pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH 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 reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
This pCODR Expert Review Committee (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 previously untreated chronic lymphocytic leukemia/small lymphocytic lymphoma for whom fludarabine-based treatment is considered inappropriate.

Submitted By: Janssen Inc.	**Manufactured By:** Janssen Inc.
NOC Date: July 19, 2016	**Submission Date:** April 20, 2016
Initial Recommendation: September 1, 2016	**Final Recommendation:** November 3, 2016

pERC RECOMMENDATION

pERC recommends reimbursement of ibrutinib (Imbruvica) as an option for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) for whom fludarabine-based treatment is considered inappropriate, conditional on the cost-effectiveness being improved to an acceptable level. Treatment should be for patients with a good performance status and until disease progression or unacceptable toxicity.

pERC made this recommendation because it was satisfied that, compared with chlorambucil, ibrutinib demonstrated an overall net clinical benefit based on a clinically meaningful and statistically significant improvement in progression-free survival, improvement in overall survival, improvement in quality of life and a moderate but manageable toxicity profile. However, pERC acknowledged the lack of a robust direct or indirect comparison to the current standards of care and was unable to draw a conclusion on the clinical benefit of ibrutinib as compared with relevant comparators. Ibrutinib partially aligned with patient values as there is a need for effective oral treatment options for patients in this setting; however, pERC was uncertain of the clinical benefit of ibrutinib compared with other available treatments.

pERC considered ibrutinib to not be cost-effective compared with chlorambucil. pERC also highlighted that the potential budget impact of ibrutinib is likely underestimated and could be substantial.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-Effectiveness
Given that pERC was satisfied that there is a net clinical benefit with ibrutinib compared with chlorambucil, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of ibrutinib to an acceptable level. pERC further noted that there is no direct or indirect clinical evidence to inform the comparative efficacy of ibrutinib compared with current Canadian standards of care;

therefore, the cost-effectiveness of ibrutinib compared with current treatment standards is unknown.

Collecting Prospective Evidence to Reduce Uncertainty in the Magnitude of Benefit and Cost-Effectiveness

Given the considerable uncertainty in the magnitude of clinical benefit of ibrutinib compared with current Canadian standard treatments in this setting, pERC concluded that the collection of prospective evidence to inform the comparative efficacy between these regimens would better inform the true cost-effectiveness of ibrutinib versus standard treatments (e.g., obinutuzumab plus chlorambucil). To offset the considerable uncertainty in the clinical effect estimates of ibrutinib in relation to the current Canadian standard of care, pERC concluded that a substantial price reduction would likely be required in order to improve the cost-effectiveness of ibrutinib to an acceptable level.

Factors Affecting Budget Impact and Adoption Feasibility

pERC noted the unknown duration of treatment with ibrutinib, as it continues until confirmed disease progression or unacceptable toxicity, whichever comes first. In considering the high cost of ibrutinib, the large prevalent eligible population, and the unknown but potentially long duration of treatment, pERC concluded that a substantial reduction in the drug price would be required to improve affordability.

Generalizability of Results to Patients With del(17p) Mutation, Patients < 65 years and Who Have Comorbidities

pERC noted that the RESONATE-2 trial included patients older than 65 years and excluded patients with the chromosome 17p13.1 deletion [del(17p)]. pERC noted that patients for whom treatment with a fludarabine-based regimen is deemed to be inappropriate (e.g., due to comorbidities) generally receive similar systemic therapies, regardless of age. In this context, pERC was comfortable with concluding that treatment with ibrutinib should be extended to include patients who have comorbidities that preclude them from receiving a fludarabine-based regimen, regardless of age. pERC acknowledged that this is a small number of patients; however, jurisdictions will need to consider the budget impact of including these patients in the reimbursement population. pERC also considered non-randomized evidence that demonstrates ibrutinib has similar efficacy and safety in the difficult-to-treat del(17p) population. pERC acknowledged that the activity of ibrutinib in the treatment- naive del(17p) population is in alignment with prior randomized evidence, in previously treated patients. Based on the mechanism of action of ibrutinib, phase 2 data in the untreated population that supports efficacy, and on the need for a treatment option in this population, pERC was comfortable with generalizing the results of the RESONATE-2 trial to treatment-naive patients with the del(17p) mutation status.

Optimal Sequencing of Ibrutinib and Other Therapies Unknown

pERC concluded that the optimal sequencing of ibrutinib and other treatments (e.g., intravenous chemotherapy) for the treatment of previously untreated CLL/SLL is currently unknown. pERC reiterated that the comparison of ibrutinib to chlorambucil in the first-line setting is not reflective of current practice in Canada, and that there is no direct evidence to compare ibrutinib to current standard treatments in Canada. pERC also reiterated that there is currently no evidence to support the use of obinutuzumab plus chlorambucil following failure with ibrutinib in the first-line setting. Therefore, pERC acknowledged that jurisdictions will need to consider options to optimize access to treatment options for patients when making a funding decision. pERC was, therefore, unable to make an evidence-informed recommendation regarding sequencing.

	However, pERC recognized that provinces will need to address this issue upon implementation of ibrutinib funding and noted that collaboration among provinces to develop a common approach would be of value, as would the development and implementation of an evidence-based clinical practice guideline.

SUMMARY OF pERC DELIBERATIONS

CLL is a common leukemia with a long natural history. pERC noted that the management of SLL is identical to CLL, as the two are generally considered to be the same disease. New therapies have recently become available for the treatment of patients with CLL/SLL, for whom treatment with a fludarabine-based regimen is deemed to be inappropriate (e.g., most frequently, patients with advanced age [> 65 years] and who have comorbidities). The outlook for some subgroups of patients with CLL, particularly those who have high-risk disease (chromosome 17p13.1 deletion: del(17p)), is especially poor, as the presence of these mutations is associated with resistance to standard chemoimmunotherapy, and effective agents with activity in this biologically aggressive subgroup are needed. The current standard of treatment for patients with previously untreated CLL/SLL for whom fludarabine-based treatment is considered inappropriate is obinutuzumab plus chlorambucil, but there is a need for more effective treatment options in this patient group, especially for those with a 17p deletion. pERC, therefore, agreed that there is an unmet need for more effective and tolerable treatment options for patients with previously untreated CLL/SLL.

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

The pCODR systematic review included one open-label, randomized controlled trial, RESONATE-2, which evaluated ibrutinib compared with chlorambucil in patients with treatment-naive CLL/SLL. pERC considered the RESONATE-2 study to demonstrate a statistically significant and clinically meaningful improvement in progression-free survival (PFS) and overall survival (OS) in favour of ibrutinib. pERC discussed the magnitude of PFS and OS benefit with ibrutinib and noted that, while the medians were not reached for the ibrutinib group, the benefit conferred from ibrutinib demonstrated a clinically meaningful improvement compared with chlorambucil. pERC, however, agreed that longer follow-up data are required, in order to reduce the uncertainty in the magnitude of clinical benefit. Quality of life was reported in the RESONATE-2 study, demonstrating a clinically meaningful improvement in both fatigue measures and global health scores in patients receiving ibrutinib compared with those receiving chlorambucil. pERC discussed the toxicity profile of ibrutinib and noted that grade 3 or 4 adverse events observed in the RESONATE-2 study were more common in the ibrutinib arm, as were serious adverse events (atrial fibrillation and major hemorrhage). Adverse events with ibrutinib were considered to be moderate, yet manageable. pERC considered the appropriateness of chlorambucil as a comparator in this setting and acknowledged that, at the time that the RESONATE-2 trial was designed, chlorambucil monotherapy was a treatment option used in Canada. Chlorambucil has, however, since been replaced by new more effective treatment regimens (e.g., obinutuzumab in combination with chlorambucil). pERC considered the comparative efficacy of ibrutinib against the current standard treatment options in the Canadian setting and noted the absence of robust direct or indirect clinical evidence to assist with making a conclusion. Therefore, pERC was unable to come to a conclusion on the comparative efficacy of ibrutinib compared with current standards of care in this setting. The Committee noted that a feasibility study had been presented by the manufacturer; however, differences in the dosage of chlorambucil, and variability in the study population between the RESONATE-2 trial and the pivotal efficacy trial for obinutuzumab plus chlorambucil (CLL11), led to the conclusion that an indirect comparison would not be appropriate. pERC debated using indirect evidence to help quantify the uncertainty regarding the comparative efficacy and safety between ibrutinib and relevant comparators. Various opinions were expressed during deliberations, but the majority of pERC members agreed that there was sufficient reason to conclude that there is net clinical benefit with ibrutinib compared with chlorambucil. Given the considerable uncertainty in the magnitude of clinical benefit of ibrutinib compared with current Canadian standard treatments, pERC concluded that collection of prospective evidence to inform the comparative efficacy between ibrutinib and current standard treatment regimens would be important.

Upon reconsideration of the Initial Recommendation, pERC considered feedback from the Provincial Advisory Group (PAG), regarding the difficulty in implementing a recommendation that is based on a comparator that is no longer relevant in the Canadian setting. pERC acknowledged that this is a recurring challenge to jurisdictions as more than one new agent may be studied over the same time period by different companies against relevant comparators of the day. In such instances, pERC noted that it is not

uncommon for one agent to replace the existing standard of care by presenting evidence ahead of others. pERC acknowledged the difficulty to jurisdictions in implementing reimbursement recommendation when the comparative efficacy of all agents within the same space are unknown, specifically in situations where standards of care are rapidly evolving. Furthermore pERC also considered the difficulty to manufacturers in designing trials to keep up with these rapidly changing standard treatments, bearing in mind that the new comparator may no longer be current by the time a rigorous randomized controlled trial is designed, conducted, and analyzed. pERC therefore weighed the challenge to jurisdictions and the feasibility of acquiring comparative evidence in such instances and agreed that new agents within the same clinical setting may be of utility to jurisdictions if they are evaluated using a common comparator. pERC agreed that while there is no evidence to draw a conclusion on the comparative efficacy of ibrutinib against the most relevant available treatment options, there is also a lack of evidence to come to a conclusion regarding the superiority or inferiority of current first-line standard treatment options compared with ibrutinib. For the time being, pERC agreed that the current review is based on evidence presented for ibrutinib compared with chlorambucil and must be considered on its own merits. pERC also agreed, given the absence of evidence to support the superiority or inferiority of one agent over another, both ibrutinib and other standard treatments (e.g., obinutuzumab plus chlorambucil) should be available as options to patients and choice of treatment should be at the discretion of the treating oncologist. pERC also agreed there are no data available for the Committee to comment on the optimal sequencing of all agents in this clinical setting and that there is a lack of evidence to support or refute the use of obinutuzumab plus chlorambucil following failure of ibrutinib in the first-line setting.

pERC noted that patients younger than 65 years and those with the del(17p) mutation were excluded from the RESONATE-2 trial. Upon consideration of information provided by the Clinical Guidance Panel, however, the Committee was comfortable with generalizing the trial results into these two populations. pERC noted that traditionally, patients for whom treatment with a fludarabine-based regimen is deemed inappropriate (e.g., due to comorbidities) will be treated in the same manner whether they are younger or older than 65 years of age. In this context, pERC was comfortable concluding that ibrutinib treatment should be extended to include patients who have comorbidities that preclude them from receiving a fludarabine-based regimen, regardless of age. pERC acknowledged that this is a small number of patients. pERC also considered evidence presented from a phase 2, non-randomized trial of ibrutinib in treatment-naive patients in which 92% of patients harboured the del(17p) mutation. pERC agreed that the efficacy and safety of ibrutinib in this population was in alignment with its activity in the RESONATE-2 trial. Additionally, pERC acknowledged that the activity of ibrutinib in the treatment-naive del(17p) population is in alignment with prior randomized evidence, in previously treated patients. Therefore, based on the mechanism of action of ibrutinib, phase 2 data in the untreated population that supports efficacy and on the need for a treatment option in this difficult-to-treat population, and the opinion of the Clinical Guidance Panel that a phase 3 trial of patients with the del(17p) mutation is unlikely, pERC was comfortable with generalizing the results of the RESONATE-2 trial to treatment-naive patients with a del(17p) mutation.

pERC deliberated upon input from two patient advocacy groups. pERC commended the patient groups for providing very robust data and was impressed with the depth of information on patient experiences. pERC noted that patients valued having access to effective treatment options that provide disease control, and relieve cancer-related symptoms. 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 improvement in quality of life to be an important outcome as patients diagnosed with CLL/SLL are generally older and more frail and advancing disease has a considerable impact on their quality of life. Based on the results of the RESONATE-2 trial, ibrutinib provides an oral treatment option with demonstrated PFS, OS, and quality-of-life benefit and a manageable toxicity profile compared with chlorambucil. pERC recognized that these outcomes were important to patients, but in light of the shift in standard treatment practice and the absence of comparative data against the appropriate Canadian standard, the Committee was unable to conclusively agree on alignment with patient values. Various opinions were expressed during deliberations as the Committee debated the alignment of ibrutinib with patient values. Some members argued that the demonstrated efficacy compared with chlorambucil, and the availability of an oral treatment option with a manageable toxicity profile, were sufficient reasons to conclude that ibrutinib aligned with patient values. Others were concerned that treatment should be made available to patients once it has demonstrated its efficacy and safety compared with accepted treatment standards. Overall, each of the above factors was valued differently by pERC members and, following voting, the majority of pERC members agreed that ibrutinib partially aligned with patient values.

pERC deliberated upon the cost-effectiveness of ibrutinib compared with chlorambucil. pERC noted several limitations in the submitted analysis and accepted the pCODR Economic Guidance Panel's (EGP) range of reanalysis estimates. Given the short duration of the trial follow-up period, there were limited OS data available for long-term extrapolation. pERC agreed with the EGP's method of exploring the uncertainty in the long-term OS benefit with ibrutinib, which subsequently had the largest impact on the incremental cost-effectiveness ratio (ICER). pERC also noted that the price of ibrutinib is high and that treatment would be continued until disease progression or unacceptable toxicity, which would further contribute to total cost. Overall, pERC accepted the EGP's range of reanalysis estimates and concluded that ibrutinib could not be considered cost-effective. Given the absence of follow-up trial data to determine the long-term OS benefit with ibrutinib and the potentially long duration of treatment with ibrutinib, pERC agreed that the price of ibrutinib would need to be reduced substantially in order for it to be considered cost-effective. pERC further discussed chlorambucil monotherapy as the comparator arm in the cost-effectiveness analysis and noted that it does not reflect Canadian clinical practice. While acknowledging that ibrutinib provides a clinically and statistically significant benefit to patients in comparison to chlorambucil, in the absence of direct or indirect clinical evidence, pERC was unable to determine the cost-effectiveness of ibrutinib as compared with relevant comparators in the Canadian setting. pERC therefore agreed that the collection of prospective evidence to inform the comparative efficacy between ibrutinib and the current Canadian standard option (e.g., obinutuzumab plus chlorambucil) would provide a better estimate of the cost-effectiveness of ibrutinib in Canadian patients.

Upon reconsideration of the Initial Recommendation, pERC considered feedback from PAG regarding challenges faced by jurisdictions in determining cost-effectiveness of treatment options where there is a lack of evidence on comparative efficacy. pERC agreed that this presents a significant challenge to jurisdictions. Therefore, to offset the considerable uncertainty in the clinical effect estimates, pERC concluded that a substantial price reduction would be required, as well as prospective data collection should be conducted to understand the comparative efficacy of currently available first-line agents. pERC also considered feedback from the submitter regarding model inputs modified by the EGP in its reanalysis estimates. pERC noted clarifications provided by the EGP and agreed that three-year follow-up data from a phase 1b/2 trial comprising 31 patients is not sufficient for modelling survival estimates over a 10-year time horizon. pERC also agreed with the EGP that it is unlikely that all benefit from ibrutinib would cease at the end of the trial follow-up period. In the absence of robust alternative data sources, the short duration of the trial follow-up period, and the lack of rationale to support modelling of post-progression benefit in the ibrutinib arm, pERC agreed that assuming that the risk of dying was the same between treatments at the end of the trial follow-up period (by setting the hazard ratio [HR] to 1 after the trial follow-up period) was the best available approach to control for these uncertainties.

pERC also re-considered the EGP's assumption that 50% of patients would go on to receive idelalisib-based therapies in subsequent treatment. In this instance, pERC agreed with the submitter that 50% of patients may not move on to receive idelalisib-based regimens in subsequent therapies. In acknowledging this, the Committee noted that the mix of subsequent therapies used in the submitted model likely underrepresents the potential use of expensive antibody-based therapies that patients could receive in subsequent treatments. Therefore, the Committee considered that the impact on the ICER of assuming that 50% of patients would receive idelalisib-based treatment in subsequent therapies likely reflects the cost associated with other expensive therapies that patients would receive in subsequent lines.

pERC considered the feasibility of implementing a reimbursement recommendation for ibrutinib and noted several factors. Based on the available evidence and clinical opinion, pERC was comfortable with generalizing the results of the RESONATE-2 trial to patients who are younger than 65 years but who are unable to receive fludarabine-based regimens due to comorbidities. pERC noted that patients are typically treated in a similar manner, regardless of age, provided they have underlying comorbidities that preclude them from receiving fludarabine-based treatment regimens. Likewise, pERC also generalized the trial results to patients with the del(17p) mutation status. pERC noted that patients who have del(17p) karyotypes have an especially poor prognosis and are in need of effective treatment options. A prior indication reviewed by pERC has also demonstrated that ibrutinib's mechanism of action is active in this mutation status. Overall, pERC was confident in generalizing the results of RESONATE-2 to this patient population. pERC noted that del(17p) testing is not widely available in all jurisdictions; however, pERC does not expect the availability of testing to be an issue for jurisdictions, as ibrutinib demonstrates efficacy in all subgroups, regardless of del(17p) mutation status. Therefore, testing will not be required in front-line treatment. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the PAG regarding scenarios in which patients may require del(17p) testing upfront. Given that the

pERC reimbursement recommendation is to provide ibrutinib as an option in front-line treatment of patients with previously untreated, irrespective of del(17p) mutation status, the committee felt that upfront testing may not be required to determine eligibility for ibrutinib. The committee agreed, as indicated by PAG, that testing may be required at subsequent relapses to determine if a mutation has occurred and that testing may also be helpful toward any potential collection of prospective evidence.

pERC considered factors affecting the budget impact and noted that the front-line CLL/SLL population is large. In addition, given the high cost of the drug, treatment until disease progression or unacceptable toxicity and an unknown duration of treatment are a concern. pERC also noted that several parameters were underestimated in the submitted budget impact analysis, including number of patients with CLL, the market share that ibrutinib is expected to occupy, the number of eligible patients, the expected adherence of patients to treatment, and the duration of treatment. pERC agreed these factors are likely to affect the true budget impact of ibrutinib and agreed that provinces will need to consider pricing arrangements and/or cost structures to improve the affordability of ibrutinib during implementation.

Given the absence of evidence to inform optimal treatment sequencing, pERC recognized that provinces would need to address this issue upon implementation of ibrutinib reimbursement and noted that collaboration among provinces to develop an evidence-based guideline would be of value.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis
- Guidance from pCODR clinical and economic review panels
- Input from two patient advocacy groups (Lymphoma Canada and the CLL Patient Advocacy Group)
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- Two patient advocacy groups: Lymphoma Canada and the CLL Patient Advocacy Group
- The PAG
- The submitter, Janssen Inc.

The pERC Initial Recommendation was to recommend reimbursement of ibrutinib (Imbruvica) for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) for whom fludarabine-based treatment is considered inappropriate, conditional on the cost-effectiveness being improved to an acceptable level. Feedback on the pERC Initial Recommendation indicated that the patient advocacy groups agreed; the manufacturer agreed in part; and the PAG disagreed with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of this review is to evaluate the safety and efficacy of ibrutinib (Imbruvica) as compared with an appropriate comparator in patients with untreated CLL or SLL for whom fludarabine-based treatment is considered inappropriate.

Studies included: Comparator of chlorambucil no longer the standard of care

The pCODR systematic review included one open-label, randomized controlled trial (RCT), RESONATE-2, that compared ibrutinib (n = 136) with chlorambucil (n = 133) in patients with CLL/SLL who are treatment naive and for whom treatment with a fludarabine-based regimen would be deemed inappropriate. Key inclusion criteria included adult patients (≥ 65 years) and an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 2. Key exclusion criteria included any known involvement of the central nervous system by lymphoma or leukemia, history of Richter's transformation or prolymphocytic leukemia, or having the del(17p) mutation in more than 20% of cells examined.

Patients received ibrutinib at a dose of 420 mg orally once daily. Chlorambucil was given at a dose of 0.5 mg/kg orally on days 1 and 15 of each 28-day cycle, for a maximum of 12 cycles. Both ibrutinib and chlorambucil were given until disease progression or unacceptable toxic effects. Patients in the chlorambucil group could cross over to receive ibrutinib in this study. As of the May 28, 2015 cut-off date, 15 months had elapsed after the last patient was randomized. For this reason, and in alignment with the trial protocol, the RESONATE-2 study was deemed complete and was closed. As of study closure, 25% of patients from the chlorambucil group had crossed over to the ibrutinib group. After the study closure, the remaining study participants were transferred to a non-randomized observational study, PCYC-1116, for further follow-up and ibrutinib treatment. pERC noted that chlorambucil is no longer a standard treatment option in this setting.

Patient populations: Generalizability into patients younger than 65 years, with comorbidities

Baseline patient characteristics appeared to be balanced between the two treatment groups in the RESONATE-2 trial. The median age of patients was 73 and 72 in the ibrutinib and chlorambucil groups, respectively, with the majority of patients (96% and 93%, respectively) being older than 70 years. The

majority of patients were also male (65% and 61%), had stage II or IV CLL (44% and 47%), and had an ECOG PS of 0 (44% and 41%) or 1 (48% and 50%) in the ibrutinib and chlorambucil groups, respectively. Eleven patients in the ibrutinib group (8%) and 12 patients in the chlorambucil group (9%) had an ECOG PS of 2. A small proportion of patients had SLL (10% and 5%). At the time of analysis, 87% and 40% of patients were still on treatment in the ibrutinib or chlorambucil groups, respectively.

pERC noted that, regardless of age, patients for whom treatment with a fludarabine-based regimen is deemed to be inappropriate (e.g., due to comorbidities) receive similar systemic therapies. pERC also noted registered clinician input that highlighted the importance of ibrutinib in patients whose age or existing comorbidities may preclude them from treatment with standard options. Despite the exclusion of patients younger than 65 from the RESONATE-2 trial, in this context, pERC was comfortable with concluding that treatment should be extended to include patients who have comorbidities precluding them from receiving a fludarabine-based regimen, regardless of age. pERC acknowledged that this is a small number of patients.

Key efficacy results: Improved progression-free survival, overall survival

The key efficacy outcomes deliberated on by pERC were progression-free survival (PFS), the primary outcome of the RESONATE-2 trial, and overall survival (OS). Ibrutinib demonstrated a statistically significant improvement in PFS compared with chlorambucil (hazard ratio [HR], 0.16; 95% confidence interval [CI], 0.09 to 0.28; $P < 0.001$). The median PFS was not reached for patients in the ibrutinib group compared with 18.9 months for those in the chlorambucil group. pERC noted that the absolute magnitude of benefit in the HR for median PFS was impressive and meaningful in this patient population. OS was a secondary end point in the RESONATE-2 study. The OS rate at 24 months was 98% and 85% for the ibrutinib and chlorambucil groups, respectively, with a relative risk of death that was 84% lower than with chlorambucil (HR, 0.16; 95% CI, 0.05 to 0.056; $P = 0.001$). pERC considered that the RESONATE-2 study demonstrated a statistically significant and clinically meaningful improvement in PFS and OS in favour of ibrutinib. pERC discussed the magnitude of PFS and OS benefit with ibrutinib and noted that, while the medians were not reached for the ibrutinib group, the benefit conferred through ibrutinib demonstrated a clinically meaningful improvement compared with chlorambucil.

pERC noted that the study had a short follow-up period and agreed that longer follow-up data are required to reduce the uncertainty in the magnitude of clinical benefit. At the study closure, when the remaining study participants were transferred to the non-randomized observational study PCYC-1116, an interim analysis was conducted for OS (28.1-month analysis). The HR for OS in the collective data set was 0.44 (95% CI, 0.21 to 0.92). At this time, 41% of patients had crossed over into the ibrutinib group. The OS rate for the ibrutinib and chlorambucil treatment groups were 94.7% and 84.3%, respectively.

Patient-reported outcomes: Clinically meaningful improvement in quality of life

Patient-reported outcomes were collected in the RESONATE-2 study as a secondary end point for the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) instrument and as exploratory secondary end points for the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and EuroQol 5-Dimensions 5-Levels (EQ-5D-5L). Higher rates of minimally important improvement from baseline were observed with ibrutinib versus chlorambucil in FACIT-F (62% versus 53%; $P = 0.164$). Higher rates of minimally important improvement from baseline were also observed with ibrutinib versus chlorambucil in EORTC QLQ-C30 global health status score (60% versus 48%; $P = 0.045$). Results were not reported for the EQ-5D-5L instrument.

Questionnaire completion rates were high in the ibrutinib group for all time points (at least 85%) for all three instruments, while there was variability in the chlorambucil group, dropping down to below 50% by cycle 12. Overall, pERC agreed that ibrutinib demonstrated a clinically meaningful improvement in quality of life.

Safety: Moderate but manageable toxicities with ibrutinib

pERC discussed the toxicity profile of ibrutinib and noted that fatal treatment-emergent adverse events were reported in three and four patients in the ibrutinib and chlorambucil groups, respectively. Grade 3 or worse drug-related adverse events were more frequent among patients in the ibrutinib group than in those in the chlorambucil group (84.4% versus 76.5%, respectively). Adverse events of interest including atrial fibrillation (eight and zero patients) and major hemorrhage (six and two patients) were observed more frequently in the ibrutinib compared with chlorambucil groups, respectively. Treatment-emergent

adverse events leading to discontinuation were less frequent among patients in the ibrutinib group compared with those in the chlorambucil group (9% versus 23%). pERC discussed the toxicity profile of ibrutinib and noted that grade 3 or 4 adverse events observed in the RESONATE-2 study were more common in the ibrutinib arm, as were adverse events of interest (atrial fibrillation and major hemorrhage). Overall, pERC concluded that the adverse events with ibrutinib were considered to be moderate, yet manageable.

Comparator information: Absence of robust direct or indirect evidence

pERC noted that chlorambucil is no longer a widely used treatment option in the Canadian setting and considered the comparative efficacy of ibrutinib against the current standard treatment options (e.g., obinutuzumab plus chlorambucil). Given the absence of robust direct or indirect clinical evidence, pERC was unable to come to a conclusion on the comparative efficacy of ibrutinib compared with current standards of care. The Committee noted that a feasibility study had been presented by the manufacturer that demonstrated the inappropriateness of conducting an indirect comparison between the RESONATE-2 trial and the pivotal trial for obinutuzumab plus chlorambucil (CLL11). pERC debated the value of indirect evidence, despite the limitations, to help quantify the uncertainty in the comparative efficacy and safety between ibrutinib and relevant comparators. Various opinions were expressed during deliberations. Ultimately, the majority of pERC members considered that there was sufficient reason to recommend the reimbursement of ibrutinib in this setting and conclude that there is net clinical benefit with ibrutinib compared with chlorambucil. Given the considerable uncertainty in the clinical benefit of ibrutinib compared with current Canadian standard treatments, pERC concluded that the collection of prospective evidence to inform the comparative efficacy between ibrutinib and current standard treatment regimens would be important.

Upon reconsideration of the Initial Recommendation, pERC considered feedback from the Provincial Advisory Group (PAG), regarding the difficulty in implementing a recommendation that is based on a comparator that is no longer relevant in the Canadian setting. pERC acknowledged that this is a recurring challenge to jurisdictions as more than one new agent may be studied over the same time period by different companies against relevant comparators of the day. In such instances, pERC noted that it is not uncommon for one agent to replace the existing standard of care by presenting evidence ahead of others. pERC acknowledged the difficulty to jurisdictions in implementing reimbursement recommendation when the comparative efficacy of all agents within the same space are unknown, specifically in situations where standards of care are rapidly evolving. Furthermore pERC also considered the difficulty to manufacturers in designing trials to keep up with these rapidly changing standard treatments, bearing in mind that the new comparator may no longer be current by the time a rigorous randomized controlled trial is designed, conducted, and analyzed. pERC therefore weighed the challenge to jurisdictions and the feasibility of acquiring comparative evidence in such instances and agreed that new agents within the same clinical setting may be of utility to jurisdictions if they are evaluated using a common comparator. pERC agreed that while there is no evidence to draw a conclusion on the comparative efficacy of ibrutinib against the most relevant available treatment options, there is also a lack of evidence to come to a conclusion regarding the superiority or inferiority of current first-line standard treatment options compared with ibrutinib. For the time being, pERC agreed that the current review is based on evidence presented for ibrutinib compared with chlorambucil and must be considered on its own merits. pERC also agreed, given the absence of evidence to support the superiority or inferiority of one agent over another, both ibrutinib and other standard treatments (e.g., obinutuzumab plus chlorambucil) should be available as options to patients and choice of treatment should be at the discretion of the treating oncologist. pERC also agreed there are no data available for the Committee to comment on the optimal sequencing of all agents in this clinical setting and that there is a lack of evidence to support or refute the use of obinutuzumab plus chlorambucil following failure of ibrutinib in the first-line setting.

Upon reconsideration of the Initial Recommendation, pERC considered additional comments provided by the pCODR Clinical Guidance Panel (CGP) on the comparative efficacy between ibrutinib and obinutuzumab plus chlorambucil. pERC noted the CGP's caution in using such evidence, given the limitations associated with making naive comparisons of trials. pERC reiterated that a feasibility study had been presented by the manufacturer that demonstrated the inappropriateness of conducting an indirect comparison between the RESONATE-2 trial and the pivotal trial for obinutuzumab plus chlorambucil (CLL11). Therefore, pERC agreed that there is currently a lack of evidence to support the efficacy of one regimen over another.

Contextual Information: Generalizability into del(17p) mutation-positive population

The pCODR review also provided contextual information on the results of two phase 2 studies, Farooukі et al. 2015 and O'Brien et al. 2014 (including a three-year follow-up analysis by Byrd et al. 2015), which addressed the efficacy and safety of ibrutinib in previously untreated patients with CLL and the del(17p) mutation. The Farooukі study was a phase 2, single-arm trial of ibrutinib monotherapy that recruited 51 previously treated and untreated patients. Although results were not reported based on del(17p) status, 92% (47/51) of patients harboured the mutation and 70% (35/51) were previously untreated. Objective response was measured in 97% of patients (95% CI, 86 to 100). The estimated OS was 84% (95% CI, 72 to 100) at 24 months and the estimated cumulative incidence of progression was 9% (1 to 27) in patients. Grade 3 or worse treatment-related adverse events were neutropenia in 12 patients (24%) (grade 4 in one patient), anemia in seven patients (14%), and thrombocytopenia in five patients (10%) (grade 4 in one patient). Grade 3 pneumonia occurred in three patients (6%), and grade 3 rash in one patient (2%). The O'Brien et al. 2014 study was a smaller study in which only 6% (n = 2/31) had the 17p13.1 deletion. While the results of the study are difficult to interpret in the previously untreated population with the 17p13.1 deletion, the overall results aligned with the results of the Farooukі et al. study.

pERC considered evidence presented from these non-randomized trials of ibrutinib in treatment-naive patients with the del(17p) mutation and agreed that the efficacy and safety of ibrutinib in this population was in alignment with its activity in the RESONATE-2 trial. Additionally, pERC acknowledged that the activity of ibrutinib in the treatment-naive del(17p) population is in alignment with prior randomized evidence, in previously treated patients. Therefore, based on the mechanism of action of ibrutinib, phase 2 data in the untreated population supporting efficacy and the need for a treatment option in this difficult-to-treat population, and the opinion of the CGP that a phase 3 trial of patients with the del(17p) mutation is unlikely, pERC was comfortable with generalizing the results of the RESONATE-2 trial to treatment-naive patients with the del(17p) mutation status. Input from registered clinicians also indicated that ibrutinib would be the drug of choice for the first-line treatment of patients with the del(17p) mutation.

Need and burden of illness: Greater need in the del(17p) mutation-positive population

CLL represents the most common leukemia in Western countries and has a long natural history. pERC noted that the management of SLL is identical to that of CLL, as they are generally considered to be the same disease. In Canada in 2010, the latest year for which statistics are available, 2,195 patients were diagnosed with CLL and 600 died of it. While many patients remain in observation for several years before starting treatment, OS from the time that patients start chemotherapy is only four years, with most patients receiving chemotherapy in one form or another for most of this time. Patients with CLL die either as a result of bone marrow failure (typically from infection or bleeding) or of CLL transformation to an aggressive non-Hodgkin lymphoma, a process known as Richter's transformation.

New therapies have recently become available for the treatment of patients with CLL/SLL, for whom treatment with a fludarabine-based regimen is deemed to be inappropriate (e.g., most frequently, patients with advanced age [> 65 years] and who have comorbidities). The current standard of treatment in these patients is obinutuzumab plus chlorambucil. The outlook of some subgroups of patients with CLL, particularly those who have high-risk disease (chromosome 17p13.1 deletion: del(17p)) is especially poor, as the presence of these mutations is associated with resistance to standard chemoimmunotherapy, and agents with activity in this biologically aggressive subgroup are needed. Input from registered clinicians supported this need and noted that presence of the del(17p) mutation (or related Tp53 mutations) severely limits the value of other therapies. Therefore, pERC agreed that there is a need for new and effective therapies for patients with CLL/SLL, particularly in those who have the del(17p) mutation, which provide improvements in survival, have more favourable toxicity profiles, and improve quality of life.

Registered clinician input: Growing incident cases of chronic lymphocytic leukemia, need for oral treatment option, and concern with grade 3 or 4 adverse events of interest

According to registered clinician input, CLL is a common malignancy; however, more incident cases are to be expected, given the aging Canadian population. In this elderly and frail population — typically median of 72 years at diagnosis — an oral treatment option without chemotherapy-associated infusion-related adverse events is favourable. As ibrutinib is a new therapy, concerns remain regarding rare, but concerning, toxicities such as bleeding and atrial fibrillation. pERC noted that grade 3 or higher bleeding and atrial fibrillation were observed in the RESONATE-2 trial and will require monitoring. pERC

acknowledged input from registered clinicians indicating that ibrutinib would displace other first-line treatment options into second line. pERC was, however, unable to comment on the potential sequencing of treatment in this setting, as there is no evidence to inform the optimal sequencing of available treatment regimens. pERC recognized that provinces would need to address this issue upon implementation of ibrutinib reimbursement and noted that collaboration among provinces to develop an evidence-based guideline would be of value. Upon reconsideration of the Initial Recommendation, pERC considered feedback from PAG regarding the potential for ibrutinib to displace available first-line options into the second-line setting. pERC reiterated that there is currently a lack of evidence to support or refute the use of ibrutinib followed by obinutuzumab plus chlorambucil in sequence. However, pERC agreed that ibrutinib is available as a second-line option, and in the absence of evidence to inform optimal sequencing of therapies, pERC agreed that choice of using ibrutinib as a first- or second-line treatment should be left to the treating oncologist.

PATIENT-BASED VALUES

Values of patients with chronic lymphocytic leukemia: Symptom management, quality of life improvement and treatment option

pERC deliberated upon patient advocacy group input for ibrutinib for CLL and discussed the values of patients with untreated CLL. pERC commended the patient groups for providing robust data and was impressed with the depth of information on patient experiences. Patients reported minimal symptoms with early-stage disease; however, quality of life is affected with advanced disease. Patients experience anxiety, difficulty sleeping, depression, and stress. Patients expressed difficulties with concentration, emotions, stress levels, insomnia, and mood swings. Patients noted that the symptoms that have the most impact on day-to-day living were fatigue and/or lack of energy, followed by increased lymphocyte count, enlarged lymph nodes, and frequent infections. Frequent infections (due to compromised immunity), shortness of breath (attributed to anemia), and easy bruising (caused by low platelet counts) were also reported. These symptoms, along with several others, are important symptoms of CLL/SLL to control for patients.

Patients providing input had received a variety of treatments in the first-line setting and were at various stages of their treatment course (first- to fifth-line). The most common side effects of treatment experienced by patients were fatigue, anemia or neutropenia, nausea, low platelets, mouth sores, skin rashes or severer itching, and infections. Patients rated tumour lysis syndrome and breathing difficulties or pneumonia as short-term side effects of treatments they are least willing to tolerate, while fatigue, cough, diarrhea, nausea, and fever were short-term side effects patients would be willing to tolerate. Overall, patients described treatment options currently available in Canada to be associated with increased toxicity, reduced anti-tumour activity, unpleasant side effects, and relapse. Current treatment options available tend to be associated with increased toxicity, reduced anti-tumour activity, unpleasant side effects, and relapse. pERC acknowledged that patients indicated that it is important to have access to therapies that provide less interference with their performance, delay the progression of disease, and relieve cancer-related symptoms.

Some patients expressed difficulty in accessing treatment and having to travel great distances to receive treatments in Canada, meeting specific provincial drug funding criteria, and paying out-of-pocket costs for treatments and associated travel. Most patients were, however, able to access treatment in their communities. Patients considered having the ability for themselves and their physicians to have choice in deciding which drug to take based on known side effects and expected outcomes to be of high importance.

Caregivers experience emotional and psychological burdens of caring for a loved one. Caregivers stated that they experience anxiety and difficulty managing side effects of treatment, with the most common side effects related to emotional and safety issues. Caregivers also experience accessibility issues, with the most commonly reported factors being financial burden and distance to access treatment.

Patient values on treatment: Treatment option, ease of administration, quality-of-life improvement

Patients who are unable to benefit from chemotherapy wish to have an additional choice of therapy, particularly patients who are unable to take a fludarabine-based treatment. Patients indicate that as an

oral treatment, ibrutinib is associated with less impact in terms of tolerability, ability to complete treatment cycles, number and frequency of infections, ability to do usual activities, infusion times, and infusion-related reactions. Patients also indicate that they would be willing to tolerate side effects if they could live longer, achieve a remission, have control of their disease, and have improved quality of life.

Among respondents, 18 patients had experience with ibrutinib and six had the del(17p) mutation. The majority of patients stated that the side effects with ibrutinib were mild and quickly dissipated. Many experienced more than one side effect; however, patients reported that the side effect profile of ibrutinib was easy to tolerate. Patients indicated that the symptoms ibrutinib managed most was their increasing lymphocyte counts and enlarged lymph nodes, followed by controlling night sweats and enlarged spleens. Some patients indicated that ibrutinib managed all their symptoms. Patients also indicated that ibrutinib allowed them to have a rapid and dramatic improvement in quality of life. pERC noted that this improvement in quality of life was an important outcome as patients diagnosed with CLL/SLL are generally older and more frail and advancing disease has a considerable impact on their quality of life.

pERC deliberated upon the alignment of ibrutinib with patient values and noted that based on the results of the RESONATE-2 trial, ibrutinib provides an oral treatment option with demonstrated PFS, OS, and quality-of-life benefit, and a manageable toxicity profile in comparison with chlorambucil. pERC recognized that these outcomes were important to patients, but in light of the shift in standard treatment practice and the absence of comparative data against the appropriate Canadian standard, the Committee was unable to conclusively agree whether ibrutinib aligned with patient values. Some members argued that the availability of an oral treatment option with a manageable toxicity profile was sufficient to conclude alignment. Others were concerned that treatment should be made available to patients once it has demonstrated its efficacy and safety compared with accepted treatment standards. Various opinions were expressed during deliberations, as the Committee debated the alignment of ibrutinib with patient values. Overall, each of the above factors was valued differently by pERC members, but the majority of pERC members agreed that ibrutinib partially aligned with patient values.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analysis and cost-effectiveness analysis

The pCODR Economic Guidance Panel (EGP) assessed a cost-utility analysis and a cost-effectiveness analysis of ibrutinib with chlorambucil in patients with previously untreated CLL/SLL who are inappropriate for fludarabine-based treatment.

pERC considered the appropriateness of chlorambucil as a comparator in this setting and acknowledged that at the time of the RESONATE-2 trial design, chlorambucil was an appropriate comparator in the Canadian setting. However, the Canadian standard treatment option has since changed to obinutuzumab plus chlorambucil. The submitter considered an indirect comparison between the CLL11 study and RESONATE-2; however, differences in the dosage of chlorambucil, and variability in the study population, led to a conclusion that an indirect comparison would not be appropriate. Therefore, while acknowledging that ibrutinib provides a clinically and statistically significant benefit to patients in comparison to chlorambucil, in the absence of robust direct or indirect clinical evidence comparing ibrutinib with current Canadian standard treatment, the cost-effectiveness of ibrutinib as compared with relevant comparators in the Canadian setting remains unknown. Upon reconsideration of the Initial Recommendation, pERC considered additional comments provided by the CGP on the comparative efficacy between ibrutinib and obinutuzumab plus chlorambucil. pERC noted commentary on the possibility of one agent being superior to another and reiterated that there are considerable limitations associated with making such side-by-side naive comparisons of trials. pERC reiterated that a feasibility study had been presented by the manufacturer that demonstrated the inappropriateness of conducting an indirect comparison between the RESONATE-2 trial and the pivotal trial for obinutuzumab plus chlorambucil (CLL11). Therefore, pERC agreed that there is currently a lack of evidence to support the superior efficacy of one regimen over another.

Basis of the economic model: Clinical and economic inputs

Costs considered in the model included drug costs, drug administration costs, adverse event costs, and end-of-life costs. The key clinical outcomes considered in the model were PFS, OS, and utilities. Given the

absence of long-term follow-up data for the ibrutinib group, the submitter used data from a different study using chlorambucil (the Ladyzinki chlorambucil curves) to which the OS HR from the RESONATE-2 trial for ibrutinib was applied for extrapolation over the time horizon beyond the trial period.

Drug costs: High drug cost, treatment until disease progression

Ibrutinib costs $90.65 per 140 mg capsule. At the recommended dose of 420 mg once daily, ibrutinib costs $271.95 per day and $7,614.60 per 28-day course. Chlorambucil costs $1.43 per 2 mg tablet. At a dose of 0.5 mg/kg orally on days 1 and 15 of each 28-day cycle, chlorambucil costs $1.79 per day and $50.22 per 28-day course.

Having noted the potentially large patient population with previously untreated CLL/SLL and that ibrutinib is administered until disease progression or unacceptable toxicity, with a median treatment duration that is not yet known, pERC noted that the cost of treating patients with ibrutinib may be substantial.

Cost-effectiveness estimates: Not cost-effective compared with chlorambucil

pERC deliberated upon the cost-effectiveness of ibrutinib compared with chlorambucil. pERC noted that the EGP provided a wide range of cost-effectiveness estimates that reflected uncertainty in the incremental cost-effectiveness ratio (ICER) of ibrutinib compared with chlorambucil. pERC noted that the main factor that influenced the ICER was the HR for OS. Given the short duration of the trial follow-up period, there were limited data available on OS estimates for long-term extrapolation. pERC agreed that the method used by the submitter likely overestimated the incremental benefit with ibrutinib and disagreed with the assumption that the HR for ibrutinib observed during the trial period would be maintained over a 10-year time horizon. In the absence of alternative data sources, pERC agreed with the EGP's approach of providing a range of estimates using the collective HR for ibrutinib from the open-label extension study (PCYC1116) and equal HR for PFS and OS following the trial period over the 10 years of extrapolation. pERC agreed that the latter approach is likely more conservative, but alternative data sources are not available to determine the long-term benefit of ibrutinib relative to chlorambucil. This subsequently had the largest impact on the ICER.

pERC also noted that shortening the time horizon from 15 years to 10 years was appropriate, as it better reflects the clinical course of the disease. Overall, pERC accepted the EGP's range of reanalysis estimates and concluded that ibrutinib could not be considered cost-effective. Given the absence of longer-term follow-up data from the trial to determine the long-term OS benefit with ibrutinib and the potentially long duration of treatment with ibrutinib, pERC agreed that the price of ibrutinib would need to be reduced substantially in order for it to be considered cost-effective.

Upon reconsideration of the Initial Recommendation, pERC considered feedback from PAG regarding challenges faced by jurisdictions in determining cost-effectiveness of treatment options where there is a lack of evidence on comparative efficacy. pERC agreed that this presents a significant challenge to jurisdictions. Therefore, to offset the considerable uncertainty in the clinical effect estimates, pERC concluded that a substantial price reduction would be required. pERC also considered feedback from the submitter regarding model inputs modified by the EGP in its reanalysis estimates. pERC noted clarifications provided by the EGP and agreed that 3 year follow up data from a Phase 1b/2 trial comprised of 31 patients is not sufficient to model survival estimates over a 10 year time horizon. pERC also agreed with the EGP that it is unlikely that all benefit from ibrutinib would cease at the end of the trial follow up period. In the absence of robust alternative data sources, the short duration of the trial follow up period and the lack of rationale to support modelling of post-progression benefit in the ibrutinib arm, pERC agreed that assuming that the risk of dying was the same between treatments at the end of the trial follow-up period (by setting the HR to 1 after the trial follow-up period) was the best available approach to control for these uncertainties.

pERC also considered the EGP's assumption that 50% of patients would go on to receive idelalisib-based therapies in subsequent treatment. In this instance, pERC agreed with the submitter that 50% of patients are unlikely to move onto receive idelalisib-based regimens in subsequent therapies. In acknowledging this, the Committee noted that the mix of subsequent therapies used in the submitted model likely underrepresents the potential use of expensive antibodybased therapies that patients would receive in subsequent treatments. Therefore, the Committee considered that the impact on the ICER of assuming that 50% of patients would receive idelalisib-based treatment in subsequent therapies likely reflects the cost associated with other expensive therapies that patients would receive in subsequent lines.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Potentially large budget impact
pERC discussed the feasibility of implementing a funding recommendation for ibrutinib. Given the considerable uncertainty in the comparative efficacy of ibrutinib compared with current Canadian treatment standards, pERC agreed that the collection of prospective evidence to inform the comparative efficacy between these regimens would better inform the true cost-effectiveness of ibrutinib versus standard treatments (e.g., obinutuzumab plus chlorambucil). pERC also agreed that ibrutinib may have a substantial budget impact due to a number of factors, including the high cost of the drug, the potentially large patient population with previously untreated CLL/SLL, and the unknown duration of treatment, as treatment is until disease progression or unacceptable toxicity. pERC also noted that several parameters were underestimated in the submitted budget impact analysis, including the number of patients with CLL, the market share ibrutinib is expected to occupy, the number of eligible patients, the expected adherence of patients to treatment, and the duration of treatment. pERC agreed these factors are likely to have an impact on the true budget impact of ibrutinib. Therefore, pERC agreed that jurisdictions will need to consider pricing arrangements and/or cost structures to improve the affordability of ibrutinib during implementation.

pERC noted that the once daily-oral route of administration should enhance patient compliance and provide ease in administration to patients and is an enabler to implementation, yet the differential mechanisms to fund oral medications (i.e., not the same as intravenous medications) in some jurisdictions may also be a barrier to implementation. This differential mechanism of funding would place financial and practical limitations on patients and caregivers. Furthermore, the drug's high cost is a barrier to implementation. pERC also noted that dose adjustments are not expected to lead to wastage, as only one strength is available. Given concerns regarding drug-specific adverse events (e.g., grade 3 or 4 bleeding and atrial fibrillation), pERC acknowledged that additional resources will be required to monitor patients on ibrutinib as well as to monitor the drug–drug interactions associated with ibrutinib, especially as it is metabolized in the liver by the CYP3A and cytochrome P450.

In the absence of evidence to inform optimal treatment sequencing, pERC was unable to make an evidence-informed recommendation on sequencing. However, pERC recognized that provinces would need to address this issue upon implementation of ibrutinib reimbursement and noted that collaboration among provinces to develop an evidence-based guideline would be of value.

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	• Newly diagnosed chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)
Burden of Illness	• CLL is the most common leukemia in Western countries • In Canada in 2010, the latest year in which statistics are available, 2,195 patients were diagnosed with CLL and 600 died of it
Current Standard Treatment	• Obinutuzumab plus chlorambucil
Limitations of Current Therapy	• Ineffective for current genetic mutations of CLL, such as a 17p deletion

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

pERC Membership During Deliberation of the Initial Recommendation

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Dr. Kelvin Chan, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Craig Earle, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Don Husereau, Health Economist
Dr. Anil Abraham Joy, Oncologist
Karen MacCurdy Thompson, Pharmacist
Valerie McDonald, Patient Member Alternate
Carole McMahon, Patient Member
Dr. Catherine Moltzan, Oncologist
Jo Nanson, Patient Member
Danica Wasney, Pharmacist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Jo Nanson, who did not vote due to her role as a patient member alternate.
- Matthew Cheung and Kelvin Chan, who were not present.

pERC Membership During Deliberation of the Final Recommendation

Dr. Maureen Trudeau, Oncologist (Chair)	Dr. Anil Abraham Joy, Oncologist
Dr. Paul Hoskins, Oncologist (Vice-Chair)	Dr. Marianne Taylor, Oncologist
Dr. Scott Berry, Oncologist	Karen MacCurdy Thompson, Pharmacist
Dr. Kelvin Chan, Oncologist	Valerie McDonald, Patient Member Alternate
Dr. Matthew Cheung, Oncologist	Carole McMahon, Patient Member
Dr. Craig Earle, Oncologist	Dr. Catherine Moltzan, Oncologist
Dr. Allan Grill, Family Physician	Jo Nanson, Patient Member
Don Husereau, Health Economist	Danica Wasney, Pharmacist

All members participated in deliberations and voting on the Final Recommendation, except:

- Allan Grill, who was not present.
- Valerie McDonald, who did not vote due to her role as a patient member alternate.

Avoidance of conflicts of interest

All members of pERC 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 chronic lymphocytic leukemia or small lymphocytic lymphoma, 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 was excluded from voting.

Information sources used

pERC 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 its 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 pERC for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this Recommendation document.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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