

pCODR EXPERT REVIEW COMMITTEE (pERC) INITIAL 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.

Providing Feedback on This Initial Recommendation

Taking into consideration feedback from eligible stakeholders, the pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with the *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug:
Venetoclax (Venclexta)

Submitted Reimbursement Request:
As monotherapy for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy and who have failed a B-cell receptor inhibitor (BCRi)

Submitted by:
AbbVie Corporation

Manufactured by:
AbbVie Corporation

NOC Date:
September 30, 2016

Submission Date:
July 10, 2017

Initial Recommendation Issued:
November 30, 2017

Drug Costs

Approximate per Patient Drug Costs, per Month (28 Days)	Venetoclax (Venclexta) costs \$6.80 per 10 mg, \$33.99 per 50 mg, and \$67.99 per 100 mg. Ramp-up dose: \$62.89 per day and \$1,760.88 per 28-day course. Subsequent doses: \$271.95 per day and \$7,614.60 per 28-day course.
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pERC RECOMMENDATION

pERC does not recommend reimbursement of venetoclax for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy and who have failed a B-cell receptor inhibitor (BCRi). The Committee made this recommendation because it was unable to conclude that, based on the submitted evidence, there is a net clinical benefit of venetoclax compared with appropriate comparators. While pERC noted that there is a need for additional effective treatments in this setting and that venetoclax produces antitumour activity, the Committee concluded that there was considerable uncertainty in the magnitude of clinical benefit of venetoclax compared with available comparators and based on immature interim analysis (only available in abstract form) with regard to outcomes important to decision-making, such as overall survival (OS) and progression-free survival (PFS). pERC concluded that venetoclax partially aligned with patient values because it is an additional treatment option with an oral route of administration and it produces antitumour activity; however, whether antitumour activity prolongs survival is uncertain.

pERC noted that, at the submitted price, venetoclax could not be considered cost-effective compared with available therapies. pERC also highlighted that the potential budget impact of venetoclax is likely underestimated and could be substantial.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

No next steps were identified.

SUMMARY OF pERC DELIBERATIONS

CLL is a common leukemia with a long natural history. Each year, approximately 2,400 Canadians are diagnosed with CLL and 650 die from it, with a median age at diagnosis of 72 years. There is currently no consensus on treatment options for patients who have previously received treatment with ibrutinib and/or idelalisib and who have relapsed on treatment or have experienced progression after discontinuation of either of these agents. Available agents for use may include single-agent rituximab or rituximab plus high-dose methylprednisolone (HDMP). In these patients with relapsed or refractory disease, the median overall response rates are poor (20% to 50%), and PFS has typically been less than six months. The outlook for some subgroups of patients with CLL, particularly those who have high-risk disease – chromosome 17p13.1 deletion, or 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. pERC therefore concluded that there is a need for effective treatment options in this patient population and particularly in those with the del(17p) mutation.

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 non-randomized, non-comparative, open-label, phase II trial (M14-032) examining the efficacy and safety of venetoclax in patients with CLL who have previously received treatment with ibrutinib and/or idelalisib and who have relapsed on treatment or have experienced progression after discontinuation of either of these agents. pERC considered that the M14-032 trial demonstrated promising biological activity based on improvements in objective response rate (ORR). However, the Committee was not satisfied that the available evidence demonstrated a net overall clinical benefit of treatment compared with available treatments. pERC noted that objective response rate, on its own, was not considered to be sufficient evidence of clinical effectiveness. Additionally, although ORRs were high, a small number of patients experienced complete responses while the majority of patients who responded experienced partial responses. pERC acknowledged that the current evidence suggests that there is promising antitumour activity with venetoclax; however, the magnitude of effect was uncertain given immaturity of the interim data and the lack of comparative data on long-term outcomes important to patients, such as OS and PFS. The Clinical Guidance Panel (CGP) indicated that at least a one-year to two-year OS benefit would be anticipated with the use of venetoclax in this setting. pERC noted that this conclusion was based on clinical opinion. Furthermore, the results of the M14-032 trial are based on an interim analysis that is published in abstract form and that have not been peer-reviewed.

pERC noted that the M14-032 trial evaluated patient-reported outcomes using a number of questionnaires to measure global health status (GHS), functional status and symptoms. When evaluated within the individual cohorts of the trial, clinically meaningful improvements were seen in a number of quality of life scales. pERC considered the totality of the available QoL data, and agreed that there were variable changes in quality of life measures, with improvements from baseline and declines from baseline observed. However, there were no data to determine the impact of venetoclax on patient quality of life compared with available options. Furthermore, the interim nature of the results decreased pERC's confidence in the available non-comparative data. pERC discussed the safety profile of venetoclax and noted it to be manageable. Although the M14-032 trial did not report any incidences of tumour lysis syndrome (TLS), concerns about TLS remain because of severe cases reported in early phase clinical trials. Therefore, the use of venetoclax would require that patients at high risk for TLS be identified and be treated in hospital when venetoclax treatment is initiated.

Input from the pCODR CGP indicated that a randomized controlled trial is unlikely to be conducted in this setting because there is no accepted standard treatment option to use as a comparator. It was also noted that the results of earlier phases of studies were compelling enough to make randomized studies unethical. pERC acknowledged that a standard treatment option is not available in this setting; however, the Committee agreed that it would have been feasible to conduct a randomized controlled trial versus available treatment options. While pERC considered the ORR with venetoclax in the M14-032 trial to be

important, the Committee felt that it was not sufficient evidence of effectiveness and that only limited conclusions could be drawn from this non-comparative study with a short follow-up period. pERC noted that it has accepted evidence from non-comparative studies in previous submissions for reasons that are context (drug and disease)- specific. However, in this instance, the Committee was unable to draw a conclusion on the comparative effectiveness of venetoclax in this patient population because of: the absence of mature PFS and OS data; the interim nature of the available data; the feasibility of conducting a randomized trial in this disease setting; the short trial follow-up; and low rates of complete responses to treatment. pERC recognized the significant need for treatment options in this setting, as the prognosis for patients resistant or intolerant to available tyrosine kinase inhibitors is very poor and these patients would have no reasonable treatment options remaining.

Furthermore, the Committee agreed that, in patients with del(17p) who have previously been treated with ibrutinib or idelalisib plus rituximab, there is a significant unmet need for effective treatments. However, given the considerable uncertainty regarding the available evidence from study M14-032, pERC was unable to come to a conclusion on the comparative efficacy and safety in this population. The Committee noted that nearly half of patients in the M14-032 trial had the del(17p) status or TP53 mutation or both. While the Committee agreed that the results were promising, the absence of comparative effectiveness data against available treatment options made it difficult to formulate a conclusion in this population. pERC noted the results of the Mato et al. studies, which were retrospective analyses of patients relevant to the current reimbursement request. The results of these analyses, though promising, are prone to several forms of bias and must be interpreted with caution.

pERC considered input provided by patient advocacy groups for venetoclax and noted that patients desire a new treatment option that provides disease control and improvements in QoL while offering ease of administration relative to other options. pERC agreed that, as an oral treatment option with a manageable toxicity profile and promising biological activity, venetoclax aligns with patient values. However, considering the lack of robust clinical evidence on the PFS and OS, worsening of some symptoms, the Committee concluded that venetoclax only partially aligns with patient values.

pERC deliberated upon the cost-effectiveness of venetoclax compared with rituximab monotherapy or rituximab plus HDMP. In the absence of an established standard of care, pERC accepted that rituximab monotherapy or rituximab plus HDMP are reasonable options to use as comparators. Although these are considered to be ineffective treatment options, pERC noted that the clinical effect estimates were largely based on immature PFS and OS data from a non-randomized study and extrapolating beyond the available trial data. Given the uncertainty in these estimates, pERC agreed with the Economic Guidance Panel's (EGP) reanalysis exploring the upper and lower bounds of the confidence interval on the hazard ratio for PFS and OS. pERC noted that OS had the largest impact on the incremental cost-effectiveness ratio. Therefore, due to limitations in the available non-randomized clinical evidence for venetoclax and the absence of long-term data on the potential survival benefit gained in this setting, pERC concluded that it was challenging to determine the true incremental cost-effectiveness ratio. Overall, pERC concluded that, at the submitted price, venetoclax could not be considered cost-effective compared with available therapies.

pERC considered the feasibility of implementing a reimbursement recommendation for venetoclax. pERC noted that the continued risk for TLS associated with venetoclax and patients at high risk would need to be assessed and treated in hospital when treatment is initiated. As noted by the Provincial Advisory Group, this monitoring would require additional health care resources. pERC discussed that there is a significant unmet need for effective treatments in patients with del(17p) who have previously been treated with ibrutinib or idelalisib plus rituximab; however, the currently available data did not demonstrate conclusive evidence that there is a net clinical benefit in this population or the broader population of patients with CLL who have relapsed following BCRi treatment.

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 the pCODR clinical and economic review panels
- joint input from two advocacy groups: Lymphoma Canada and CLL Patient Advocacy Group
- input from registered clinicians
- input from pCODR's Provincial Advisory Group.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of venetoclax (Venclexta) as monotherapy for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy and who have failed a B-cell receptor inhibitor (BCRi).

Studies included: Non-randomized trial, parallel arms, and unpublished interim results

The pCODR systematic review included one non-randomized, non-comparative, open-label, phase II trial (M14-032), which evaluated the use of venetoclax in patients who have previously received treatment with ibrutinib and/or idelalisib and who have relapsed on treatment or have experienced progression after discontinuation of either of these agents. Although the study was multi-centre, no Canadian sites were included. Key inclusion criteria required that patients must have had relapsed or refractory disease with an indication for treatment. Refractory disease or recurrence must have occurred after treatment with either one of the B-cell receptor signalling pathway inhibitors ibrutinib or idelalisib and met one of the following criteria: (1) treatment failure with either of these agents or (2) progression during treatment or after discontinuation or either of these agents. The M14-032 trial data are based on interim analysis of data that have not been peer-reviewed or published.

The pCODR review also provided contextual information on two retrospective studies. Mato et al. 2016 (n = 178) investigated reasons for BCRi discontinuation, outcomes after stopping therapy, and the impact that BCRi sequencing had on outcomes. Mato et al. 2017 (n = 683) investigated rates and causes of discontinuation to assess outcomes following discontinuation and to define the best sequencing strategy utilizing kinase inhibitors and venetoclax. Data were gathered through chart reviews for both studies, and Mato et al. 2017 also utilized institutional clinical or pathological databases and electronic medical records. Both studies reported that among patients treated with an alternate BCRi (after an initial BCRi), those who were intolerant to the initial BCRi had a superior PFS as compared with those for whom disease progression was the reason for discontinuation. Mato et al. 2017 concluded that ibrutinib appears superior to idelalisib as the first BCRi and, in the setting of BCRi failure, alternate BCRis or venetoclax appear superior to chemoimmunotherapy combinations. Further, the use of venetoclax might be superior to idelalisib upon ibrutinib failure. However, this evidence has not been confirmed by results from comparative clinical trials. pERC acknowledged that retrospective analyses is prone to reporting bias and these results, though promising, must be interpreted with caution.

Patient populations: Relapsed or refractory CLL after treatment with ibrutinib and/or idelalisib

A total of 127 patients were enrolled in the M14-032 trial: 43 into arm A (patients with relapsed or refractory CLL after ibrutinib treatment), 21 into arm B (patients with relapsed or refractory CLL after idelalisib treatment), and 63 into the expansion cohort (patients previously treated with either ibrutinib (n = 53) or idelalisib (n = 22)). A total of 22 out of 127 patients (17.3%) received both ibrutinib and idelalisib as a prior line of therapy. Most patients had Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 (32.3%) or 1 (59.1%). Patients were classified into three risk categories based on their tumour burden prior to venetoclax administration, and 35 out of 127 patients (28%) were at high risk for tumour lysis syndrome (TLS). A total of 57 patients (44.9%) harboured the chromosome 17p13.1

deletion (del(17p)) and/or TP53 mutation or both as assessed by the investigator's local laboratory. Most patients were male (70.1%) and white (92.1%), and 58.3% were at or above the age of 65.

All patients received single daily oral doses of venetoclax, starting with 20 mg and increasing weekly to a target dose of 400 mg over four to five weeks. Patients were able to continue receiving venetoclax for up to two years provided they continued to tolerate the drug, had no evidence of disease progression, and did not meet any of the criteria for discontinuation. The anticipated median duration of treatment was approximately one year.

To further reduce the risk of TLS, patients received prophylaxis with uric acid-lowering agents starting at least 72 hours prior to the first venetoclax dose, and patients with high tumour burden were hospitalized. Patients also received oral hydration irrespective of TLS risk category starting at least 48 hours prior to each dose. Patients unable to maintain adequate oral hydration or those with medium or high risk for TLS were also given intravenous hydration. Patients were monitored for TLS at the first dose and at dose increases, and any changes that identified increased risk were immediately addressed.

Key efficacy results: Immature progression-free survival and overall survival

The key efficacy outcome deliberated on by pERC was objective response rate (ORR). No formal a priori statistical hypothesis plan was conducted on the primary end point of ORR. However, a sample size of 60 patients ensured that the distance of the true rate would be within 14% of the observed rate with 95% confidence.

Investigator-assessed ORR was 56.7% (n = 72) in all patients (95% confidence interval, 47.6 to 65.5). Among these, 8.7% (n = 11) were complete response and 48% (n = 61) were partial response. In the subgroup of patients with 17p deletion and/or p53 mutation or both, ORR was reported in 66.7%, 80.0%, and 50.0% in arm A, arm B, and the expansion cohort, respectively. pERC considered that the M14-032 trial demonstrated promising biological activity based on improvements in ORR. However, the Committee was not satisfied that the available evidence demonstrated a net overall clinical benefit of treatment. pERC noted that objective response rate, on its own, was not considered to be sufficient evidence of clinical effectiveness. Additionally, although ORRs were high, a small number of patients experienced complete responses while the majority of patients who responded experienced partial responses.

Secondary outcomes deliberated by pERC included progression-free survival (PFS) and overall survival (OS). Medians were not reached for either outcome by the January 31, 2017, cut-off date. Kaplan-Meier estimates demonstrated that, at 12 months, 74.2% of patients had not progressed. In the subgroup of patients with 17p deletion and/or p53 mutation or both, the 12-month PFS rates were 65.4%, 80.0%, and 72.8% in arm A, arm B, and the expansion cohort, respectively. As of the January cut-off date, 14 deaths had occurred (out of 127 patients). Kaplan-Meier estimates reported that, at 12 months, OS rates were 88.2%, 95.2%, and 96.2% in arm A, arm B, and the expansion cohort, respectively. Among the subgroup of patients harbouring the 17p deletion or TP53 mutation or both, the 12-month OS rates were 87.5%, 80.0%, and 95.7% in arm A, arm B, and the expansion cohort, respectively. pERC noted input from CGP indicating that at least a one-year to two-year OS benefit would be anticipated with the use of venetoclax in this setting. However, pERC noted that this conclusion was based on clinical opinion and lacked supportive evidence. pERC further noted that, historically, median overall response rates in this patient population are poor (20% to 50%) and PFS has typically been less than six months. In the absence of comparative evidence against available treatment options, pERC agreed that it is difficult to determine whether venetoclax provides meaningful clinical benefit superior to these historical outcomes. pERC also noted that outcomes in the population of patients with del(17p) mutation were promising. However, pERC concluded that, in the absence of comparative effectiveness data against available treatment options, a definitive conclusion on clinical benefit could not be made.

Patient-reported outcomes: Clinically meaningful worsening from baseline on a number of scales

Patient-reported outcomes were evaluated in the M14-032 study using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30), the EORTC QLQ for CLL 16 (QLQ-CLL16) and the EuroQol Visual Analogue Scale. Patient-reported outcomes as an exploratory outcome in the M14-032 trial.

In arm A, minimally important improvements were measured at all time points for global health status, role functioning, and social functioning. Financial difficulties had clinically meaningful improvement at

some measurement time points. Clinically meaningful worsening was measured for diarrhea. In arm B, clinically meaningful worsening of diarrhea, pain, and cognitive functioning was reported between baseline and the final observation. In Cohort B, some of the measured quality of life scales demonstrated changes greater than 5 points (both minimally important improvement and decline) at different measurement time points. Based on aggregate data for all three cohorts, both the EORTC QLQ-CLL16 and the EORTC QLQ-C30 scales demonstrated clinically important improvement of fatigue. Moderate to large changes from baseline scores were also reported for social problems, with minimal clinically important worsening being reported at all time points. pERC discussed the quality of life data available and agreed that there is indication of both improvement and worsening on a number of scales both in the aggregate data and in individual cohorts.

Safety: Manageable toxicity, risk of TLS

pERC discussed the safety profile of venetoclax and noted it to be manageable. Grade 3 or 4 adverse events were reported in 93.0% of patients in arm A, 81.0% of patients in arm B, and 71.4% of patients in the expansion cohort. The three most common grade 3 or 4 adverse events by study arm were as follows:

- arm A: anemia (32.6%), decreased neutrophil count, and neutropenia (27.9% each)
- arm B: neutropenia (42.9%), thrombocytopenia (23.8%), and anemia (14.3%)
- expansion cohort: neutropenia (33.3%), anemia (23.8%), and decreased neutrophil count (17.5%).

Notably, most of these were disease-related symptoms that patient input had outlined as being most important to control with new treatments. Treatment-emergent serious adverse events were reported in 46.5% of all patients.

pERC noted that TLS is an adverse event that required monitoring in this population during treatment. There were no cases of clinical TLS reported in the trial. As of the January 31, 2017, cut-off date, 14 patients had died. Seven patients died within 30 days of the last dose of venetoclax and experienced fatal adverse events, and seven deaths were reported during survival follow-up. Among the seven deaths that occurred within 30 days of treatment, causes included septic shock, death not otherwise specified, multiple organ dysfunction syndrome, asphyxia, malignant neoplasm attributed to disease progression, *corynebacterium* sepsis (not related to venetoclax), and cytokine release syndrome (also not related to disease progression based on the investigator's assessment).

Need and burden of illness: Need in patients with and without the del(17p) mutation

CLL is a common leukemia with a long natural history. Each year, approximately 2,400 Canadians are diagnosed with CLL and 650 die from it, with a median age at diagnosis of 72 years. The most important prognostic markers currently in clinical practice are those that detect a defective TP53 gene (either by interphase FISH [fluorescence in situ hybridization] cytogenetics as del(17p) or by sequencing to assess for gene mutations); a functioning p53 is an essential cofactor for programmed cell death, and patients with this abnormality are generally resistant to chemotherapy and radiotherapy. In patients without the del(17p) mutation, front-line treatment typically involves fludarabine/cyclophosphamide/rituximab in fit patients and chemoimmunotherapy in frail patients. This is followed by ibrutinib in the relapsed or refractory setting. The outlook of patients following relapse is poor as there are no effective treatment options. For the subgroups of patients who have CLL and high-risk disease (i.e., del(17p)) prognosis is especially poor, as the presence of these mutations is associated with resistance to standard chemoimmunotherapy, and front-line treatment would employ ibrutinib or idelalisib plus rituximab. There is currently no consensus on treatment options for patients who have previously received treatment with ibrutinib and/or idelalisib and who have relapsed on treatment or have experienced progression after discontinuation of either of these agents. Available agents for use may include single-agent rituximab or rituximab plus high-dose methylprednisolone (HDMP). In these patients with relapsed or refractory disease, the median overall response rates are poor (20% to 50%), and PFS has typically been less than six months. Therefore, more effective agents with activity in this biologically aggressive subgroup are needed. In previously untreated patients, the incidence of TP53 gene abnormalities is approximately 10% to 12%. In the relapsed or refractory setting, through the process of clonal evolution, the incidence of TP53 abnormalities can increase up to approximately 30%. Patients with the del(17p) mutation typically receive ibrutinib in the front-line setting. For patients who develop resistance or intolerance to available tyrosine kinase inhibitors (TKIs), there is currently no effective alternative therapy and prognosis is very poor. Therefore, pERC agreed that there is a need for additional effective therapies in this patient population, particularly in patients with the del(17p) mutation.

Registered clinician input: High response rates with venetoclax

According to registered clinician input, patients in whom TKIs fail have a very short life expectancy (approximately three months based on prior studies) and no other viable treatment options. Clinician input indicates that venetoclax is the only agent with documented efficacy in this population. Registered clinician input indicated that the key benefits of venetoclax were its high response rates and durable responses in a patient population with no other effective treatment options. Response rates with venetoclax were also indicated to be considerably higher when compared with treatment with alternate TKI after failure of a first TKI. pERC acknowledged that the current evidence (M14-032 trial) suggests that there is promising antitumour activity with venetoclax; however, the magnitude of effect was uncertain given the lack of comparative data on long-term outcomes important to patients, such as OS and PFS.

Clinician input identified the possibility of discontinuing treatment following deep molecular remission. pERC noted input from the Clinical Guidance Panel (CGP) indicating that deep molecular remission is assessed through minimal residual disease. Given that minimal residual disease was an exploratory end point, it is difficult to determine if patients have truly achieved benefit from it. Therefore conclusions on treatment discontinuation cannot be made based on this criterion. As an oral therapy, venetoclax is also a convenient option.

PATIENT-BASED VALUES

Values of patients with chronic lymphocytic leukemia: Symptom control and quality-of-life impact

pERC deliberated upon patient advocacy group input for venetoclax and discussed the values of patients with previously treated CLL.

Patient input indicated the top three CLL symptoms that affected QoL at diagnosis and on an ongoing basis were fatigue/lack of energy, increasing lymphocyte count, and enlarged lymph nodes. Psychological aspects of CLL (and small lymphocytic lymphoma) affecting patients and caregivers the most included stress of diagnosis, anxiety/worry, difficulty sleeping, and depression. Some patients also experienced difficulties with concentration, emotions, and mood swings. Infections, thrombocytopenia, neutropenia, viral infections, anemia, fatigue/lack of energy, white blood cell count decrease, fever, lymph node size, and enlarged spleen or abdominal discomfort were rated as being important symptoms to control by 60% or more of patients providing input.

Among 179 individuals providing input, most indicated that their current treatments are unable to manage their symptoms. Patients indicated that the most difficult to tolerate side effects were fatigue, nausea, and frequency of infections. Some patients indicated that they were unable to access treatment in their own communities. Caregivers providing input indicated that their ability to travel, spend time with family or friends, concentrate and fulfill family obligations are impacted significantly as a result of caring for a patient with CLL.

pERC considered that symptom control and QoL improvement were important outcomes for patients. Based on the results of the M14-032 trial, there appears to be worsening of QoL in a number of scales but the toxicity profile of treatment was deemed to be manageable.

Patient values on treatment: Treatment options, oral administration, targeted therapy, increased effectiveness

Among 301 patients providing input, nearly all (n = 286) indicated the importance of having choice in therapy. A large number of patients (133 out of 301) indicated that they would be willing to take a drug with potentially serious side effects if it was recommended to be the best option for them by their doctor. When asked to prioritize the important aspects of a new therapy, 72 out of 162 patients prioritized increased effectiveness, 40 rated decreased toxicities as most important, 12 rated remissions as most important, 12 wanted accessible and affordable treatments, 11 wanted an improved QoL, and nine stressed the importance of an oral therapy. Patients want to transition from an era of chemotherapy to an era of targeted therapy with proven efficacy in treating a range of patients, including those with poor prognostic factors and those with advanced age and existing comorbidities. Patients seek individualized choice in treatment that will offer disease control and improve QoL while offering ease of use relative to other available treatments.

Twenty-one patients had direct experience with venetoclax, among whom four were from Canada. Only 8 out of 21 patients had previously been treated with ibrutinib and/or idelalisib and experienced resistance, failure, or intolerance. Side effects of venetoclax were rated to be mild and quickly dissipating or effectively treated with medication. Side effects reported by participants included diarrhea (n = 8), neutropenia (n = 7), fatigue (n = 6), nausea (n = 5), thrombocytopenia (n = 2), upper respiratory tract infection (n = 1), and TLS (n = 1).

pERC noted that uncertainty in the net clinical benefit of venetoclax tempered its conclusion on alignment with patients' values. The Committee agreed that the availability of an additional treatment option, its ability to control disease symptoms, and its oral route of administration align with patient values; however, in the absence of conclusive data on the clinical effectiveness of venetoclax, the Committee concluded that venetoclax only 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 venetoclax compared with rituximab monotherapy or rituximab plus HDMP in patients with CLL who have received at least one prior therapy and who have failed a BCRI.

Basis of the economic model: Uncertain clinical inputs

Costs considered in the economic model included drug costs, costs to manage adverse events, TLS prophylaxis, and routine care and monitoring costs. The key clinical outcomes considered in the model were PFS, OS, and utilities.

Given the absence of robust direct evidence, the clinical effect considered in the analysis was based on data for the comparator arm from published survival curves from NICE (National Institute for Health and Care Excellence) submissions for idelalisib in the relapsed or refractory CLL setting. pERC acknowledged considerable limitations in the results of this analysis and agreed that caution should be used in interpreting the results.

Drug costs: Treatment until progression or maximum 2 years

Venetoclax costs \$6.80 per 10 mg, \$33.99 per 50 mg, and \$67.99 per 100 mg. The recommended ramp-up dosage for venetoclax includes 2 × 10 mg daily on week one, 1 × 50 mg daily on week two, 1 × 100 mg daily on week three, and 2 × 100 mg daily on week four. All subsequent dosages are 4 × 100 mg daily. At the recommended ramp-up and subsequent dosages, venetoclax costs \$62.89 per day and \$1,760.88 per 28-day course for the ramp-up stage and \$271.95 per day and \$7,614.60 per 28-day course for subsequent cycles.

Rituximab costs \$4.71 per mg. When used as combination therapy and at the recommended dosage of 375 mg/m² on day 1 of cycle 1, 500 mg/m² on day 1 and day 5 of cycle 2 and cycle 3, and then 500 mg/m² on day 1 of cycles 3 to 6, every 21 days, rituximab costs \$190.45 per day and \$5,332.54 per 28-day cycle. When used as a single agent and at the recommended dosage of 375 mg/m² on day 1 of cycle 1, 500 mg/m² on day 1 of cycles 2 to 7, every 28 days for six cycles, rituximab costs \$142.84 per day and \$3,999.40 per 28-day cycle.

HDMP costs 0.0722 per mg. At the recommended dose of 1 g/m² daily for five consecutive days every 21 days for six cycles, HDMP costs \$5.85 per day and \$163.65 per 28-day course.

Clinical effect estimates: Uncertainty in PFS and OS estimates

pERC deliberated on the cost-effectiveness of venetoclax compared with rituximab or rituximab plus HDMP. In the absence of an established standard of care, pERC agreed that rituximab monotherapy or rituximab plus HDMP are reasonable options to use as comparators. Although these are considered to be ineffective treatment options, the Committee expressed uncertainty in the estimates for long-term benefit with venetoclax given the immaturity of the trial results and lack of direct comparative trials. pERC noted that the clinical effect estimates were largely based on immature PFS and OS data and extrapolating beyond the available trial data. Given the uncertainty in these estimates, pERC agreed with EGP's reanalysis exploring the upper and lower bounds of the confidence interval on the hazard ratio for PFS and OS. pERC noted that OS had the largest impact on the incremental cost-effectiveness ratio. pERC

considered input from CGP indicating that a one-year to two-year OS benefit is anticipated with venetoclax and agreed that this is based on clinical opinion. Therefore, due to limitations in the available non-randomized clinical evidence for venetoclax and the absence of long-term data on the potential survival benefit gained in this setting, pERC concluded that it was challenging to determine the true incremental cost-effectiveness ratio. Based on EGP's reanalysis estimates, pERC agreed that venetoclax could not be considered cost-effective compared with available therapies.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: TLS monitoring, potential large budget impact

pERC considered the feasibility of implementing a reimbursement recommendation for venetoclax. pERC noted that concerns remain regarding TLS with the use of venetoclax, and therefore intensive monitoring and prophylactic measures would need to be taken to prevent TLS in patients. As noted by the Provincial Advisory Group input, this would require additional health care resources to monitor. pERC agreed that there is a significant unmet need for effective treatments in patients with del(17p) mutation who have previously been treated with ibrutinib or idelalisib plus rituximab; however, the current evidence did not demonstrate concrete data indicating net clinical benefit in this population or the broader population of patients with CLL who have relapsed following BCRi treatment. pERC also noted that the packaging of the venetoclax ramp-up dose requires monitoring to ensure that patients are taking the correct dose on the right day.

pERC agreed that venetoclax' oral route of administration creates ease of administration for patients and is an enabler to implementation, but pERC acknowledged that patients may periodically need hospitalization during the first month of treatment to appropriately manage potential toxicities during the ramp-up phase of treatment. Therefore, patients would need to be within close proximity of a hospital for the first month of therapy. pERC considered factors affecting the budget impact and noted that the front-line CLL population is large. pERC therefore agreed that the potential budget impact of venetoclax is uncertain but likely to be high. Furthermore, pERC noted that the drug's high cost is a barrier to implementation.

DRUG AND CONDITION INFORMATION

Drug Information	<ul style="list-style-type: none"> • Selective inhibitor of B-cell lymphoma 2 (bcl-2) gene • 10 mg, 50 mg, and 100 mg tablet sizes • Recommended dosage of 20 mg daily (week 1), 50 mg daily (week 2), 100 mg daily (week 3), 200 mg daily (week 4), and 400 mg daily for all subsequent doses
Cancer Treated	<ul style="list-style-type: none"> • Relapsed or refractory chronic lymphocytic leukemia (CLL) previously treated with a B-cell receptor inhibitor (BCRi)
Burden of Illness	<ul style="list-style-type: none"> • CLL is the most common leukemia in Western countries • Approximately 2,400 Canadians are diagnosed with CLL each year and 650 die from it •
Current Standard Treatment	<ul style="list-style-type: none"> • No standard treatment option • Single-agent chemotherapies (i.e., rituximab)
Limitations of Current Therapy	<ul style="list-style-type: none"> • No effective treatment options in patients who have failed prior treatment with ibrutinib or idelalisib plus rituximab

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:

Dr. Maureen Trudeau, Oncologist (Chair)
 Dr. Catherine Moltzan, Oncologist (Vice-Chair)
 Dr. Kelvin Chan, Oncologist
 Lauren Flay Charbonneau, Pharmacist
 Dr. Matthew Cheung, Oncologist
 Dr. Winson Cheung, Oncologist
 Dr. Avram Denburg, Pediatric Oncologist
 Mike Doyle, Health Economist

Dr. Craig Earle, Oncologist
 Leela John, Pharmacist
 Dr. Anil Abraham Joy, Oncologist
 Dr. Christine Kennedy, Family Physician
 Cameron Lane, Patient Member Alternate
 Valerie McDonald, Patient Member
 Carole McMahon, Patient Member
 Dr. Marianne Taylor, Oncologist

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

- Lauren Flay Charbonneau and Dr. Craig Earle, who were not present for the meeting
- Dr. Matthew Cheung, who was excluded from voting due to a conflict of interest
- Cameron Lane, 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 venetoclax (Venclexta) for chronic lymphocytic leukemia, through their declarations, seven members had a real, potential, or perceived conflict and, based on application of the *pCODR Conflict of Interest Guidelines*, one 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 the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

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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