pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

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 *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 Funding Request:
In combination with rituximab for the treatment of adult patients with chronic lymphocytic leukemia who have received at least one prior therapy, irrespective of their 17p deletion status.

Submitted by:
AbbVie Corporation

Manufactured by:
AbbVie Corporation

NOC Date:
September 21, 2018

Submission Date:
October 24, 2018

Initial Recommendation Issued:
April 4, 2019

Approximate per Patient Drug Costs, per Month (28 Days)	Venetoclax (oral) costs $0.68 per mg Dose ramp-up period to 400 mg per day over five weeks; 400 mg daily should be continued for 24 months First 28-day cycle (ramp-up cycle): $1,760.80 Subsequent 28-day cycles: $7, 614.60

pERC RECOMMENDATION

☐ **Reimburse**
☒ **Reimburse with clinical criteria and/or conditions***
☐ **Do not reimburse**

* If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends reimbursement of venetoclax (Venclexta) in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy, irrespective of their 17p deletion status, only if the following condition is met:

- cost-effectiveness being improved to an acceptable level.

Patients should have a good performance status and treatment should be continued until disease progression or unacceptable toxicity up to a maximum of two years, whichever comes first.

pERC made this recommendation because it was satisfied that, compared with bendamustine plus rituximab, there is a net clinical benefit of venetoclax plus rituximab based on a statistically significant and clinically meaningful improvement in progression-free survival (PFS) and a manageable toxicity profile in a patient population with a need for more effective treatment options. The Committee acknowledged that the data on quality of life (QoL) were inconclusive.

pERC concluded that venetoclax plus rituximab aligns with patient values in that it provides additional treatment choice, delays disease progression, has manageable side effects, a fixed treatment duration, and a partially oral route of administration.

	In addition, the Committee considered evidence provided through an indirect treatment comparison with B-cell receptor inhibitors (ibrutinib and idelalisib plus rituximab). pERC could not conclude on the comparative efficacy of venetoclax plus rituximab compared with B-cell receptor inhibitors due to the lack of robust direct or indirect comparative evidence. pERC concluded that at the submitted price, venetoclax plus rituximab could not be considered cost-effective compared with bendamustine plus rituximab and would require a substantial price reduction to improve the cost-effectiveness to an acceptable level. pERC further noted that there was considerable uncertainty in the cost-effectiveness estimates of venetoclax plus rituximab compared with ibrutinib and idelalisib plus rituximab because of a lack of robust direct or indirect comparative effectiveness data in the submitted economic evaluation. pERC also noted that the submitted potential budget impact of venetoclax plus rituximab was likely underestimated.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness and Decrease Budget Impact** Given that pERC was satisfied that there is a net clinical benefit of venetoclax plus rituximab, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of venetoclax plus rituximab to an acceptable level. pERC noted that a substantial reduction in the price of venetoclax plus rituximab would be required in order to improve the cost-effectiveness to an acceptable level and to decrease the predicted budget impact. **Optimal Sequencing of Venetoclax Plus Rituximab and Other Therapies is Unknown** pERC concluded that the optimal sequencing of venetoclax plus rituximab and other therapies, such as B-cell receptor inhibitors, in relapsed CLL is currently unknown, as there is insufficient evidence to inform this clinical situation. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of venetoclax plus rituximab, and noted that a national approach to developing evidence-based clinical practice guidelines addressing the sequencing of treatments would be of value. **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 venetoclax plus rituximab compared with B-cell receptor inhibitors (i.e., ibrutinib and idelalisib plus rituximab) in patients with relapsed CLL who have received at least one prior therapy, pERC concluded that the collection of data on comparative efficacy of outcomes important for decision-making, such as PFS, overall survival (OS), and QoL, would better inform the true cost-effectiveness of venetoclax plus rituximab compared with B-cell receptor inhibitors. Please note: Provincial Advisory Group questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

CLL is an incurable malignancy of B lymphocytes. With an incidence of approximately four to five out of 100,000 in the general population, it is the most common adult leukemia in the Western hemisphere. Approximately 2,400 Canadians are diagnosed with and 650 die from CLL each year. The median age at diagnosis is 72 years, and within incident cases there is a male predominance. For patients with CLL that has relapsed or is refractory to standard front-line therapies, there is no agreed-upon standard treatment. Common treatment options include chemoimmunotherapy regimens and B-cell receptor inhibitors for most patients with CLL, although patients with the chromosome 17p deletion do not respond to chemoimmunotherapy. OS of patients with relapsed CLL is between three and five years. pERC agreed with the pCODR Clinical Guidance Panel (CGP) that there is a need for effective treatment options that delay disease progression, with manageable toxicity and activity that is independent of genetic and other mechanisms of treatment resistance.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

pERC deliberated the results of one well-conducted, open-label, phase III randomized controlled trial (MURANO) that evaluated the efficacy and safety of venetoclax plus rituximab compared with bendamustine plus rituximab in patients with relapsed or refractory CLL who have received at least one prior therapy. pERC considered that the difference in PFS, the primary outcome, was statistically significant and clinically meaningful in favour of venetoclax plus rituximab. Improvements in PFS were seen across all subgroups, including patients with a chromosome 17p deletion. pERC noted that the results for OS, a secondary outcome, were immature at present and that *P* values were considered descriptive. pERC noted that, in order to adjust for multiple testing of key secondary outcomes, the MURANO trial design pre-specified a fixed sequence hierarchical testing of outcomes for statistical significance in the following order: best response of complete response rate, best overall response rate, and OS. pERC acknowledged that OS was statistically significant when assessed on its own; however, given that the difference in complete response rates was not statistically significant, subsequent analyses of the other secondary outcomes (i.e., overall response rate and OS) were considered exploratory in nature and *P* values were descriptive only. pERC agreed with CGP that PFS is an appropriate and well agreed-upon primary end point in relapsed CLL, as the heterogeneous disease biology as well as the application of further therapies after progression may influence OS. pERC concluded that, while the median PFS had not been reached in the venetoclax plus rituximab group, it extended beyond two years, which is a meaningful outcome in relapsed CLL.

pERC deliberated the toxicity profile of venetoclax plus rituximab and noted that the incidence and severity of adverse reactions were broadly similar between the two treatment groups and consistent with the safety profile of common second-line chemoimmunotherapy therapies in this setting. The most frequently reported adverse event of any grade was neutropenia, which occurred more frequently in the venetoclax plus rituximab group. pERC noted that the incidence of grade 3 or 4 febrile neutropenia or infections was higher in the bendamustine plus rituximab group. Other common adverse events included diarrhea, infections and infestations, nausea, and fatigue. pERC discussed that approximately one-half of patients in both arms received growth factor support and agreed with CGP that myelosuppression requiring supportive measures is common in this setting and can be successfully managed and prevented. pERC noted that tumour lysis syndrome in the MURANO study was rare and managed well with appropriate supportive and preventive measures. Overall, pERC agreed with CGP and the registered clinicians providing input that venetoclax plus rituximab has a manageable safety profile.

pERC discussed the available patient-reported outcomes data from the MURANO trial and noted that, due to administrative errors, baseline health-related QoL assessments were only partially collected, which resulted in a significant extent of missing patient-reported outcomes data. pERC agreed with the pCODR Methods Team that, due to these limitations, the patient-reported outcomes data were inconclusive.

pERC concluded that there is a net clinical benefit to venetoclax plus rituximab compared with bendamustine plus rituximab in the treatment of adult patients with CLL who have received at least one prior therapy. In coming to this conclusion, pERC considered the statistically significant and clinically meaningful result in PFS, a manageable toxicity profile, and a need for more effective treatment options that delay disease progression.

pERC discussed at length whether the results of the MURANO trial can be generalized to patients who may have progressed on ibrutinib. pERC noted that phase II trial data (the M14-032 trial that pERC deliberated upon in 2018) suggest that single-agent venetoclax is active after treatment with a B-cell receptor inhibitor and that there is no biological rationale to assume that the outcomes of venetoclax plus rituximab observed in the MURANO trial would be different in patients previously treated with ibrutinib. Therefore, pERC agreed with CGP and the majority of registered clinicians providing input that the MURANO trial results can be generalized to patients with CLL who have progressed on ibrutinib.

pERC deliberated a joint submission from two patient advocacy groups. pERC noted that patients with experience using venetoclax plus rituximab had overall a favourable impression. The majority of patients saw a reduction in commonly reported symptoms with CLL. pERC discussed that most of the respondents indicated that they were willing to tolerate potentially serious or significant side effects. The most commonly reported side effects were neutropenia, fatigue, and diarrhea. In addition, patients noted that clinician visits and infusions were burdensome and welcomed the potential availability of subcutaneous rituximab. pERC concluded that the use of venetoclax plus rituximab aligned with patient values in that it delays disease progression, provides additional treatment choice, has manageable side effects, a fixed treatment duration, and a partially oral route of administration.

pERC deliberated a submitter-provided indirect treatment comparison (ITC) comparing the efficacy of venetoclax plus rituximab with ibrutinib and idelalisib plus rituximab. pERC noted that the results of the ITC favoured venetoclax plus rituximab for OS in the comparison with ibrutinib and for PFS and OS in the comparison with idelalisib plus rituximab. pERC agreed with the pCODR Methods Team and the pCODR Economic Guidance Panel (EGP) that, given the unknown amount of bias in the unanchored effect estimates, overlapping confidence intervals, the immaturity of PFS and OS data, the lack of individual patient data, and the absence of indirect comparisons for safety data and QoL, the comparative effectiveness of venetoclax plus rituximab versus ibrutinib and idelalisib plus rituximab remained uncertain.

pERC deliberated the cost-effectiveness of venetoclax plus rituximab compared with bendamustine plus rituximab, ibrutinib, and idelalisib plus rituximab. pERC noted that the EGP reanalysis of cost-effectiveness presented incremental cost-effectiveness ratios (ICERs) as lower bounds with no upper bounds, due to the uncertainty in the effectiveness estimates. pERC also noted that the submitted base-case ICERs were lower than the EGP's lower bound ICER estimates. pERC discussed that EGP made the following changes to the model to address some of its limitations: 1) a shorter time horizon to address the uncertainty in survival estimates based on extrapolation of short-term trial data and to align the time horizon to previous pCODR reviews in the relapsed CLL setting, (2) incorporating a waning treatment effect of venetoclax plus rituximab, which in the submitted base-case was assumed to continue for the full model time horizon, and (3) choosing a different model to parameterize the survival curves, which does not assume proportionality of hazards between PFS and OS of venetoclax plus rituximab. pERC noted the factors that most influence the incremental cost of venetoclax plus rituximab include the availability of rituximab as a biosimilar and in subcutaneous form. The key factor impacting the incremental effect were the effectiveness estimates derived from the submitter-provided ITC. Given the high uncertainty in the comparative effectiveness estimates, EGP elected to not place upper bound ICERs on the comparisons in order to reflect this uncertainty. Further, pERC noted that approximately one-half of patients across both arms in the MURANO trial received growth factor support, which is costly, and was not considered in the economic model. Overall, pERC agreed with the EGP's reanalyses and concluded that venetoclax plus rituximab could not be considered cost-effective when compared with bendamustine plus rituximab, and that the cost-effectiveness is uncertain when compared with ibrutinib and idelalisib plus rituximab.

pERC discussed the feasibility of implementing a reimbursement recommendation for venetoclax plus rituximab for patients with CLL who have received at least one prior therapy. pERC noted that the key factors influencing the incremental budget impact were the proportion of patients actively treated, the assumed market share of venetoclax plus rituximab, and the cost of rituximab (biosimilar and/or subcutaneous application). pERC discussed that sequencing of treatments for this group of patients is rapidly evolving. If ibrutinib was to be used more commonly to treat patients in the first line, given its

efficacy reported in recent studies, the market share of venetoclax plus rituximab in the second line would likely increase. Further, pERC noted that approximately one-half of patients across both arms in the MURANO trial received growth factor support, which is costly, and was not considered in the economic model. pERC noted that access to growth factors may vary across jurisdictions and that additional health care resources will be required for their provision. The Committee discussed that jurisdictions will need to consider the uncertainty in these factors upon implementation, and that the submitted Canada-wide budget impact is likely underestimated.

EVIDENCE IN BRIEF

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

- 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
- A joint 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.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the efficacy and safety of venetoclax plus rituximab compared with bendamustine plus rituximab in patients with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.

Studies included: One randomized, open-label, phase III trial

The pCODR systematic review included one randomized, placebo-controlled, phase III trial: MURANO. The MURANO trial evaluated the efficacy and safety of venetoclax plus rituximab compared with bendamustine plus rituximab in patients with R/R CLL who have received at least one prior therapy.

A total of 389 patients were randomized (1:1) in MURANO, with 194 assigned to venetoclax plus rituximab and 195 assigned to bendamustine plus rituximab. Patients in the experimental group were treated with oral venetoclax plus rituximab at an initial dose of 20 mg per day, which was gradually increased to 400 mg per day according to a five-week schedule. Prophylactic and monitoring measures, including administering oral uric acid reducer beginning ≥ 72 hours before dose administration, were instituted to mitigate the potential for developing tumour lysis syndrome (TLS). After completion of the dose ramp-up period for venetoclax, IV rituximab was initiated in a 28-day treatment cycle for six cycles while the daily oral venetoclax continued. The first dose of rituximab, given on day one of cycle 1, was 375 mg per square metre of body-surface area. The remaining five doses were 500 mg/m^2 each, administered on day one of subsequent cycles — thus, cycle 2 through cycle 6. For patients in the bendamustine plus rituximab arm, IV bendamustine was administered at a dose of 70 mg/m^2 of body-surface area on days one and two of each 28-day cycle for six cycles, alongside IV rituximab using the same dosage schedule as described for the venetoclax plus rituximab group. After the six cycles of combination, patients in the venetoclax plus rituximab arm were expected to continue venetoclax monotherapy for a total treatment duration of two years. In line with standard practice recommended in its product monograph, the treatment with bendamustine was not continued after the six-cycle combination therapy ended.

The median duration of exposure to venetoclax was 22.1 months. The median duration of exposure with bendamustine was not specified, although it was expected to be shorter given that the drug was not continued after the sixth cycle. The exposure to rituximab was similar in the two treatment groups, with patients in either group receiving rituximab for a median of six cycles.

The key inclusion criteria included adult patients (age ≥ 18 years) with diagnosis of R/R CLL that required therapy, prior treatment with one to three lines of treatment (including at least one chemo-containing regimen), and a response duration of at least 24 months if prior treatment included bendamustine. The exclusion criteria included transformation of CLL to aggressive or central nervous system involvement, previous allogeneic or autologous stem-cell transplant, major organ dysfunction, active infection, other active malignancy, current pregnancy or breastfeeding, and treatment with warfarin (during venetoclax dose ramp-up) or strong CYP3A4 inhibitors or inducers.

Patient population: Median age 65 years; > 57% of patients had a single previous anti-CLL therapy; less than 3% of patients had prior B-cell receptor inhibitors

The study population was predominantly male (> 70% in each group) and the median age was 64.5 and 66.0 years in the venetoclax plus rituximab and bendamustine plus rituximab groups, respectively. The

majority of patients in each group had an ECOG performance status score of 0 (> 55%) or 1 (> 42%), and chromosome 17p deletion was absent in 73% of patients in both treatment groups. Most patients (≥ 85%) in each group had lymph nodes with largest diameter < 10 cm and the proportion of patients with a single previous anti-CLL therapy was 57% and 60% in the venetoclax plus rituximab and bendamustine plus rituximab groups, respectively. The majority of patients were at medium risk of developing TLS (>50% in each group). The proportion of patients at high risk of developing TLS was 27.8% and 28.2% in the venetoclax plus rituximab and bendamustine plus rituximab groups, respectively. Patients who were at high-risk of developing TLS were to be admitted to hospital as per the monitoring measures in the study protocol. Overall, the baseline demographic and disease characteristics were similar across the two treatment groups. The majority of patients in both treatment arms had prior anti-CLL therapy with an alkylating agent, purine analogue, and anti-CD20 antibody. The proportion of patients with prior B-cell receptor inhibitors was less than three per cent in both arms.

Key efficacy results: Clinically meaningful improvement in progression-free survival in favour of venetoclax plus rituximab

The primary efficacy end point was investigator-assessed progression-free survival (PFS), which was defined as the time from random assignment to the first occurrence of progression, relapse, or death, whichever occurred first. Key secondary end points included overall survival (OS), overall response rate, safety, and quality-of-life (QoL) outcomes. The assessment of minimal residual disease (MRD) was a pre-specified exploratory end point.

At the time of the primary analysis, the median PFS was 17 months in the bendamustine plus rituximab group but was not reached in the venetoclax plus rituximab group. However, the hazard ratio (HR) indicated a significantly longer PFS with venetoclax plus rituximab than with bendamustine plus rituximab (HR = 0.17; 95% confidence interval [CI], 0.12 to 0.26). An updated analysis performed with one more year of follow-up after the primary analysis (a median follow-up period of 36 months) showed that the PFS with venetoclax plus rituximab remained superior to bendamustine plus rituximab (HR = 0.16; 95% CI, 0.12 to 0.23).

As of the May 8, 2017, data cut (primary analysis), median OS was not reached in either treatment arm. The Kaplan-Meier estimates of 24-month OS were higher in the venetoclax plus rituximab arm than the bendamustine plus rituximab arm (24-month OS: 91.9% versus 86.6%, respectively). The OS difference between the treatment groups was only descriptive given that the first formal statistical test in a pre-specified hierarchical testing to adjust for multiple testing of the key secondary efficacy end points was not statistically significant. The median OS was not reached in either treatment arm at the time of the updated analysis (data cut-off May 2018). The three-year estimates showed a consistently higher improvement in OS rate with venetoclax plus rituximab (87.9%) than with bendamustine plus rituximab (79.5%), with HR = 0.50 (95% CI, 0.30 to 0.85; *P* = .0093). However, the investigators reported that no statistical provision to account for multiple testing of the end points of the updated analysis was conducted. Therefore, all reported *P* values were for descriptive purposes only without indicating statistical significance.

The assessments at the primary analysis demonstrated that the peripheral blood MRD-negativity rate was higher in the venetoclax plus rituximab group than in the bendamustine plus rituximab group at the end of the combination treatment period (the nine-month time point) (62.4% versus 13.3%), and at any time during the trial (83.5% versus 23.1%). At the end of the combination therapy, patients with low-level MRD had a longer duration of PFS compared with those with high-level MRD in both the venetoclax plus rituximab arm (HR = 0.24; 95% CI, 0.08 to 0.72), and the bendamustine plus rituximab arm (HR = 0.22; 95% CI, 0.13 to 0.38). At the May 2018 updated analysis, the overall MRD-negativity rate was 82.5% in the venetoclax plus rituximab group compared with 23.1% in the bendamustine plus rituximab group.

Patient-reported outcomes: QoL results collected in the MURANO trial were inconclusive

QoL was a secondary outcome in the MURANO trial. Health-related QoL was assessed with the MD Anderson Symptom Inventory, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30), the EORTC QLQ-CLL16, and the EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) questionnaire. Due to administrative errors the baseline PRO assessments (EORTC QLQ-c30 and QLQ-CLL16) were partially collected. Additionally, the MD Anderson Symptom Inventory was only administered until the end of cycle 3, also due to administrative error. In the evaluable sample there was no clinically meaningful difference observed between venetoclax plus rituximab and bendamustine plus rituximab in any of the QoL domains during treatment and through follow-up. However, given the

administrative errors, which resulted in a significant extent of missing patient-reported outcomes data, the health-related QoL results collected in the MURANO trial were inconclusive.

Safety: Manageable toxicity profile, similar between groups

The incidence and severity of adverse reactions with venetoclax plus rituximab were broadly similar to those in the bendamustine plus rituximab group. All the patients (100.0%) in the venetoclax–rituximab group and 98.4% in the bendamustine plus rituximab group had at least one adverse event (AE) of any grade (in at least 10% of the safety population). Neutropenia was the most common AE of any grade in both treatment groups (60.8% of the patients in the venetoclax plus rituximab group and 44.1% of the patients in the bendamustine plus rituximab group). Other AEs reported commonly in the venetoclax plus rituximab group (versus bendamustine plus rituximab) included diarrhea (39.7% versus 16.5%), infections and infestations (34.0% versus 42.3%), upper respiratory tract infection (22.2% versus 15.4%), nausea (21.1% versus 34.0%), and fatigue (17.5% versus 20.7%).

Grade 3 or 4 AEs were reported in 82.0% of patients in the venetoclax plus rituximab group and in 70.2% in the bendamustine plus rituximab group, with neutropenia being the most common. The incidence of grade 3 or 4 neutropenia was higher in the venetoclax plus rituximab group than in the bendamustine plus rituximab group (57.7% versus 38.8%). However, the incidence of febrile neutropenia was lower in the venetoclax plus rituximab group than in the bendamustine plus rituximab group (3.6% versus 9.6%). Protocol-mandated dose interruption for all grade 3 or 4 events of neutropenia occurred in 43.3% of the patients in the venetoclax plus rituximab group.

The incidence of serious AEs was similar in the two groups (46.4% of the patients in the venetoclax plus rituximab group and 43.1% of the patients in the bendamustine plus rituximab group). AEs that resulted in death were reported in 5.2% of the patients in the venetoclax plus rituximab group and in 5.9% of the patients in the bendamustine plus rituximab group. Infections or infestations were the most common AEs that resulted in death, accounting for four fatalities in each group.

The percentage of patients with at least one AE leading to treatment discontinuation was 12.9% with venetoclax and 9.0% with bendamustine. The treatment discontinuation rate due to AEs with rituximab was 5.2% in the venetoclax plus rituximab arm compared with 6.9% in the bendamustine plus rituximab arm.

Grade 3 or 4 TLS was reported in six patients (3.1%) in the venetoclax plus rituximab group and in two patients (1.1%) in the bendamustine plus rituximab group. One patient in each treatment group had clinical TLS. Other instances of TLS were based on changes in laboratory values only.

In total, 47.9% of the patients in the venetoclax plus rituximab group and 43.1% of the patients in the bendamustine plus rituximab group received growth factor support.

Limitations: No direct comparative data to B-cell receptor inhibitors (ibrutinib and idelalisib plus rituximab)

The pCODR Methods Team summarized and critically appraised a submitter-provided indirect treatment comparison (ITC). The ITC provided comparative efficacy estimates between venetoclax plus rituximab and ibrutinib and between venetoclax plus rituximab and idelalisib plus rituximab. The results of the ITC favoured venetoclax plus rituximab for OS in the comparison with ibrutinib and for PFS and OS in the comparison with idelalisib plus rituximab. The pCODR Methods Team and the pCODR Economic Guidance Panel (EGP) identified several limitations with the ITC. Most notably, the unanchored ITC assumed that absolute outcomes can be predicted from the covariates, accounting for all effect modifiers and prognostic factors. This assumption is mostly considered impossible to meet, leading to an unknown amount of bias in the unanchored estimates. Other factors that increased the uncertainty in the effect estimates included overlapping CIs, the immaturity of PFS and OS data, the lack of individual patient data, and the absence of indirect comparisons for safety data and QoL. pERC agreed with the Methods Team that, given these limitations, the comparative effectiveness of venetoclax plus rituximab versus B-cell receptor inhibitors remained uncertain.

Need and burden of illness: Need for treatment that delays disease progression

CLL is an incurable malignancy of B lymphocytes. With an incidence of approximately four to five out of 100,000 in the general population, it is the most common adult leukemia in the Western hemisphere. Approximately 2,400 Canadians are diagnosed with and 650 die from CLL each year. Median age at

diagnosis is 72 years, and within incident cases there is a male predominance. For patients with CLL that has relapsed or is refractory to standard front-line therapies, there is no agreed-upon standard treatment, and there are few randomized trials to guide practice. Common treatment options in second line include chemoimmunotherapy regimens and B-cell receptor inhibitors for most patients with CLL, although patients with the chromosome 17p deletion do not respond to chemoimmunotherapy. CLL is characterized as a heterogeneous disease with several prognostic and predictive variables that correlate with the tempo of disease progression and survival, as well as response to therapy. OS of patients with relapsed CLL is between three and five years. There is a need for new effective treatment options that delay disease progression, with favourable toxicity and activity that is independent of genetic and other mechanisms of treatment resistance.

Registered clinician input: Venetoclax plus rituximab is an attractive treatment option due to fixed treatment duration; Ibrutinib most relevant comparator; sequencing of alternative therapies remains unknown

Clinician input was provided as one joint submission from 13 clinicians and two individual clinician submissions. The clinicians mentioned that for the specified indication, the most relevant comparator for venetoclax plus rituximab would be ibrutinib. However, evidence comparing the two regimens is lacking. Clinicians have a positive experience with venetoclax plus rituximab and view the time-limited treatment of two years as more attractive to patients and payers, although IV administration of rituximab remains a challenge. The fewer contraindications of venetoclax plus rituximab compared with ibrutinib also make it an attractive option for patients with cardiovascular conditions. The use of MRD testing was mentioned by some but not all clinicians as a metric to inform treatment decisions and discontinuation. Sequencing of alternative therapies before and after venetoclax plus rituximab remains theoretical with little supporting data, but many clinicians would prefer venetoclax plus rituximab as first line/second line and use ibrutinib after venetoclax plus rituximab has failed.

PATIENT-BASED VALUES

Values of patients with CLL: Individualized treatment options, delaying disease progression, reducing side effects, improving quality of life, having accessible and affordable treatments, and an oral route of administration

One patient input was provided to pCODR through a joint submission from two patient advocacy groups. Patients expressed a number of negative symptoms associated with CLL. Fatigue or lack of energy and enlarged lymph nodes were the most commonly reported symptoms related to CLL affecting QoL. Patients reported that their QoL was mainly affected in the advanced stages of their disease and highlighted fatigue and frequent infections as greatly impacting patients on an ongoing basis. Respondents also indicated experiencing emotional and mental distress due to their condition. With regard to patients' experience with current therapy for CLL, fatigue, anemia or neutropenia, nausea, thrombocytopenia, diarrhea, and infections were side effects most frequently cited by patients. Patients reported that the most difficult side effects to tolerate were fatigue, nausea, and frequency of infections. Patients viewed IV therapy as having a larger negative impact on QoL than oral therapy.

In terms of expectations for alternative treatment options, focus was placed on individualized treatment options, delaying disease progression, reducing side effects, improving QoL, having accessible and affordable treatments, and an oral route of administration.

Patient values on treatment: Favourable experience; reduction in CLL symptoms; subcutaneous rituximab

A total of 14 patients had experience with venetoclax plus rituximab. Overall, patients had a favourable experience. Most patients saw a reduction in commonly reported symptoms with CLL. The majority of patients experienced improvement in lymph node size, lymphocyte counts, and fatigue. Treatment with venetoclax plus rituximab led to various side effects; most commonly reported were neutropenia, fatigue, and diarrhea. The majority of respondents indicated that they were willing to tolerate potentially serious or significant side effects. Overall, treatment did not have a significant negative impact on QoL and daily living. However, patients noted that clinician visits and infusions were burdensome and welcomed the potential availability of subcutaneous rituximab.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analyses

The pCODR EGP assessed one cost-utility analysis (clinical effects measured by quality-adjusted life-years gained) of venetoclax plus rituximab compared with 1) bendamustine plus rituximab, 2) ibrutinib, and 3) idelalisib plus rituximab, for patients with R/R CLL who have received at least one prior therapy.

Basis of the economic model: Clinical and economic inputs

The key clinical outcomes considered in the cost-utility analysis were PFS, OS, and utilities.

Costs considered in the analysis included those related to drug treatment, disease management, treatment-specific monitoring (i.e., TLS), end of life, and AEs.

Drug costs: Treatment cost of venetoclax plus rituximab and comparators

- Venetoclax plus rituximab (oral) costs $0.68 per mg ($6.79 per 10 mg, $33.99 per 50 mg, and $67.98 per 100 mg)
  Dosage schedule: first 5-week dose ramp-up and subsequent daily maintenance dose: week 1: 20 mg; week 2: 50 mg; week 3: 100 mg; week 4: 200 mg; week 5 and onward: 400 mg for up to 24 months
  Cost per 28-day cycle: first cycle (ramp-up cycle): $1,760.80; subsequent cycles: $7, 614.60

- Rituximab (IV) costs 4.75 per mg ($453.10 per 100 mg vial and $2,265.50 per 500 vial)
  Dosage schedule: 375mg/m^2 day 1, cycle 1; 500 mg/m^2 day 1, cycles 2 to 6
  Cost per 28-day cycle: first cycle: $3,058.40; subsequent cycles: $4,077.90

- Bendamustine (IV) costs $12.50 per mg ($1,250 per 100 mg)
  Dosage schedule: 70mg/m^2 day 1 and day 2 per 28-day cycle; six cycles
  Cost per 28-day cycle: $3,375.00

- Ibrutinib (oral) costs $0.67 per mg ($92.19 per 140 mg tablet)
  Dosage schedule: 420 mg daily
  Cost per 28-day cycle: $7,744.00

- Idelalisib (oral) costs $0.57 per mg ($85.35 per 150 mg tablet)
  Dosage schedule: 150 mg twice daily
  Cost per 28-day cycle: $4,779.60

Cost-effectiveness estimates: Not cost-effective at the submitted price; uncertainty in comparative effect estimates derived from ITC

The submitter-provided economic analyses assessed the cost-effectiveness of venetoclax plus rituximab compared with bendamustine plus rituximab, ibrutinib, and idelalisib plus rituximab. The EGP reanalysis of cost-effectiveness presented incremental cost-effectiveness ratios (ICERs) as lower bounds with no upper bounds, given the uncertainty in the effectiveness estimates, which were derived from an ITC. The submitted base-case ICERs were lower than EGP's lower bound ICER estimates. EGP made the following changes to the model to address some of its limitations:

(1) a shorter time horizon (five years instead of 10 years) to address the uncertainty in survival estimates based on extrapolation of short-term trial data and to align the time horizon to previous pCODR reviews in the relapsed CLL setting,

(2) incorporating a waning treatment effect of venetoclax plus rituximab, which in the submitted base-case was assumed to continue for the full model time horizon,

(3) choosing a different model to parameterize the survival curves, which does not assume proportionality of hazards between PFS and OS of venetoclax plus rituximab.

The factors that most influence the incremental cost of venetoclax plus rituximab include the availability of rituximab as a biosimilar and in subcutaneous form. The key factor impacting the incremental effect was the effectiveness estimates derived from the submitter-provided ITC. Given the high uncertainty in the comparative effectiveness estimates, EGP elected to not place upper bound ICERs on the comparisons in order to reflect this uncertainty. Approximately one-half of patients across both arms in the MURANO

trial received growth factor support, which is costly, and was not considered in the economic model. Overall, pERC agreed with the EGP's reanalyses and concluded that venetoclax plus rituximab is not cost-effective when compared with bendamustine plus rituximab, and that the cost-effectiveness is uncertain when compared with ibrutinib and idelalisib plus rituximab.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget impact likely underestimated

The submitter provided a Canada-wide budget impact analysis to assess the feasibility of implementing a reimbursement recommendation for venetoclax plus rituximab for patients with CLL who have received at least one prior therapy. The key factors influencing the incremental budget impact over a three-year time frame was the proportion of patients actively treated, the assumed market share of venetoclax plus rituximab, and the cost of rituximab (biosimilar and/or subcutaneous application). EGP noted that, should ibrutinib be used more commonly to treat patients in the first-line, given its efficacy as found by recent studies, the market share of venetoclax plus rituximab in the second line would likely increase. Approximately one-half of patients across both arms in the MURANO trial received growth factor support, which is costly, and was not considered in the economic model. Access to growth factors may vary across jurisdictions and additional health care resources will be required for their provision. Overall, the Committee concluded that the submitted Canada-wide budget impact was likely underestimated.

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)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

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

- Drs. Marianne Taylor and Kelvin Chan, who were not present for the meeting
- Daryl Bell, who did not vote due to his 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 plus rituximab for chronic lymphocytic leukemia, through their declarations, none of the 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 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.

Disclaimer

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APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
• PAG is seeking clarity on whether or not the following patients would be eligible for treatment with venetoclax plus rituximab: ○ patients with ECOG performance status ≥ 2 ○ patients previously treated with first-line ibrutinib ○ patients previously treated with obinutuzumab plus chlorambucil.	• MURANO required study participants to have an ECOG performance status of 0 or 1. The benefit for patients with ECOG 2 cannot be formally concluded from the study. However, pERC agreed with CGP that it would be reasonable to expand venetoclax plus rituximab to patients with a good performance status, based on clinical experience and the manageable side-effect profile. • In MURANO less than 3% of patients in both arms received B-cell receptor (BCR) inhibitors. pERC noted that phase II trial data (the M14-032 trial that pERC deliberated upon in 2018) suggest that venetoclax single agent is active after treatment with a B-cell receptor inhibitor and that there is no biological rationale to assume that outcomes of venetoclax plus rituximab observed in the MURANO trial would be different in patients previously treated with ibrutinib. Therefore, pERC agreed with the CGP that the results of the MURANO trial can be generalized to patients who have previously received first-line ibrutinib. • The study population in the MURANO trial was obinutuzumab plus chlorambucil naive. pERC agreed with CGP that it would be reasonable to expand eligibility for venetoclax plus rituximab to patients who have failed obinutuzumab plus chlorambucil, based on biological plausibility.
• For patients treated with a first-line rituximab-containing regimen (e.g., fludarabine, cyclophosphamide, and rituximab [FCR] or bendamustine plus rituximab), what is the appropriate minimum treatment-free interval before starting treatment with venetoclax plus rituximab?	• pERC agreed with CGP that patients who have responded to rituximab-containing therapy such as FCR or obinutuzumab-containing therapy would be considered to have CLL that is sensitive to a CD20 antibody if the treatment-free interval is 12 months or longer.
• PAG is seeking clarity on whether or not the following patients would be eligible for treatment with venetoclax plus rituximab and if so, at what point in their treatment: ○ patients who currently receive monotherapy venetoclax for previously treated CLL (i.e., who have received at least one prior therapy and who have failed a B-cell receptor inhibitor.	• pERC agreed with CGP that there are no data specifically addressing the addition of rituximab to patients who are responding to venetoclax single agent. However, pERC agreed with CGP that it would be reasonable to add rituximab at any point at the discretion of the treating physician. • Further, pERC and CGP do not recommend the addition of rituximab to those patients who are progressing on venetoclax single agent, as there is no data that doing so would result in disease response.

• For patients on venetoclax plus rituximab, who do not experience progression, are there instances where venetoclax treatment should continue beyond the 24 months of treatment? • For patients who have completed the 24 months of venetoclax treatment and experience progression, should re-treatment with venetoclax plus rituximab be an option?	• The MURANO trial studied patients who continued oral venetoclax treatment for up to 24 months post-ramp-up schedule. pERC agreed with CGP that currently there is insufficient evidence to make an informed recommendation on the use of venetoclax beyond the 24-month treatment duration. • pERC agreed with CGP that for patients who showed benefit and were able to tolerate venetoclax plus rituximab during the initial 24 months of treatment, re-treatment with venetoclax plus rituximab should be an option.
• PAG is seeking guidance on the appropriate treatment options in the first-line and relapsed/refractory CLL setting: o For patients who have received one prior therapy, what would be the best treatment (e.g., venetoclax plus rituximab, ibrutinib, or idelalisib plus rituximab)? o What is the optimal sequencing of venetoclax/rituximab treatment with other treatments (e.g., first-line chemoimmunotherapy, ibrutinib, idelalisib plus rituximab)? o What is the optimal sequencing for patients with del(17p) who have received first-line ibrutinib (e.g., venetoclax monotherapy, venetoclax plus rituximab)?	• pERC agreed with CGP that ibrutinib is currently the most relevant comparator for venetoclax plus rituximab in this setting. pERC noted that idelalisib plus rituximab is less frequently used due to its toxicity concerns. pERC further agreed with CGP that there is insufficient evidence at this point to recommend either venetoclax plus rituximab or ibrutinib over the other. pERC noted that the choice between venetoclax plus rituximab and ibrutinib will likely depend upon the relative overall cost, treatment availability, patient values and preferences (e.g., fixed versus indefinite treatment duration), and clinical factors such as tolerability to adverse events. • pERC was unable to make an informed recommendation on the optimal sequencing of venetoclax plus rituximab with other therapies in CLL as current data do not inform this clinical situation. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of venetoclax plus rituximab and noted that a national approach to developing evidence-based clinical practice guidelines would be of value. • pERC was unable to make an informed recommendation on the optimal sequencing of venetoclax plus rituximab with other therapies in CLL as current data do not inform this clinical situation. However, pERC noted that phase II trial data (the M14-032 trial that pERC deliberated upon in 2018) suggest that venetoclax single agent is active after treatment with a B-cell receptor inhibitor and that there is no biological rationale to assume that the outcomes of venetoclax plus rituximab observed in the MURANO trial would be different in patients previously treated with ibrutinib. Therefore, pERC agreed with CGP that the results of the MURANO trial can be generalized to patients who have previously received first-line ibrutinib.
• PAG is seeking guidance on whether subcutaneous rituximab in combination with venetoclax would be used clinical practice, if available.	• pERC agreed with CGP that there are no published data on the use of subcutaneous rituximab in the management of CLL. The use of the subcutaneous preparation in patients who tolerate an initial IV rituximab infusion, would be considered appropriate in combination with venetoclax as given in the MURANO trial.

CLL = chronic lymphocytic leukemia; FCR = fludarabine, cyclophosphamide, and rituximab; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; CGP = pCODR Clinical Guidance Panel.