulitis(legs), prostatic abscess
- Patient 9: orchitis
- Patient 10: dehydration, syncope

Adverse Events

PCYC-1118E
All patients (n=63) experienced at least one adverse event in study PCYC-1118E. Half (n=32) of the patients in study PCYC-1118E experienced an adverse event rated grade 3 or higher.[4] The most common adverse events of grade 3 or 4 severity were neutropenia (n=11), thrombocytopenia (n=8), pneumonia (n=2), anaemia (n=2), atrial fibrillation (n=2), febrile neutropenia (n=2), pyrexia (n=2), abdominal pain (n=1), cellulitis (n=1), dehydration (n=1), hypertension (n=1).[4] The most common adverse events occurring in study PCYC-1118E are listed in Table 11.

In study PCYC-1118E, 44.4% of the patients experienced a haemorrhagic adverse event of any grade. At a median treatment duration of 19.1 months, there was one report of grade 3 hematoma (post procedural bleeding event). There were no grade 4 bleeding events.[25] The most common haemorrhagic events (≥5%) of any severity were epistaxis (19.0%), contusion (11.1%), and purpura (6.3%). One (1.6%) patient with von Willebrands disease experienced a major haemorrhagic event consisting of a non-fatal, Grade 3, post-procedural haematoma that was assessed as possibly related to study treatment; the event occurred in association with a bone marrow biopsy, reoccurred at a later time-point at the same site and ibrutinib was discontinued. All other haemorrhagic events in this study were Grade 1 or 2.[4]

Cardiac arrhythmias including atrial fibrillation (7.9%), sinus tachycardia and sinus bradycardia (1.6% each), were reported in the PCYC-1118E study. No cases of atrioventricular block or atrial flutter were reported. Atrial fibrillation was reported for 5 patients (three Grade 1-2 and two Grade 3). For 3 subjects, these events were reported as related to ibrutinib. Three out of the 5 patients had a prior history of atrial fibrillation. Discontinuation of ibrutinib therapy was reported for one patient with Grade-2 atrial fibrillation which worsened to Grade-3 atrial fibrillation and led to treatment discontinuation. [4]

Conjunctival hemorrhage and blurred vision occurred at a rate of 4.8% each in study PCYC-1118E. Retinal hemorrhage was reported for one patient. Each of these events was Grade 1-2 in severity. Retinal detachment, which occurred in two patients (3.2%), was of Grade-3 severity in one subject[4]

Table 11. Adverse events occurring in ≥10% of patients in study PCYC-1118E[4]

Adverse event, (n%)	N=63
Diarrhoea	23(36)
Neutropenia	16(25)
Nausea	13(21)
Fatigue	13(21)
Muscle spasms	13(21)
Upper respiratory tract infection	12(19)
Sinusitis	12(19)
Epistaxis	12(19)
Thrombocytopenia	11(18)
Anaemia	10(16)
Stomatitis	9(14)
Gastrointestinal reflux	8(13)
Arthropathy	8(13)
Dizziness	9(14)
Headache	8(13)
Cough	8(13)
Folliculitis	7(11)
Contusion	7(11)
Pruritis	7(11)
Rash	7(11)
Vomiting	6(10)

PCYC-1127

There were 30 patients (97%) who experienced an adverse event in study PCYC-1127 according to the most recent abstract.[5] Twenty patients (65%) experienced an adverse event with severity ≥3. Any-grade adverse events occurring at an incidence greater than

15% included diarrhea (42%); upper respiratory tract infections, hypertension, increased tendency to bruise (23% each); nausea, thrombocytopenia, neutropenia (19% each); and pyrexia, arthralgia, back pain (16% each). Common adverse events (≥ grade 3) included neutropenia (13%), hypertension (10%), anemia and diarrhea (6% each). There were no events of IgM flare or atrial fibrillation. There were no grade 3 or 4 bleeding events reported.

Withdrawals due to Adverse Events
In study PCYC-1118E, adverse events leading to ibrutinib discontinuation (each occurred once) included: atrial fibrillation, B-cell lymphoma, myelodysplastic syndrome, pleural effusion, post procedural haematoma, and thrombocytopenia.

In study PCYC-1127, one patient discontinued ibrutinib because of gastrointestinal amyloidosis and another patient discontinued ibrutinib because of diarrhea.[3]

6.4 Ongoing Trials

Table 12. Ongoing trials of Ibrutinib in Waldenström's Macroglobulinemia

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
NCT02604511[27] Site: Dana Farber Cancer Institute (sponsor) Phase II Study of Ibrutinib in Patients With Symptomatic, Previously Untreated WM, and Impact on Tumor Genomic Evolution Using Whole Genome Sequencing Open label N=30 Jan 2016 to Feb 2023	Key Inclusion Criteria: ECOG≤2 with normal organ and marrow function Key Exclusion Criteria: Prior systemic therapy for WM	Ibrutinib 420 mg daily in 4 week cycles, up to 48 cycles	Primary outcomes: Major Response Rate and Best Overall Response Rate at 2 years.
TrialTroveID-209601 Phase II Randomized Study[27]	Previously Untreated Waldenström's Macroglobulinemia (WM)	Bortezomib and Rituximab With or Without Ibrutinib	No other information is available for this study.

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review.

8 COMPARISON WITH OTHER LITERATURE

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

Following discussion with the Clinical Guidance Panel, a literature search was performed to identify relevant literature providing data on relevant comparator drugs for treatment of adults with Waldenström's macroglobulinemia who have received at least one prior therapy. A search was conducted for systematic reviews and network meta analyses of ibrutinib in WM. There were very few published, high quality, up-to-date systematic reviews identified. One recent review was identified within the European Medicines Agency 2015 Assessment Report for ibrutinib in WM.[4] Within this review, a summary is presented providing context for the results from studies PCYC 1118E and PCYC-1127, as compared to selected trial data from single-agent studies in WM. Data collection processes for these studies was not described in the European Medicines Agency report, and therefore, the pCODR Methods was not able to critically appraise the methodology used to select studies for this summary.

Table 13. Summary of selected WM studies (single agent studies)[4]

Agent Primary author	Population/N	Median Prior Therapies n (range)	Characteristics at Baseline						Major RR (≥PR) (%)	ORR (≥MR) (%)	DOR (months)	Median PFS/TTP (months) All-treated
			Age (med)	% male	IgM (g/L)	Hg (g/L)	Platelets (10^9/L)	β2-m (mg/L)				
Ibrutinib **Study 1118E**	R/R (n=63)	2 (1-11)	63	76.2	34.9	10.5	11.1% <100	3.9	69.8	87.3	Med. not reached; 18-mo. DOR rate: 86.1%	Med. not reached; 18-mo. PFS rate: 83.2%
Rituximab												
Dimopoulos 2002	R/R (n=12) TN (n=15)	26% ≥3 prior	72	67%	33.5	44% <100	15% <100	37% ≥4.0	44	NR	NR	16 (TTP)
Gertz 2004	TN (n=34) R/R (n=35)	0 NR	68.6	52%	44	9.6	197.5	3.5	35.3 20	52.9 51.4	27 NR	NR
Treon 2005	TN (n=12) R/R (n=17)	1 (0-2)	65	NR	35.6	NR	185	NR	48.3	65.5	18+ (≥PR) 20+ (≥MR)	17 (TTP) 14 (TTP)
Chlorambucil												
LeBlond 2013[c]	TN (n=170)	0	67.8	67%	27.4	9.9	204	3.6	35.9	NR	21.3	27.1 (PFS)
Fludarabine												
LeBlond 2001	R/R (n=46)	1 (no range)[a]	64	73.9%	36.3	107	188	2.6	30	NR	19	NR-
LeBlond 2013[c]	TN (n=169)	0	68.2	67%	28.0	9.9	229	3.2	45.6	NR	38.5	37.8 (PFS)
Cladribine												
Dimopoulos 1995	R/R (n=46)	≥1	60	45.6%	42% >20	52% <100	NR	42% ≥4.0	43	NR	NR	12 (PFS)
Bortezomib												
Chen 2007	TN (n=12) R/R (n=15)	0 2 (1-2)	65	52%	37.6	10.8	259	NR	44	78	10 (1.4-14.9)	16.3 (PFS)
Treon 2007	TN (n=1) R/R (n=26)	2 (0-3)	62	66.7%	46.6	NR	225	NR	48.1	85	NR	6.6 (TTP)

DOR=duration of response; Hg=hemoglobin; IgM=immunoglobulin; med=median; MR=minor response; NR=not reported; ORR=overall response rate; PFS=progression free survival; PR=partial response; R/R=relapsed/refractory; RR=response rate; TN=treatment naïve; TTP=time to progression

[a] Subjects in this study had to be in first relapse or primary refractory

[b] No longer commercially available in the EU for Hodgkin's lymphoma

[c] Baseline characteristics represent all subjects in the treatment arm, not exclusively subjects with WM

Chakraborty and colleagues recently published a non-systematic review of emerging therapeutic options for WM/lymphoplasmacytic lymphoma(LPL).[28] They provided a brief summary of the available data, including bendamustine, which was a comparator of interest in the protocol for this report. Chakraborty et al commented that bendamustine, was studied in WM/LPL in conjunction with rituximab (B-R), both in treatment naıve and in relapsed/refractory settings.[12,18,29] The summary included a study of B-R in 30 patients with relapsed/refractory WM that reported an ORR of 83.3%, all being major responses, with prolonged myelosuppression seen in patients with prior nucleoside analog therapy.[18] There was also a study that compared B-R versus R-CHOP using a randomized Phase II noninferiority design as frontline therapy for indolent lymphoma and showed a superior median PFS with B-R in the WM/LPL subgroup (69.5 vs 28.1 months with B-R and R-CHOP, respectively; p = 0.0033).[12] Another study of B-R as a salvage regimen in relapsed/refractory WM showed an ORR and major response rate of 80.2 and 74.6%, respectively, with grade 3/4 neutropenia occurring in only 13% of patients and none developing large cell transformation or myelodysplastic syndrome over a median follow-up of 19 months."[29]

9 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 Waldenström's macroglobulinemia. 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.

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 medical oncologists .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

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials March 2016; Embase 1974 to 2016 May 02; Epub Ahead of Print, 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 JNJ02 or PC32765 or PC 32765 or PCI32765 or PCI 32765 or 1X70OSD4VX or 936563-96-1).ti,ab,ot,kf,kw,hw,rn,nm.	2490
2	Waldenstrom Macroglobulinemia/ or (waldenstrom* or waldenstroem*).ti,ab,kf,kw.	12719
3	(macroglobulinemia* or macroglobulinaemia* or macro globulinemia* or macro globulinaemia* or macroglobinemia* or macroglobinaemia* or macrocryoglobulinaemia* or macrocryoglobulinemia*).ti,ab,kf,kw.	8483
4	(Plasmacytoid adj5 lymphocytic adj5 lymphoma*).ti,ab,kf,kw.	92
5	(lymphoplasmacytic adj3 lymphoma*).ti,ab,kf,kw.	1476
6	or/2-5	14363
7	1 and 6	173
8	7 use ppez	48
9	7 use cctr	1
10	*ibrutinib/	601
11	(Imbruvica* or ibrutinib* or CRA032765 or "CRA 032765" or "JNJ 02" or JNJ02 or PC32765 or PC 32765 or PCI32765 or PCI 32765 or 1X70OSD4VX).ti,ab,kw.	1809
12	or/10-11	1835

13	exp Waldenstrom Macroglobulinemia/ or (waldenstrom* or waldenstroem*).ti,ab,kw.	13350
14	(macroglobulinemia* or macroglobulinaemia* or macro globulinemia* or macro globulinaemia* or macroglobinemia* or macroglobinaemia* or macrocryoglobulinaemia* or macrocryoglobulinemia*).ti,ab,kw.	8467
15	(Plasmacytoid adj5 lymphocytic adj5 lymphoma*).ti,ab,kw.	92
16	(lymphoplasmacytic adj3 lymphoma*).ti,ab,kw.	1467
17	or/13-16	14796
18	12 and 17	158
19	18 use oemezd	111
20	8 or 9 or 19	160
21	limit 20 to english language	148
22	remove duplicates from 21	118

2. Literature search via PubMed

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

Search	Query	Items found
#9	Search #8 AND publisher [sb]	4
#8	Search #1 AND #7	47
#7	Search #2 OR #3 OR #4 OR #5 OR #6	6631
#6	Search lymphoplasmacytic [tiab] AND lymphoma* [tiab]	786
#5	Search Plasmacytoid [tiab] AND lymphocytic [tiab] AND lymphoma* [tiab]	121

Search	Query	Items found
#4	Search macroglobulinemia*[tiab] OR macroglobulinaemia*[tiab] OR macro globulinemia*[tiab] OR macro globulinaemia*[tiab] OR macroglobinemia*[tiab] OR macroglobinaemia*[tiab] OR macrocryoglobulinaemia*[tiab] OR macrocryoglobulinemia*[tiab]	3758
#3	Search waldenstrom* [tiab] OR waldenstroem* [tiab]	3377
#2	Search Waldenstrom Macroglobulinemia [mh]	4923
#1	Search Imbruvica OR ibrutinib OR CRA032765[tiab] OR "CRA 032765"[tiab] OR "JNJ 02"[tiab] OR JNJ02[tiab] OR PC32765[tiab] OR "PC 32765"[tiab] OR PCI32765[tiab] OR "PCI 32765"[tiab] OR 1X70OSD4VX[tiab] OR "936563-96-1"[tiab]	567

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/

   Search: Waldenstrom's Macroglobulinemia | ibrutinib OR imbruvica

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

   Search: ibrutinib; Imbruvica

   Select international agencies including:

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

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

   Search: ibrutinib, Imbruvica

   Conference abstracts:

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

American Society of Hematology (ASH)
http://www.hematology.org
Retrieved via Embase, except one poster from 2013

Search: ibrutinib, Imbruvica, Waldenstrom's macroglobulinemia

APPENDIX B: DETAILED METHOLODGY OF LITERATURE REVIEW

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-) with Epub ahead of print, in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (March 2016) 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 Waldenstrom's macroglobulinemia.

No filters were applied to limit the retrieval by study type. The search was limited to English-language documents, but not limited by publication year.

The search is considered up to date as of August 2, 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. Conference abstracts were retrieved through a search of the Embase database. Abstracts from the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) were searched manually, limited to the past five years, for conference years not available in Embase at the time of the database search. 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.

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. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

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.

Data Analysis

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

Writing of the Review Report

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

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

REFERENCES

1. PrImbruvica® (ibrutinib) capsules: 140 mg [product monograph]. Toronto: Janssen Inc.; 2016 Jul 19.

2. Treon SP, Tripsas CK, Meid K, Warren D, Varma G, Green R, et al. Ibrutinib in previously treated Waldenstrom's macroglobulinemia. N Engl J Med [Internet]. 2015 Apr 9 [cited 2016 May 16];372(15):1430-40. Available from: http://www.nejm.org/doi/full/10.1056/NEJMoa1501548#t=article

3. Dimopoulos MA, Trotman J, Tedeschi A, Matous J, Macdonald D, Tam C, et al. Ibrutinib therapy in rituximab-refractory patients with Waldenström's macroglobulinemia: initial results from an international, multicenter, open-label phase 3 substudy (iNNOVATE™). Poster presented at: 57th American Society of Hematology Annual Meeting and Exposition. 2015; Dec 5-8; Orlando (FL).

4. Committee for Medicinal Products for Human Use (CHMP). Imbruvica [Internet]. London: European Medicines Agency; 2015 May 21. [cited 2016 May 26]. (EPAR assessment report). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/003791/WC500191947.pdf

5. Dimopoulos MA, Trotman J, Tedeschi A, Matous J, Macdonald J, Tam C, et al. Single-agent ibrutinib in rituximab-refractory patients with Waldenstrom's macroglobulinemia (WM): updated results from a multicenter, open-label phase 3 substudy (iNNOVATE™). Poster presented at: European Hematology Association (EHA) Annual Congress; 2016; Jun 9-12; Copenhagen.

6. CADTH pCODR Expert Review Committee (pERC) final recommendation: bendamustine hydrochloride (Treanda) [Internet]. Ottawa: CADTH; 2012 Nov 29. [cited 2016 Aug 10]. Available from: https://www.cadth.ca/sites/default/files/pcodr/pcodr-treandanhl-fn-rec.pdf

7. Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. World health organization classification of tumours: pathology and genetics of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon (France): IARC Press; 2001. 352 p.

8. Treon SP, Cao Y, Xu L, Yang G, Liu X, Hunter ZR. Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenstrom macroglobulinemia. Blood [Internet]. 2014 May 1 [cited 2016 Aug 9];123(18):2791-6. Available from: http://www.bloodjournal.org/content/123/18/2791.long

9. Dimopoulos MA, Kastritis E, Owen RG, Kyle RA, Landgren O, Morra E, et al. Treatment recommendations for patients with Waldenstrom macroglobulinemia (WM) and related disorders: IWWM-7 consensus. Blood [Internet]. 2014 Aug 28 [cited 2016 Aug 9];124(9):1404-11. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4148763

10. Vos JM, Minnema MC, Wijermans PW, Croockewit S, Chamuleau ME, Pals ST, et al. Guideline for diagnosis and treatment of Waldenstrom's macroglobulinaemia. Neth J Med. 2013 Mar;71(2):54-62.

11. Dimopoulos MA, Anagnostopoulos A, Kyrtsonis MC, Zervas K, Tsatalas C, Kokkinis G, et al. Primary treatment of Waldenstrom macroglobulinemia with dexamethasone, rituximab, and cyclophosphamide. J Clin Oncol. 2007 Aug 1;25(22):3344-9.

12. Rummel MJ, Niederle N, Maschmeyer G, Banat GA, von Grunhagen U, Losem C, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients

with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet. 2013 Apr 6;381(9873):1203-10.

13. Treon SP, Ioakimidis L, Soumerai JD, Patterson CJ, Sheehy P, Nelson M, et al. Primary therapy of Waldenstrom macroglobulinemia with bortezomib, dexamethasone, and rituximab: WMCTG clinical trial 05-180. J Clin Oncol [Internet]. 2009 Aug 10 [cited 2016 Aug 9];27(23):3830-5. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2727288

14. Buske C, Hoster E, Dreyling M, Eimermacher H, Wandt H, Metzner B, et al. The addition of rituximab to front-line therapy with CHOP (R-CHOP) results in a higher response rate and longer time to treatment failure in patients with lymphoplasmacytic lymphoma: results of a randomized trial of the German Low-Grade Lymphoma Study Group (GLSG). Leukemia. 2009 Jan;23(1):153-61.

15. Olszewski AJ, Treon SP, Castillo JJ. Evolution of Management and Outcomes in Waldenstrom Macroglobulinemia: A Population-Based Analysis. Oncologist. 2016 Jul 29.

16. Morel P, Duhamel A, Gobbi P, Dimopoulos MA, Dhodapkar MV, McCoy J, et al. International prognostic scoring system for Waldenström macroglobulinemia. Blood [Internet]. 2009 [cited 2016 Aug 9];113(18):4163-70. Available from: http://www.bloodjournal.org/content/113/18/4163

17. Rummel M, Kaiser U, Balser C, Stauch M, Brugger W, Welslau M, et al. Bendamustine plus rituximab versus fludarabine plus rituximab for patients with relapsed indolent and mantle-cell lymphomas: a multicentre, randomised, open-label, non-inferiority phase 3 trial. Lancet Oncol. 2016 Jan;17(1):57-66.

18. Treon SP, Hanzis C, Tripsas C, Ioakimidis L, Patterson CJ, Manning RJ, et al. Bendamustine therapy in patients with relapsed or refractory Waldenstrom's macroglobulinemia. Clin Lymphoma Myeloma Leuk. 2011 Feb;11(1):133-5.

19. Treon SP, Tripsas CK, Meid K, Warren D, Varma G, Green R, et al. Ibrutinib in previously treated Waldenstrom's macroglobulinemia. Supplementary appendix. N Engl J Med [Internet]. 2016 Apr 9 [cited 2016 May 25];372(15). Available from: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1501548/suppl_file/nejmoa1501548_appendix.pdf

20. Treon SP, Tripsas CK, Meid K, Warren D, Varma G, Green R, et al. Ibrutinib in previously treated Waldenstrom's macroglobulinemia. Protocol. N Engl J Med [Internet]. 2016 Apr 9 [cited 2016 May 25];372(15). Available from: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1501548/suppl_file/nejmoa1501548_protocol.pdf

21. Treon SP. Ibrutinib (PCI-32765) in Waldenstrom's macroglobulinemia. 2012 May 17 [cited 2016 May 25; last updated 2015 Nov 11]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT01614821 Identifier: NCT01614821.

22. Dimopoulos MA, Leleu X, Matous J, Macdonald D, Trotman J, Oriol A, et al. A randomized, double-blind, placebo-controlled, phase 3 study of rituximab with or without ibrutinib for Waldenstrom's macroglobulinemia (PCYC-1127-CA). Poster presented at: ASCO Annual Meeting; 2016; May 29 - Jun 2; Chicago (IL).

23. Dimopoulos MA, Trotman J, Tedeschi A, Matous J, Macdonald D, Tam C, et al. Ibrutinib therapy in rituximab-refractory patients with Waldenström's macroglobulinemia: initial results from an

international, multicenter, open-label phase 3 substudy (iNNOVATE™) [abstract]. Blood. 2015;126(23):2745. (Presented at American Society of Hematology 57th Annual Meeting and Exposition; 2016 Dec 5-8; Orlando (FL)).

24. Pharmacyclics. Ibrutinib with rituximab in adults with Waldenström's macroglobulinemial. 2014 Jun 9 [cited 2016 May 25; last updated 2016 Apr 14]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/study/NCT02165397 Identifier:NCT02165397.

25. Janssen Inc. response to checkpoint clinical questions on the pCODR submission of ibrutinib (Imbruvica®) for the treatment of patients with Waldenström's macroglobulinemia who have received at least one prior therapy **[CONFIDENTIAL]**. Toronto: Janssen Inc.; 2016 Jun 23.

26. Kyle RA, Treon SP, Alexanian R, Barlogie B, Bjorkholm M, Dhodapkar M, et al. Prognostic markers and criteria to initiate therapy in Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. Semin Oncol. 2003 Apr;30(2):116-20.

27. pan-Canadian Oncology Drug Review manufacturer submission: Imbruvica (ibrutinib) for Waldenström's macroglobulinemia, 140 mg capsules. Company: Janssen Inc. Toronto: Janssen Inc.; 2016 Apr 21.

28. Chakraborty R, Kapoor P, Ansell SM, Gertz MA. Emerging therapeutic options for Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma. Expert Rev Anticancer Ther. 2015;15(10):1143-56.

29. Tedeschi A, Picardi P, Ferrero S, Benevolo G, Margiotta CG, Varettoni M, et al. Bendamustine and rituximab combination is safe and effective as salvage regimen in Waldenstrom macroglobulinemia. Leuk Lymphoma. 2015;56(9):2637-42.