pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug:
Ibrutinib (Imbruvica)

Submitted Funding Request:
For the treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) with or without deletion 17p who have received at least one prior therapy and are not considered appropriate for treatment or re-treatment with a purine analog (e.g., fludarabine)

Submitted By: Janssen Inc.	**Manufactured By:** Janssen Inc.
NOC Date: November 17, 2014	**Submission Date:** August 15, 2014
Initial Recommendation: January 9, 2015	**Final Recommendation:** March 5, 2015

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding ibrutinib (Imbruvica) conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) who have received at least one prior therapy and are considered inappropriate for treatment or retreatment with a fludarabine-based regimen. The Committee was satisfied that there is a net clinical benefit of ibrutinib based upon a meaningful improvement in progression-free survival, and one year overall survival rate compared to ofatumumab, and high patient need for effective treatments. However, the Committee noted that ibrutinib could not be considered cost-effective at the submitted price and the resulting Economic Guidance Panel's range of estimated incremental cost-effectiveness ratios.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-effectiveness
Given that pERC was satisfied that there is a net clinical benefit of ibrutinib in patients with relapsed and/or refractory chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of ibrutinib to an acceptable level.

Tumour groups to help develop guidelines on appropriate definition of refractory disease
pERC noted that patients developing refractory disease may have a long period of progression-free survival from the time of first line treatment to progression. pERC considered that the definition of refractory disease used in the pivotal trial for ibrutinib involved a prolonged period (disease progression after a progression free interval of 3 years) and may not reflect the common clinical practice in Canada. pERC agreed that a definition for refractory disease, based upon input from provincial tumour groups, would be helpful in determining clinically reasonable eligibility parameters for ibrutinib.

Expansion in scope of review
pERC acknowledged that the submitter's funding request and Health Canada (HC) approved indication for ibrutinib differ in that the HC approved indication includes first line patients with del(17)p mutation. The scope of the current review, however, only covered patients who have relapsed on at least one previous line of therapy. pERC was, therefore, unable to comment on the use of ibrutinib in the first line del(17p) mutation patient population. pERC agreed that a recommendation in the first line setting would require a submission with supportive clinical and economic information.

SUMMARY OF pERC DELIBERATIONS

pERC's Deliberative Framework for drug funding recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

Chronic lymphocytic leukemia (CLL) is a common leukemia with a long natural history. pERC noted that the management of small lymphocytic lymphoma (SLL) is identical to CLL as they are generally considered to be the same disease. While there is an increasing number of options for frontline treatment of CLL, there is no standard of care for patients who have refractory or relapsed disease. The outlook of some subgroups of patients with relapsed CLL, including those who are frail or have high risk disease (chromosome 17p13.1 deletion, del(17p)) is especially poor. Current treatment options for relapsed or refractory CLL/SLL include retreatment with regimens from earlier lines of therapy with patients generally receiving multiple lines of treatment and experiencing increasingly short time intervals to disease progression. Generally these treatments also have increased toxicity and reduced anti-tumour activity as the disease becomes more difficult to treat as it progresses. pERC, therefore, agreed that there is a need for more effective and tolerable treatment options for patients with a poor prognosis.

pERC deliberated upon one randomized controlled trial, RESONATE (Byrd 2014), that evaluated ibrutinib compared with ofatumumab in patients with CLL/SLL who had relapsed or refractory disease, had received at least one previous therapy, and for whom treatment or retreatment with purine analog based therapy was considered inappropriate. pERC considered that the RESONATE study demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) in favour of ibrutinib. Improvements in PFS were seen across all subgroups including patients with del(17)p mutation. One year overall survival (OS) rates were also improved in favour of the ibrutinib arm. pERC discussed the magnitude of PFS and OS benefit with ibrutinib and noted that, while the medians have not been reached for these outcomes, ibrutinib demonstrated a clinically meaningful benefit in patients who currently only have treatment options associated with high toxicity and limited effectiveness. pERC, however, agreed that longer follow-up data will reduce the uncertainty in the magnitude of clinical benefit. Quality of life was reported in the RESONATE study and a clinically meaningful improvement in both fatigue measures and global health scores occurred in more patients receiving ibrutinib compared to those receiving ofatumumab. pERC noted the concordance of these results with the input from the patient advocacy groups and concluded that ibrutinib may improve patient's quality of life. pERC discussed the toxicity profile of ibrutinib and noted that adverse events observed in the RESONATE study were generally manageable but more common in the ibrutinib arm. Finally, pERC discussed the use of ofatumumab as the comparator arm in the RESONATE study noting that ofatumumab is not available in the relapsed or refractory setting in Canada. pERC concluded that the magnitude of clinical benefit of ibrutinib as compared to appropriate comparators in the Canadian setting remains unknown. The Committee, however, acknowledged that currently available treatment options do not generally provide meaningful benefit and are associated with substantial toxicity. After deliberating on all of these factors, pERC concluded that there is a net clinical benefit associated with ibrutinib.

pERC further considered input from three patient advocacy groups with experience using ibrutinib. pERC noted that patients valued having an additional treatment option that provided longer remission, improvement in quality of life, and an improved toxicity profile. Patients who had direct experience with ibrutinib reported a rapid and dramatic improvement in quality of life and the ability to return to normal life. pERC noted this perceived improvement in quality of life to be an important outcome as patients in the relapsed or refractory setting are generally older, more frail, and may have undergone several lines of therapy. Having noted that debilitating fatigue is a concern to patients, pERC agreed that a reduction in fatigue, as well as a decrease in size of enlarged lymph nodes and a drop in white blood cell counts in more than half of patients using ibrutinib was an important benefit to patients. Patients also reported that the toxicity associated with ibrutinib was mild and easily managed. Overall, pERC agreed that ibrutinib aligned with patient values. pERC noted the breadth and depth of the patient input, which was

well structured and organized, provided pERC with a much deeper understanding of patients' experiences with relapse or refractory CLL/SLL and its treatment.
pERC deliberated upon the cost effectiveness of ibrutinib compared with a treatment mix reflecting different local standards of care and noted there is currently no single standard of care in Canada in this clinical setting. pERC accepted the Economic Guidance Panel's (EGP) wide range of estimates and noted several limitations in the submitted analysis. pERC noted that the clinical data for overall survival estimates were based upon a short (9.4 month) follow up period in the trial. pERC accepted the EGP's use of the upper and lower bounds of the confidence interval for the hazard ratio (HR) in the overall survival estimates to account for the uncertainty in the magnitude of clinical benefit. pERC noted that in a disease with a long natural history, the EGP's reduction of the time horizon to 5 years was appropriate to further account for the uncertainty introduced by the immaturity of the clinical data. pERC also agreed that the shortened time horizon accounts for the lack of inclusion of subsequent therapies, which would affect costs and clinical effects over a longer time period. The Committee, therefore, agreed that the immaturity of the clinical data inputs introduced a large amount of uncertainty into the cost-effectiveness estimates provided by the submitter and re-analyses provided by the EGP and concluded that the true estimate of the ICER is likely in the upper range. Upon reconsideration of the initial recommendation, pERC noted feedback from the manufacturer regarding the use of a 5 year time horizon by the EGP. pERC confirmed that the shortened time horizon attempted to account for multiple factors, such as the immaturity of the clinical data, which created uncertainty in the extrapolation of the benefits and costs of ibrutinib over time. These also included the lack of inclusion of subsequent therapies; structural limitations within the model resulting in inability to separately account for post progression survival gains; and the uncertainty in inputs used for the comparator arm. pERC also noted that the price of ibrutinib is very high and that treatment would be continued until disease progression or unacceptable toxicity, which would contribute to total cost. While longer follow up data will help determine the median progression free survival and median treatment duration, pERC agreed that the cost-effectiveness of ibrutinib will be substantially impacted by greater gains in PFS, as treatment is given until disease progression. pERC noted that the price of ibrutinib would need to be reduced substantially in order for it to be considered cost-effective. pERC discussed the standard of care treatment mix used as the comparator arm in the cost-effectiveness analysis and noted that it does not reflect Canadian clinical practice. While acknowledging that there is currently no standard of care for patients with relapsed or refractory CLL/SLL and that ibrutinib provides a clinically and statistically significant benefit to patients, pERC was unable to determine the cost-effectiveness of ibrutinib as compared to other relevant comparators in the Canadian setting. Overall, pERC accepted the EGP's range of estimates and concluded that ibrutinib could not be considered cost-effective at the submitted price.

pERC discussed the feasibility of implementing a funding recommendation for ibrutinib. pERC noted that the current number of patients with relapsed or refractory disease is expected to be larger than the number of patients eligible for treatment in the first line setting as there is a large prevalent population due to the long course of this disease compared to other cancers. Additionally, pERC agreed that treatment duration and the cost of ibrutinib may have a considerable budgetary impact and provinces will need to consider pricing arrangements and or cost structures to improve the affordability of ibrutinib during implementation. pERC noted that the RESONATE study included patients who have relapsed following several previous lines of therapy and agreed that ibrutinib should be used in patients with relapsed or refractory disease regardless of the number of previous lines of therapy.

Del(17)p testing is not available in all jurisdictions. However, pERC does not expect the availability of testing to be an issue for jurisdictions since ibrutinib demonstrates efficacy in all subgroups, including del(17)p patients. pERC also noted that the use of ibrutinib in the first line setting or for other indications such as mantle cell lymphoma or other lymphomas was outside the scope of this current review and would require a separate submission to pCODR. Upon reconsideration of the Initial recommendation, pERC noted feedback from the Provincial Advisory Group regarding the use of ibrutinib in the front line setting. pERC acknowledged that the Health Canada approval for ibrutinib included first line patients with a del(17)p mutation, but noted that the scope of the current review did not include patients in the first line setting. pERC re-iterated that a recommendation by the Committee on the use of ibrutinib in the first line setting would need to be informed by supportive clinical and economic information.

EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- input from three patient advocacy groups (CLL Patient Advocacy Group, The Leukemia & Lymphoma Society of Canada, and Lymphoma Canada)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- input from pCODR's Provincial Advisory Group.
- three patient advocacy groups (CLL Patient Advocacy Group, The Leukemia & Lymphoma Society of Canada, and Lymphoma Canada)
- the Submitter (Janssen Inc.)

The pERC initial recommendation was to recommend funding ibrutinib (Imbruvica) conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with or without del(17)p who have received at least one prior therapy and are considered inappropriate for treatment or retreatment with a fludarabine-based regimen.

Feedback on the pERC Initial Recommendation indicated that the patient advocacy group and pCODR's Provincial Advisory Group agreed with the initial recommendation while the manufacturer agreed in part with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of ibrutinib (Imbruvica) as compared to an appropriate comparator in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with or without del(17)p who have received at least one prior therapy and are not considered appropriate for treatment or retreatment with a purine analog.

Studies included

The pCODR systematic review included one open-label randomized controlled trial, RESONATE (Byrd 2014), comparing ibrutinib (n=195) to ofatumumab (n=196) in patients with CLL/SLL who had relapsed or refractory disease, had received at least one previous therapy, and for whom treatment or retreatment with purine analog based therapy was considered inappropriate. Patients for whom therapies with a purine analog based therapy was considered inappropriate by the investigators included those with short progression-free interval of less than 3 years after chemo immunotherapy or coexisting illnesses, an age of 70 years or more, or a chromosome 17p13.1 deletion [del(17)p]. pERC discussed the progression-free interval period of less than 3 years that was used in the trial and agreed that this criterion may not align with Canadian clinical practice. The committee agreed that input from provincial tumour groups should be used to define patients with refractory disease and to determine eligibility for treatment with ibrutinib. Patients in the ofatumumab arm were allowed to cross over to ibrutinib following progression of disease.

pERC discussed the appropriateness of ofatumumab as the comparator arm and noted that it is currently not available in the relapsed or refractory CLL/SLL clinical setting in Canada. pERC is, therefore, unable to comment on the comparative efficacy of ibrutinib to other treatment options available to Canadian patients. However, pERC also noted that there is currently no accepted standard of care in this setting and considered that current treatment options do not generally provide meaningful benefit and have substantial toxicity.

Patient populations: Treatment until progression

Patient characteristics were balanced between arms. Differences were noted for the presence of bulky disease of 5 cm or more (64% vs. 52% in the ibrutinib vs. ofatumumab arms, respectively) which could bias results against ibrutinib. Differences were also noted in the median time from last therapy (8 vs. 12 months in the ibrutinib vs. ofatumumab arms, respectively). Among patients enrolled in the trial, 53% and 46% of patients received 3 or more previous treatments in the ibrutinib and ofatumumab arms, respectively. pERC, therefore, agreed that ibrutinib should be administered in patients with relapsed or refractory disease regardless of the number of previous lines of therapy patients have failed. Ibrutinib was administered until disease progression or unacceptable toxicity. pERC noted that the median duration of treatment is currently unknown and follow up data from the RESONATE study will be important to make this determination.

Key efficacy results: Statistically significant improvement in PFS and meaningful improvement in one year OS rate

The key efficacy outcome deliberated on by pERC was progression-free survival (PFS). Ibrutinib demonstrated a statistically significant improvement in PFS compared to ofatumumab (hazard ratio (HR) 0.22, 95%CI: 0.15-0.32, p<0.001). The improvement in PFS was seen in all subgroups examined, including patients with del(17)p of whom 83% were alive and progression-free at six months, compared with 49% with this deletion in the ofatumumab group. While medians for overall survival (OS) have also not been reached, ibrutinib significantly improved the rate of overall survival (HR=0.43, 95%CI: 0.24-0.79, p=0.005). One year OS rate was 90% vs. 81% in the ibrutinib vs. ofatumumab arms, respectively. pERC discussed the median follow up period of 9.4 months in the trial and agreed there remains considerable uncertainty in the magnitude of clinical benefit with ibrutinib as the median PFS and OS have not been reached. While acknowledging that there is a net clinical benefit with ibrutinib as demonstrated by the statistically significant and clinically meaningful PFS and OS benefit in a patient population that has limited effective treatment options, pERC agreed that longer follow-up data should be collected to reduce the uncertainty in the magnitude of clinical benefit.

Quality of life: Clinically meaningful improvement in QoL

pERC noted that three questionnaires were used to assess the quality of life (QoL) of patients in the RESONATE study. A clinically meaningful improvement in both fatigue measures and global health scores occurred in more patients receiving ibrutinib compared to those receiving ofatumumab. However, pERC noted that the trial compared ibrutinib to ofatumumab, a treatment option that is not available to patients with relapsed or refractory CLL/SLL in Canada. pERC was therefore unable to determine the potential QoL difference between ibrutinib and other currently available treatment options for patients with relapsed or refractory CLL/SLL.

pERC agreed that QoL is an important outcome for patients as input was received from a large number of patients who had direct experience with ibrutinib. pERC discussed the quality of life data from the trial and the experience of patients provided through the patient input. pERC noted the dramatic improvements experienced by patients providing input. While factors such as differences in the drug used in the comparator arm may contribute to trial results which were less dramatic, pERC agreed that patients' experiences with ibrutinib were generally positive. pERC also noted the Clinical Guidance Panel's opinion for the greater difference in QoL in Canada as the comparator used in the RESONATE trial, ofatumumab, has fewer toxic side effects than the other second-line options for CLL currently licensed for use in Canada.

Safety: Increased toxicity with ibrutinib but manageable

pERC reviewed the toxicity profile of ibrutinib and concluded that the toxicities were more common with ibrutinib, but still generally manageable. Treatment related adverse events leading to death were reported in 6% vs. 8% of patients in the ibrutinib and ofatumumab arms, respectively. Overall serious adverse events and grade ≥3 adverse events occurring in at least 10% of patients were reported more frequently in the ibrutinib arm. Discontinuation of treatment because of adverse events did not differ between groups at 4%. These events were mostly infections. pERC also noted that input provided from patients who had direct experience with ibrutinib indicated that adverse events were generally easily resolved, allowing patients to continue their treatment with ibrutinib.

Need: Effective and more tolerable option

CLL represents the most common leukemia in western countries and is characterized by a long natural history with a median survival from diagnosis of 10 or more years. While there are more options for

upfront treatment of CLL/SLL, there is no standard of care for older or less fit patients who have refractory/ relapsed disease. Options for patients with relapsed/refractory disease include retreatment with regimens from earlier lines of therapy in patients who had sustained responses without toxicity. In general, treatment decisions for this group of patients take into consideration age, comorbidities, and response to prior therapy. Elderly patients may benefit from chlorambucil or fludarabine, especially if they have not been exposed to these agents previously. Newer monoclonal CD20 antibodies such as ofatumumab and obinutuzumab may result in improved outcomes for patients with relapsed or refractory CLL. However, they are not available to Canadian patients outside of compassionate access programs and/or clinical trials. pERC also noted that treatment options for relapsed or refractory disease tend to have increased toxicity and reduced anti-tumour activity. The outlook of some subgroups of patients with relapsed CLL, including those who are frail and those that have high risk disease (del(17)p) is especially poor. pERC noted that ibrutinib demonstrated efficacy in all subgroups of patients included in the RESONATE trial, including those with the del(17)p mutation. pERC agreed that ibrutinib fills a therapeutic gap by providing an effective oral treatment option with a manageable toxicity profile. While appropriate comparative data are not available with other treatment options used in the Canadian setting, pERC was confident of the net clinical benefit of ibrutinib in patients with relapsed or refractory CLL/SLL.

PATIENT-BASED VALUES

Values of patients with CLL/SLL: Quality of life, disease symptom management

pERC deliberated upon input from three patient advocacy groups on ibrutinib. Patient advocacy group input indicated that patients with CLL/SLL may experience prolonged periods of "watch and wait" while others require treatment right away. In patients with CLL, fatigue, increased white blood cell count, enlarged lymph nodes, and night sweats were noted to be the most frequently occurring disease signs and symptoms experienced by patients. Stress, anxiety and depression were also noted as psychological symptoms that have the most significant impact on patient's quality of life.

pERC noted that patients understand that all current treatment options have some degree of side effects noting both the benefits (disease control), and the risks of disease progression, adverse events and dose interruptions due to side effects associated with current treatment options. The most common treatment related side effects experienced with current therapies were fatigue and low red blood counts. Input from caregivers discussed the impact of CLL on caregiver's quality of life both in terms of the stress associated with watching a loved one cope with the illness and the financial/social impact of additional responsibilities in caring for an ill loved one.

Patient values on treatment: Treatment choice, remission, reduced toxicity

pERC discussed that patients' valued having additional choice in therapy with the majority stressing the importance of choosing a therapy based on its side effect profile. Patients expressed a need for longer remissions with less toxicity, as well as, the importance of having treatment choices that offer disease control and improved quality of life. Patients expressed a need for treatment that offers ease of use relative to other treatments. Patients also noted that current treatment options for relapsed disease tend to have increased toxicity and reduced anti-tumour activity. While ibrutinib was associated with a higher toxicity profile in the RESONATE trial, pERC noted that patients understood that all treatments have some side effects and are willing to tolerate side effects if a drug provides a survival advantage, helps achieve remission, provides control of disease and improves their quality of life.

A total of 56 patients had direct experience with ibrutinib. pERC noted that the majority of patients reported having a positive experience with ibrutinib as they obtained a remission and had improvements in quality of life during their remission. Patients reported that ibrutinib brought their disease under control and made them feel very similar to the way they did before diagnosis. Ibrutinib was described by patient advocacy group input as having returned blood counts to normal and dramatically improved quality of life, as compared to switching among multiple therapies and experiencing multiple relapses with previous treatments. Ibrutinib was reported to have controlled enlarged lymph nodes, high white blood cell counts, and fatigue, the three disease and drug related symptoms which the majority of patients expressed as being the most important to control. Patients also stated that the side effects with ibrutinib were mild and quickly resolved. As ibrutinib is an oral treatment, respondents reported the benefits of less travel and cost associated with visits to the cancer treatment center. Ibrutinib also does not increase demand for chemotherapy chair time and its once daily dosing schedule may result in greater patient compliance.

pERC, therefore, agreed that ibrutinib aligns with patient values as it is an effective oral treatment option that demonstrates both PFS and OS benefit, has a manageable toxicity profile, and provides ease of administration.

ECONOMIC EVALUATION

Economic model submitted: Cost effectiveness and cost-utility analysis

The pCODR Economic Guidance Panel (EGP) assessed a cost-effectiveness and cost-utility analysis of ibrutinib compared to a standard of care treatment mix for patients with CLL/SLL with or without del(17)p who had received at least one prior therapy and are not considered appropriate for treatment or retreatment with purine analog.

The submitter defined standard of care as a combination of possible therapies as determined through a chart review of patients who had received one or more therapies in Ontario. In general, pERC agreed that an economic comparator should reflect real life practice and not necessarily be the clinical trial comparator. In this instance, however, pERC noted that the Clinical Guidance Panel (CGP) did not consider the proportion of treatments in the standard of care treatment mix to be appropriate and reflective of clinical care across Canada. pERC also noted that the CGP considered that rituximab plus chlorambucil may be a more clinically relevant comparator. While the submitter included this comparison in a modification to the main economic analysis, only the costs of this comparator were considered not the effectiveness. Therefore, the EGP was unable to provide conclusions on the results of this sensitivity analysis.

Basis of the economic model: Clinical and economic inputs

Costs considered in the analysis included drug costs, disease management costs, and adverse events costs.

The clinical effect considered in the analysis was based on progression-free survival, overall survival, incidence of adverse events, dose intensity, and utilities**.** pERC noted that the clinical inputs for PFS and OS were based upon a trial follow up period of only 9.4 months. Given the immaturity of the clinical trial data and potential differences in efficacy and safety of ibrutinib as compared to treatment options in the Canadian clinical setting, pERC noted that there was considerable uncertainty in the estimates of clinical effect used in the submitted estimates and the EGP's re-analysis estimates.

Drug costs: Continuous once daily dosing, treatment until disease progression, high drug cost

Ibrutinib costs $90.65 per 140 mg capsule. At the recommended dose of 420mg orally daily, ibrutinib costs $271.95 per day and $7614.60 per 28 day course. Having discussed that the median treatment duration is not yet known and that ibrutinib is administered until disease progression or unacceptable toxicity, pERC noted that the cost of treating patients with ibrutinib may be substantial. pERC noted that the once daily oral route of administration should enhance patient compliance and provide ease in administration to patients. pERC also noted that dose adjustments are not expected to lead to wastage as only one strength is available.

Cost-effectiveness estimates: Uncertainty in extra clinical benefit compared to the standard of care treatment mix

pERC deliberated upon the cost-effectiveness of ibrutinib compared with the treatment mix used in the comparator arm, reflecting different local standards of care. pERC noted that the EGP provided a wide range of cost-effectiveness estimates which was substantially different from the manufacturer's estimates and reflected a large amount of uncertainty in the incremental benefit for the ibrutinib arm. This range is based on the most optimistic and pessimistic scenarios of the analysis provided by the submitter as well as reanalyses by the EGP. pERC discussed that the main factors that influence the change in effect for the best estimate is the hazard ratio for overall survival and a shortened time horizon (from 10 years to 5 years). As the clinical trial data are immature and based on a 9.4 month follow up period, pERC agreed with the EGP's use of the upper and lower bounds of the 95% confidence intervals around the hazard ratio for overall survival to explore uncertainty in this data. pERC acknowledged this had a substantial impact on the cost-effectiveness estimate and agreed it reflected the uncertainty in the magnitude of benefit. pERC also noted that shortening of the time horizon to 5 years was appropriate as it further accounts for

the immaturity of the clinical trial data as well as the lack of inclusion of subsequent therapies in the cost-effectiveness estimates. Upon reconsideration of the Initial recommendation, pERC noted feedback from the manufacturer regarding the use of a 5 year time horizon by the Economic Guidance Panel. pERC confirmed that the shortened time horizon attempted to account for multiple factors, such as the immaturity of the clinical data, that created uncertainty in the extrapolation of benefits and costs with ibrutinib over time. These uncertainties also included the lack of inclusion of subsequent therapies (which may have both clinical and economic impacts); structural limitations within the economic model that did not allow the EGP to separately account for post progression survival gains; and the uncertainty in the comparator arm (clinical input from the ofatumumab arm in the RESONATE trial and cost inputs from a standard of care treatment mix was used). pERC therefore agreed with the EGP's use of a shortened time horizon to limit the impacts of the above noted factors. pERC noted that the cost of ibrutinib is high and has a large impact on the cost-effectiveness estimates, particularly since treatment is continued until disease progression. In considering this, pERC agreed that the price of ibrutinib would need to be reduced substantially in order for it to be considered cost-effective.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: large budget impact, uncertain treatment duration

pERC discussed the feasibility of implementing a funding recommendation for ibrutinib. It noted that the current number of patients with relapsed or refractory disease is expected to be larger than the number of patients eligible for treatment in the first line setting as there is a large prevalent population due to the long natural history of the disease. pERC also discussed that the cost of ibrutinib is very high and that treatment is continued until disease progression. While the median treatment duration is currently unknown and will need to await the availability of updated analysis from the RESONATE trial, pERC agreed that the budget impact estimate for ibrutinib is uncertain and may increase due to the still undefined length of treatment duration. Consequently, pERC agreed that the budget impact of ibrutinib could be substantial and provinces will need to consider pricing arrangements and or cost structures to improve the affordability of ibrutinib.

pERC noted that the study included patients who have had several previous lines of therapy and agreed that ibrutinib should be used in patients with relapsed or refractory disease regardless of the number of previous lines of therapy. While del(17)p testing is not widely available in all jurisdictions, pERC agreed that ibrutinib demonstrates efficacy in all subgroups, including patients with the del(17)p and, therefore, the Committee does not expect testing is needed to identify eligible patients.

In addition, pERC noted that the use of ibrutinib in mantle cell lymphoma or other lymphomas and use of ibrutinib in the front line treatment of the del(17)p population (which has an approved Health Canada indication) was outside the scope of the current review. Upon reconsideration of the Initial recommendation, pERC noted feedback from the Provincial Advisory Group regarding the use of ibrutinib in the front line setting. pERC re-iterated that while the Health Canada approval for ibrutinib included first line patients with a del(17p) mutation, the current review only included patients that had relapsed on at least one previous line of therapy. pERC therefore agreed that any recommendation by the Committee on the use of ibrutinib in the first line setting would need to be supported by the appropriate clinical and economic information within a new submission.

Upon reconsideration of the Initial recommendation, pERC noted feedback from the Provincial Advisory Group seeking clarity on the potential re-treatment of patients with ibrutinib following progression. pERC noted that there is currently no evidence available to comment on the efficacy of ibrutinib for re-treatment. Additionally, in the context of a drug that is used until progression, re-treatment would not be a commonly pursued therapeutic approach.

Adverse events associated with ibrutinib were considered to be manageable and generally familiar to physicians who treat this condition. However, pERC agreed that health care professionals will need to become familiar with monitoring and managing the toxicities of ibrutinib, as well as the drug-drug interactions associated with ibrutinib, especially since it is metabolized in the liver by the CYP3A and cytochrome P450.

DRUG AND CONDITION INFORMATION

Drug Information	• Selective Bruton's tyrosine kinase (BTK) inhibitor • 140 mg capsule size • Recommended dosage of 420 mg administered orally, once daily
Cancer Treated	• Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma
Burden of Illness	• Primarily affects an older population and has a long natural history • Most common leukemia in western countries • Outlook for some patients with relapsed CLL, including those who are frail and have high risk disease (eg. del(17)p) is especially poor.
Current Standard Treatment	• No clearly established standard of care in relapsed or refractory setting
Limitations of Current Therapy	• Limited effectiveness or tolerability of available treatment options, especially in an older and less fit population.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Dr. Matthew Cheung, Oncologist
Dr. Kelvin Chan, Oncologist
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Danica Wasney, Pharmacist
Dr. Tallal Younis, Oncologist

All members participated in deliberations and voting on the initial recommendation except:

- Dr. Sunil Desai who was not present for the meeting
- Carole McMahon who did not vote due to her role as a patient member alternate

Dr. Maureen Trudeau chaired the meeting in her capacity as Vice-Chair of pERC. All members participated in deliberations and voting on the final recommendation except:

- Drs Paul Hoskins, Tallal Younis, and Kelvin Chan who were not present for the meeting
- Carole McMahon who did not vote due to her role as a patient member alternate

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of ibrutinib (Imbruvica) for CLL/SLL, through their declarations, six members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members were excluded from voting.

Information sources used

The pCODR Expert Review Committee is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions to inform their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation document.

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