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ORIGINAL RESEARCH ARTICLE

Venetoclax in Combination with Obinutuzumab in Previously Untreated Fit Patients with Chronic Lymphocytic Leukemia: A Canadian Cost-Utility Analysis

Gijs van de Wetering[1] · Carolyn Owen[2] · Versha Banerji[3,4] · Ariane Gosselin[5] · Shivani Kamdar[6] · Nancy Paul Roc[5] · Lytske Bakker[1] · Gargi Ratnaparkhi[7] · Stephane Barakat[5] · Colin Vicente[6] · Beenish S. Manzoor[8]

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Abstract

Background/Objective Chronic lymphocytic leukemia (CLL) is the most common lymphoproliferative disorder diagnosed in Canada and is associated with a significant economic burden. This study evaluates the cost effectiveness of fixed-treatment duration venetoclax plus obinutuzumab (VEN + O) for previously untreated, fit CLL patients in Canada, for whom this therapy is not universally reimbursed provincially.

Methods A three-state partitioned survival model was developed using data from the CLL13 trial and a Bayesian network meta-analysis. Health states included progression-free, progressed disease, and death. A lifetime horizon (40-year) was used and a 1.5% discount rate was applied to costs and effects. Costs included drug acquisition, administration, monitoring, adverse events, subsequent treatment, and terminal care. Utility values were derived from previous NICE technology appraisals in CLL. Extensive sensitivity and scenario analyses were conducted.

Results VEN + O was associated with lower total costs and higher quality-adjusted life years and thus dominant compared with ibrutinib, zanubrutinib, and fludarabine plus cyclophosphamide plus rituximab. Compared with acalabrutinib and venetoclax plus ibrutinib, the incremental cost-utility ratios (ICURs) were in the south-west quadrant and substantially above a CA$50,000/QALY willingness-to-pay threshold, meaning VEN + O was cost effective versus these comparators. VEN + O was cost effective versus bendamustine plus rituximab. Extensive sensitivity and scenario analyses confirmed the robustness of these results.

Conclusions This analysis demonstrates that VEN + O, a 12-month fixed duration treatment, is a cost-effective option for previously untreated fit CLL patients in Canada. VEN + O offers potential health benefits and cost savings when compared with relevant comparator treatments.

✉ Beenish S. Manzoor
beenish.manzoor@abbvie.com

1 OPEN Health, Rotterdam, The Netherlands

2 Division of Hematology and Hematological Malignancies, University of Calgary, Calgary, Canada

3 University of Manitoba and the Paul Albrechtsen Research Institute CancerCare Manitoba, Winnipeg, Canada

4 Departments of Internal Medicine and Biochemistry and Medical Genetics, Rady Faculty of Health Sciences, Rady College of Medicine, Max, University of Manitoba, Winnipeg, Canada

5 AbbVie Corporation, Saint-Laurent, Canada

6 PIVINA Consulting Inc., Mississauga, Canada

7 OPEN Health, Mumbai, India

8 AbbVie Inc., North Chicago, USA

Key Points for Decision Makers

Compared with relevant comparator treatments for previously untreated fit patients with CLL in Canada, VEN + O is a cost-effective treatment option from a Canadian public healthcare payer perspective.

When extrapolating the clinical superior efficacy associated with VEN + O in the CLL13 trial versus standard chemo-immunotherapy using a health economic model, VEN + O is expected to lead to long-term treatment benefits for CLL patients.

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1 Introduction

Chronic lymphocytic leukemia (CLL) is the most common lymphoproliferative disorder [1] with 1700 new patients diagnosed in Canada in 2019 and with a higher number of cases in men (1095 cases) compared with women (605 cases). The reported number of deaths in Canada due to CLL in 2022 was 555 [2]. The disease predominantly affects the elderly, with the average age at diagnosis of approximately 70 years [3]. CLL is an indolent lymphoproliferative disorder with many therapeutic options and increasing prevalence. In 2021, the economic burden of all leukemias combined from a Canadian societal perspective was estimated to be 1.4 billion Canadian dollars (CA$) [4].

Historically, clinical trials of CLL patients classified individuals as fit or unfit according to their age, their Cumulative Illness Rating Score (CIRS), their creatinine clearance (CrCl), and/or other factors. In clinical trials, fit patients are commonly those aged ≤ 65 years old, with a CIRS score ≤ 6 and/or CrCl ≥ 70 mL/min, and unfit patients are those aged > 65 years old, with a CIRS score > 6 and/or CrCl < 70 mL/min.

Patients are eligible for treatment depending on their age, fitness, and prognostic biomarkers [5]. For fit CLL patients who have not been previously treated, the recommended funded treatments in Canada are fludarabine, cyclophosphamide, plus rituximab (FCR) for immunoglobulin heavy chain variable region (IGHV) mutated patients and Bruton's tyrosine kinase inhibitors (BTKis), including acalabrutinib (ACA), ibrutinib (IBR), and zanubrutinib (ZANU) for IGHV unmutated patients. Venetoclax plus ibrutinib (VEN + I) has received a positive recommendation from Canada's Drug Agency (CDA-AMC), formerly known as the Canadian Agency for Drugs and Technologies in Health (CADTH), in November 2023 [6]. VEN + I is listed as a first-line treatment option in the most recent version of the CDA-AMC provisional funding algorithm for CLL [7], and is publicly reimbursed in most Canadian provinces. Venetoclax plus obinutuzumab (VEN + O) has been reimbursed in Canada for previously untreated unfit CLL patients who are ineligible for the more intensive FCR regimen since 2022. VEN + O also received a positive recommendation from the CDA-AMC for the reimbursement of previously untreated fit CLL patients in November 2024 [8], and is publicly reimbursed in some Canadian provinces.

The CLL13 trial (ClinicalTrials.gov identifier: NCT02950051) evaluated the efficacy of VEN + O in fit, previously untreated CLL patients without del17p and TP53 mutation [9]. VEN + O, a 12-month fixed-duration treatment, was compared with chemoimmunotherapies (FCR for patients aged 65 years and younger and bendamustine plus rituximab [BR] for patients over 65 years of age). Additionally, the trial assessed other venetoclax-based regimens, such as venetoclax plus rituximab and VEN + O plus ibrutinib. However, these regimens are not approved in Canada for previously untreated CLL and were not considered in this analysis. VEN + O showed superior progression-free survival (PFS) and higher rates of undetectable minimal residual disease compared with both FCR and BR.

To inform the cost effectiveness of VEN + O for previously untreated fit CLL patients in Canada, a cost-utility analysis was performed comparing VEN + O with the existing treatment options. The analysis was conducted from a Canadian public healthcare payer perspective.

2 Methods

Following a model conceptualization phase, a three-state partitioned survival model was developed in Microsoft Excel 365. Partitioned survival models are the most common decision models used to analyze cost effectiveness in oncology [10–12]. Furthermore, this approach aligns with the previous VEN + O submission to CDA-AMC for unfit CLL patients [13]. A Markov model was also considered but given the anticipated challenges in obtaining transition probabilities for comparators not included in the CLL13 trial, a partitioned survival model was preferred. The partitioned survival model uses extrapolated survival curves alongside an area under the curve approach to estimate health state distributions. Patients are allocated to these health states directly from the survival curves and as such, there is no need to explicitly define transition probabilities between health states. The health states included in the model were progression-free (PF), progressed disease (PD), and death.

The distribution of patients across the health states was based on the extrapolated survival curves. The area under the overall survival (OS) curve was used to estimate the total number of patients alive at each model cycle and the proportion of patients in the PF state was derived directly from the PFS curve. The proportion of patients in the PD state was based on the difference in the area under the OS and PFS curves. Furthermore, PFS hazard rates were capped by OS hazard rates and mortality in the model always exceeded, or was equal to, background mortality. Furthermore, to assess drug acquisition costs, time on treatment (ToT) and time to next anti-leukemic treatment (TTNT) curves were analyzed.

A 28-day cycle length was used in the model, as this aligns with the dosing schedules for VEN + O and its comparators and captures all relevant clinical events in sufficient detail. A half-cycle correction was applied, and the time horizon was 40 years, which could be considered a lifetime

horizon given the median age of patients in the CLL13 trial was 62 years. Based on CDA-AMC guidelines, a 1.5% discount rate was applied to both costs and effects [14].

2.1 Patient Population

The population in the economic model was consistent with the intention-to-treat (ITT) population in CLL13. The mean age of patients in the ITT population was 62.0 years, with a mean bodyweight of 75.7 kg and a mean height of 168.8 cm. Furthermore, the proportion of female patients was 25.3%.

2.2 Model Inputs

2.2.1 Treatment Efficacy

OS, PFS, TTNT, and ToT were estimated by first recreating individual patient-level data using the Guyot method and the corresponding data from the CLL13 trial [15]. All survival analyses were performed using the *flexsurv* package [16] in the R programming language [17]. The proportional hazard assumption (PHA) was assessed using log cumulative hazard plots and the Grambsch–Therneau test for which a significance value of 0.05 was used. Since for all treatments and endpoints there was evidence to suggest the PHA was violated (i.e., due to crossing of the log-cumulative hazard curves or a p value of < 0.05 for the Grambsch–Therneau test), independent models were used.

Model selection was based on several criteria. First, statistical fit to the observed Kaplan–Meier (KM) data was assessed using Akaike's information criterion (AIC) and Bayesian information criterion (BIC). The model with the lowest AIC/BIC score was considered best performing, with models within two points of the lowest AIC/BIC score also considered to fit the data well. In addition, median survival estimates were used to assess the fit of the model. Where median survival was observed, the estimates of median survival given by each model were compared against the observed value to determine which models gave the closest estimate. Where no median survival was observed, the range of median survival estimates given by the models were assessed to determine which model gave the most clinically plausible estimate. Finally, the long-term extrapolation plots were used to determine which models gave the most clinically plausible long-term survival estimates. Where possible, external validation was conducted to determine how the models for a particular endpoint and population compared with external data that was not included in the model fitting procedure. Furthermore, two Canadian clinical experts—renowned hematologists and associate professors with expertise in treating CLL patients—validated the survival extrapolations. Each clinical expert was consulted independently, and if their responses differed, an intermediate option was selected. Table S1 in the electronic supplementary material (ESM) summarizes the survival extrapolations selected for VEN + O, FCR, and BR. The PFS, OS and TTNT KM and survival extrapolation curves are presented in Fig. S1A, S1B, and S1C in the ESM [18]. As illustrated in Fig. S1C, the OS for BR is substantially lower than the OS for FCR and VEN + O. This is because in the CLL13 trial, patients treated with BR were older than age 65 years, whereas patients treated with FCR were aged 65 years or younger.

A Bayesian network meta-analysis (NMA) was conducted to assess treatment efficacy for treatments not assessed in CLL13. Clinical trial data for ACA, BR, FCR, IBR, VEN + I, ZANU, and obinutuzumab plus chlorambucil (O+CLB) were obtained from a systematic literature review including publications up to February 12, 2024. O+CLB was not considered a relevant comparator but was required for a connected evidence network (see Fig. S2 in the ESM). Outcomes assessed were PFS, OS, and TTNT. Heterogeneity was observed across the trials included in the network regarding physical fitness and mutational status (del(17p)/TP53 mutation). In the CLL13, FLAIR, and GLOW trials, patients with del(17p)/TP53 mutations were excluded; however, nine patients with TP53 mutations were reported in GLOW. For the ALLIANCE, ELEVATE-TN, CLL14, and SEQUOIA trials, subgroup analyses were conducted for PFS specifically for patients without del(17p)/TP53 mutation. In the CLL10 trial, patients with del(17p) were excluded whereas the frequency of TP53 mutations was not reported. Additional details concerning the input values for the NMA can be found in Tables S2 and S3 in the ESM. Thus, for the primary analyses, patients without del(17p) or TP53 mutations were included, but the population comprised fit and unfit patients for some studies to ensure a linked evidence network.

The Bayesian NMA was performed in R [17] using the *multinma* package [19] as per the National Institute for Health and Care Excellence (NICE) Decision Support Unit Technical Support Document [20]. Both fixed and random-effects models were fitted, but the best-fitting model was a random-effects model with an informative between-study heterogeneity prior. Bayesian NMA results are presented as posterior median hazard ratios (HRs) and 95% credible intervals (95% CrI). A 95% CrI can be interpreted as a 95% probability that the true treatment effect lies within this interval. There is a 95% probability that the two treatments are different if this interval excludes one (i.e., an HR indicating no difference), which is referred to as significant in the NMA results.

For PFS, VEN + O resulted in significantly better outcomes compared with FCR and BR (Table 1). There was no significant difference in PFS for VEN + O compared with ACA and VEN + I, although these treatments provided numerically better outcomes. For OS, due to the

Table 1 Pairwise hazard ratios and 95% credible intervals for posterior medians for PFS, OS, and TTNT random effects model

Treatment compared with VEN + O	PFS	OS	TTNT
ACA	0.53 (0.18–1.56)	0.87 (0.27–2.62)	ND
BR	**3.42 (1.79–7.47)**	2.01 (0.76–6.04)	**3.80 (2.03–6.58)**
FCR	**2.07 (1.17–4.23)**	1.28 (0.48–3.20)	**2.62 (1.53–4.27)**
IBR	1.29 (0.47–4.05)	2.46 (0.67–10.36)	ND
VEN + I	0.47 (0.20–1.05)	0.40 (0.15–1.03)	0.40 (0.14–1.14)
ZANU	1.30 (0.47–4.03)	2.16 (0.54–9.29)	ND

Bolded text indicates statistically significant (based on 95% credible interval) differences between VE N + O and each comparator

ACA acalabrutinib, *BR* bendamustine + rituximab, *FCR* fludarabine + cyclophosphamide + rituximab, *IBR* ibrutinib, *ITT* intention-to-treat, *ND* no data available, *OS* overall survival, *PFS* progression-free survival, *TTNT* time-to-next anti-leukemic treatment, *VEN + I* venetoclax + ibrutinib, *VEN + O* venetoclax + obinutuzumab, *ZANU* zanubrutinib

small number of events, there was no significant difference between treatments. However, VEN + I and ACA demonstrated numerical improvements relative to VEN + O whereas VEN + O demonstrated numerically better outcomes compared with BR, FCR, IBR and ZANU. For TTNT, VEN + O was associated with significantly better outcomes compared with FCR and BR whereas versus VEN + I there was no significant difference, although TTNT was numerically better for VEN + I. Pairwise hazard ratios for all treatments compared with VEN + O can be found in Table 1.

2.2.2 Quality of Life and Adverse Events

Due to the lack of access to available quality-of-life data from the CLL13 trial, utility values were derived from previous NICE technology appraisals in CLL. Specifically, the publication by Hancock et al. [21], referenced in NICE TA174 [22] for first-line CLL treatment with FCR, was used. Utility values were 0.80 for the PF health state and 0.60 for the PD health state (see Table S4 in the ESM). To account for age-related deterioration in health-related quality of life (HRQoL), utility values were adjusted using published age-specific mean utility values for the Canadian population [23]. The age-specific utility value for the starting patient age was used as a benchmark, and a decrement ratio was applied to health state utility values in each cycle. To evaluate the impact of adverse events (AEs) on quality of life, disutility values for each AE were multiplied by their duration to calculate a quality-adjusted life year (QALY) decrement, which was applied during the initial model cycle. Grade 3 or 4 AEs occurring in ≥ 5% of patients were included from the CLL13 trial and NICE TA891 for VEN + I [9]. The incidence of AEs for VEN + O, FCR, and BR were sourced from the CLL13 trial, while the incidence of AEs for the other comparators were sourced from their respective pivotal trials. AE frequency, duration, and disutility are summarized in Tables S5 and S6 in the ESM.

2.2.3 Resource Use and Cost

The base case analysis included costs for drug acquisition and administration, monitoring, AEs, subsequent treatment, and terminal care.

Drug acquisition costs for VEN + O and comparator treatments were sourced from previous CDA-AMC submissions, Ontario government resources, and the manufacturer [24–27]. Treatment duration for all treatments was informed by product monographs, protocols, and ToT data [28–33]. For VEN + O, FCR, and BR, ToT was based on CLL13 KM data, while for the external comparators (VEN + I, ACA, IBR, and ZANU), ToT was approximated using their respective PFS curves.

Administration cost for intravenous (IV), subcutaneous (SC), and oral chemotherapies were derived from Chatterjee et al. and the Ontario Schedule of Benefits (OSB [G373]), respectively [34, 35]. IV drugs included costs for administration and pharmacist time, with rapid IVs incurring half of the total infusion cost but full pharmacist time. SC drugs involved nurse-administered injections, including supervision costs and an additional cost for 20 minutes of nurse time for administration and supervision of the injection. A 13% benefit rate and 4.5% vacation pay was considered in the median hourly rate for registered nurse time derived from the Job Bank of Canada [36]. Oral chemotherapies covered lab and physician consultation costs.

Treatment monitoring costs encompassed patient condition evaluations and were associated with resource utilization in both the PF and PD health states. Additionally, a one-time laboratory tumor lysis syndrome (TLS) prophylaxis cost was applied at the beginning of treatment, derived from TA891 [37]. The frequency of TLS prophylaxis was calculated based on individual patient risk factors, such as tumor size and CrCl. The TLS prophylaxis frequencies for VEN + O, FCR, and BR were derived from CLL13 trial data. For all other comparators, TLS prophylaxis frequency was assumed to be equal to VEN + O. Unit costs for medical tests were derived from the OSB for Laboratory Services as a proxy for the rest of Canada [38], and unit costs for medical visits were derived from the OSB [35]. Treatment monitoring activities and their corresponding frequencies are summarized in Table S7 in the ESM.

AE costs were applied as one-time costs in the first model cycle and were based on data from the Canadian Institute for Health Information (CIHI) [39]. The CIHI patient cost estimator data was used for adults aged 60 years or older, assuming inpatient treatment for all Grade 3 or higher AEs, given these AEs are considered serious in nature. The cost for each AE is presented in Table S8 in the ESM.

Subsequent anti-leukemic treatment use was based on the TTNT curves for VEN + O, FCR, and BR, and based on the PFS curves for all other comparators. Total subsequent treatment costs were determined by the difference between the OS and TTNT curves. Subsequent treatment regimens and durations were informed by Canadian clinical expert opinion, whilst ensuring patients do not receive the same treatment in the second line as in the first. The duration for VEN monotherapy in second line was taken from the VENICE-1 study, while ZANU and ACA in second line were assumed to have the same duration as IBR in second line.

Terminal care costs, estimated at CA$7,919.53 based on an Ontarian study, included inpatient services and medical interventions. This one-off cost reflects the comprehensive care provided during the end-of-life phase for CLL patients, encompassing all necessary medical treatments and support [40]. All costs were reported in 2024 Canadian dollars. The Bank of Canada Inflation Calculator was used for conversion if required (Table S8 of the ESM).

2.3 Model Analyses

Model outcomes included total costs, life years (LYs), QALYs, and the incremental cost-utility ratio (ICUR). In line with CDA-AMC guidelines, a probabilistic analysis was used in the base case. Parameters were assigned probability distributions and simulations were run to reflect uncertainty. Parameters were sampled from gamma distributions for costs, beta distributions for utilities and proportions, and log-normal distributions for HRs. The probabilistic results, averaged across iterations, provided mean outcomes with confidence intervals (CIs).

To ensure stable results, model convergence was tested using convergence plots that track the ICUR over the number of probabilistic sensitivity analysis (PSA) simulations. These plots illustrate how the estimated ICUR value changes as more simulations are conducted, helping to confirm that enough iterations have been performed. The model demonstrated convergence at fewer than 600 iterations. The base case analyses were run at 1000 iterations, ensuring well-established convergence.

2.4 Sensitivity Analyses

One-way sensitivity analyses (OWSA) were performed to identify the parameters that most significantly influenced the model outcomes. These analyses assessed the robustness of the model results by varying one parameter at a time while keeping others constant. The results were presented in a tornado diagram, highlighting the parameters with the most significant influence on the ICUR. Additionally, PSAs were conducted to account for uncertainty in all model parameters simultaneously. The PSA involved running multiple simulations to reflect the variability and uncertainty in the model inputs. PSA results were used to construct a cost-effectiveness acceptability curve (CEAC), illustrating the probability of cost effectiveness at different willingness-to-pay (WTP) thresholds.

2.5 Scenario Analyses

Scenario analyses were carried out to determine the robustness of the results to variations in several key parameters. These scenario analyses are described below in Table 2. In scenario 3, caregiver costs, travel costs, and productivity losses were included. In scenario 6, a preference for non-continuous therapies in intermediate and low-risk patients was simulated by increasing the use of VEN+R as a subsequent treatment to 50% for VEN + O and VEN + I, to 80% for FCR and BR, and to 85% for ACA, IBR, and ZANU. In scenario 7, the AEs anaemia, leukocytopenia, lymphocyte count decreased, pneumonia, thrombocytopenia, atrial fibrillation, cataract, hypertension, and musculoskeletal tissue were assumed to be treated in an outpatient setting, incurring the cost of one emergency department visit (CA$358.78) [41]. In scenario 9, utilities were based on NICE technology appraisal 796 (which used the same utilities) [42], and in scenario 10, the mean time on subsequent treatment was halved for all treatments.

Table 2 List of scenario analyses

Scenario #	Description of scenario
1	Discount rate of 0% for costs and effects
2	Discount rate of 3% for costs and effects
3	Societal perspective
4	Conservative TTNT estimates used for VE N + O (gamma distribution), FCR, and BR (Gompertz distribution)
5	Time horizon of 15 years
6	Increased use of VEN+R as subsequent treatment
7	Alternate costing for adverse events
8	Comparison versus FCR and BR only
9	Utilities based on NICE technology appraisal 796
10	Mean time on subsequent treatment halved

BR bendamustine + rituximab, *FCR* fludarabine + cyclophosphamide + rituximab, *TTNT* time-to-next anti-leukemic treatment, *VEN + O* venetoclax + obinutuzumab, *VEN+R* venetoclax + rituximab

2.6 Model Validation

The model underwent rigorous validation processes and quality checks. Clinical expert validation ensured that key assumptions and the model structure accurately reflected Canadian clinical reality, while external validation of survival curves compared predictions with real-world data and published literature when available to ensure consistency, plausibility, and reliability of the model's results. For example, with respect to PFS, the generalized gamma curve was chosen for FCR as it most closely aligned with published 8-year PFS estimates from Woyach et al. [43], while the log-logistic distribution chosen for BR was most closely aligned with the published 7-year PFS estimate in Kutsch et al. [44].

3 Results

3.1 Costs and QALYs

Table 3 provides an overview of the total (discounted) costs per patient over a lifetime horizon, averaged across 1000 simulations. It can be seen that all treat-to-progression regimens (ACA, IBR, and ZANU) are associated with substantially higher costs than treatments with a fixed duration (VE N + O, FCR, BR, VE N + I). These higher costs are primarily driven by drug acquisition costs; for example, ACA incurs the highest total costs at CA$1,435,322 [95% CI 949,657–1,989,115], which can be largely attributed to drug acquisition costs, which amount to CA$1,099,002 [95% CI 566,814–1,795,267]. For treatments with a fixed duration, costs are mainly driven by drug acquisition and subsequent treatment costs, especially for treatments with relative low time between treatment discontinuation and initiation of subsequent treatment.

Table 4 shows the discounted per-patient LYs and QALYs, again averaged across 1000 simulations and shown for both the PFS and PD health states. VEN + I accrued the highest LYs at 18.82 [95% CI 18.13; 19.06], closely followed by VEN + O at 18.62 [95% CI 17.71–19.01] and ACA at 17.91 [95% CI 12.62–19.03]. VEN + I also accumulated the highest total QALYs at 12.74 [95% CI 7.94–16.02], followed by ACA and VEN + O at 12.16 [95% CI 7.20–15.72] and 11.93 [95% CI 7.99–14.84] QALYs, respectively.

3.2 Incremental Cost-Effectiveness Results

Table 5 presents the incremental costs and QALYs of VEN + O versus the comparators. VEN + O is dominant when compared with FCR, IBR, and ZANU as

Table 3 Overview of total costs per patient over a lifetime horizon (discounted)

Costs (CA$)	VE N + O	FCR	BR	VE N + I	ACA	IBR	ZANU
Total drug acquisition (mean [CI])	126,938 [126,791–126,969]	19,261 [19,254–19,263]	32,785 [32,785–32,785]	212,812 [211,010–213,240]	1,099,002 [566,814–1,795,267]	715,316 [369,071–1,289,907]	642,792 [336,633–1,139,552]
Total drug administration (mean [CI])	1949 [1365–2599]	1140 [753–1595]	3246 [2102–4581]	17 [11–24]	4713 [2105–8303]	2930 [1323–5773]	2895 [1324–5813]
Total disease management (mean [CI])	53,283 [38,041–75,728]	43,893 [10,645–72,610]	19,945 [10,124–34,874]	46,717 [29,645–66,926]	44,778 [23,529–67,438]	35,943 [12,316–63,245]	38,536 [13,217–67,713]
One-time drug, administration, monitoring (mean [CI])	503 [264–833]	344 [176–579]	629 [325–1064]	499 [307–729]	499 [307–729]	499 [307–729]	499 [307–729]
Subsequent treatment (mean [CI])	85,999 [6467–166,894]	237,421 [27,834–321,207]	107,430 [20,336–250,305]	286,016 [154,992–341,492]	278,335 [29,268–321,932]	269,289 [18,162–341,738]	294,240 [25,944–405,031]
AE (mean [CI])	3631 [2898–4516]	3646 [2694–4868]	4026 [3206–4954]	7311 [5495–9591]	2092 [1544–2768]	7092 [5508–8868]	1909 [1366–2597]
Terminal care (mean [CI])	5819 [3736–8284]	6121 [3819–9056]	7069 [4476–9993]	5796 [3711–8233]	5903 [3779–8441]	6435 [4076–9213]	6356 [4054–9158]
Total costs (mean [CI])	278,123 [198,925–358,121]	311,827 [13,855–408,478]	175,130 [39,114–325,406]	559,167 [411,354–624,203]	1,435,322 [949,657–1,989,115]	1,037,505 [681,779–1,567,191]	987,225 [651,456–1,419,819]

ACA acalabrutinib, *AE* adverse event, *BR* bendamustine + rituximab, *CI* confidence interval, *FCR* fludarabine + cyclophosphamide + rituximab, *IBR* ibrutinib, *VEN + I* venetoclax + ibrutinib, *VEN + O* venetoclax + obinutuzumab, *ZANU* zanubrutinib

Table 4 Overview of total LYs and total QALYs over a lifetime horizon (discounted)

	VE N + O	FCR	BR	VE N + I	ACA	IBR	ZANU
PFS Lys (mean [CI])	7.47 [6.00–9.26]	7.50 [4.58–16.78]	4.86 [3.94–6.00]	11.24 [6.65–17.12]	10.54 [5.43–17.21]	6.54 [3.37–11.79]	6.47 [3.39–11.47]
PD Lys (mean [CI])	11.15 [9.20–12.67]	8.60 [0.22–13.77]	3.20 [1.02–6.56]	7.58 [1.59–12.23]	7.37 [0.28–12.66]	6.85 [0.17–13.61]	7.58 [0.26–14.13]
Total LYs (mean [CI])	18.62 [17.71–19.01]	16.10 [5.84–18.99]	8.07 [5.46–11.29]	18.82 [18.13–19.06]	17.91 [12.62–19.03]	13.39 [6.84–18.87]	14.05 [7.05–18.92]
PFS QALYs (mean [CI])	5.94 [2.78–8.23]	5.89 [2.31–13.37]	3.86 [1.84–5.37]	8.73 [3.83–14.36]	8.22 [3.01–14.11]	5.19 [1.98–9.52]	5.14 [2.00–9.71]
PD QALYs (mean [CI])	6.00 [3.53–8.60]	4.68 [0.15–9.07]	1.88 [0.54–4.08]	4.01 [0.78–7.64]	3.94 [0.17–8.04]	3.81 [0.09–8.90]	4.19 [0.12–8.82]
AE disutilities (mean [CI])	−0.002 [−0.002 to −0.001]	−0.001 [−0.002 to −0.001]	−0.002 [−0.003 to −0.001]	−0.003 [−0.003 to −0.002]	−0.001 [−0.001 to −0.001]	−0.003 [−0.004 to −0.003]	−0.001 [−0.001 to −0.000]
Total QALYs (mean [CI])	11.93 [7.99–14.84]	10.56 [4.17–15.21]	5.73 [3.17–8.28]	12.74 [7.94–16.02]	12.16 [7.20–15.72]	9.00 [4.31–13.61]	9.33 [4.23–13.88]

ACA acalabrutinib, *AE* adverse event, *BR* bendamustine + rituximab, *CI* confidence interval, *FCR* fludarabine + cyclophosphamide + rituximab, *IBR* ibrutinib, *LYs* life years, *PD* progressed disease, *PFS* progression-free survival, *QALYs* quality-adjusted life years, *VEN + I* venetoclax + ibrutinib, *VEN + O* venetoclax + obinutuzumab, *ZANU* zanubrutinib

Table 5 Base case results: incremental costs, incremental QALYs and ICUR

Treatment	Total costs, CA$	Total QALYs	Incremental costs (VE N + O versus comparator), CA$	Incremental QALYs (VE N + O versus comparator)	ICUR (VE N + O versus comparator)
VE N + O	278,123	11.93			
FCR	311,827	10.56	−33,704	1.37	Dominant
BR	175,130	5.73	102,993	6.20	CA$16,621
VE N + I	559,167	12.74	−281,044	−0.81	SW quadrant: CA$347,762
ACA	1,435,322	12.16	−1,157,199	−0.23	SW quadrant: CA$5,082,177
IBR	1,037,505	9.00	−759,382	2.93	Dominant
ZANU	987,225	9.33	−709,102	2.60	Dominant

ACA acalabrutinib, *BR* bendamustine + rituximab, *FCR* fludarabine + cyclophosphamide + rituximab, *IBR* ibrutinib, *ICUR* incremental cost-utility ratio, *QALYs* quality-adjusted life years, *SW* south-west, *VEN + I* venetoclax + ibrutinib, *VEN + O* venetoclax + obinutuzumab, *ZANU* zanubrutinib

it is associated with cost savings and higher QALYs. VEN + O shows similar QALYs compared with ACA and accrues substantial cost savings. Compared with VEN + I, VEN + O is associated with slightly lower QALYs but cost savings. The ICURs lie in the south-west quadrant at CA$347,762/QALY and CA$5,082,177/QALY compared with VEN + I and ACA, respectively. Given the ICURs are in the south-west quadrant, an ICUR above the WTP threshold of CA$50,000/QALY indicates VEN + I and ACA are not cost effective versus VEN + O. Therefore, given the ICURs for VEN + I and ACA are substantially above a WTP threshold of CA$50,000/QALY, VEN + O is cost effective versus these treatments as well. Compared with BR, VEN + O is cost effective at an ICUR of CA$16,621/QALY, which is below a WTP threshold of CA$50,000/QALY.

Figure 1 showcases the cost-effectiveness frontier for all treatments. As shown, BR, VEN + O, and VE N + I are on the frontier. FCR is strictly dominated by VEN + O, and IBR is strictly dominated by VEN + O, FCR, VEN + I, and ZANU. ZANU is strictly dominated by VEN + O, FCR, and VEN + I, and ACA is strictly dominated by VEN + I.

3.3 Sensitivity Analyses Results

The OWSA results indicate that several parameters had a substantial impact on the model results. These included utility values for both PFS and PD, HRs for PFS and OS, and mean time on subsequent treatments. The ICUR tornado diagrams for VEN + O versus FCR and VEN + O versus BR are presented in Figs. 2 and 3, respectively. As can be seen, model outcomes are most sensitive to

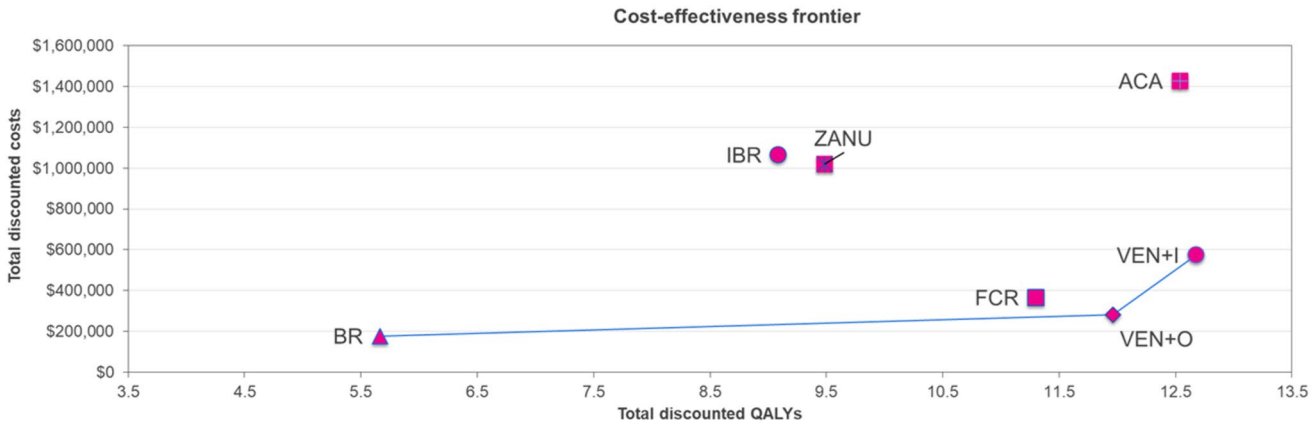

Fig. 1 Cost-effectiveness frontier.

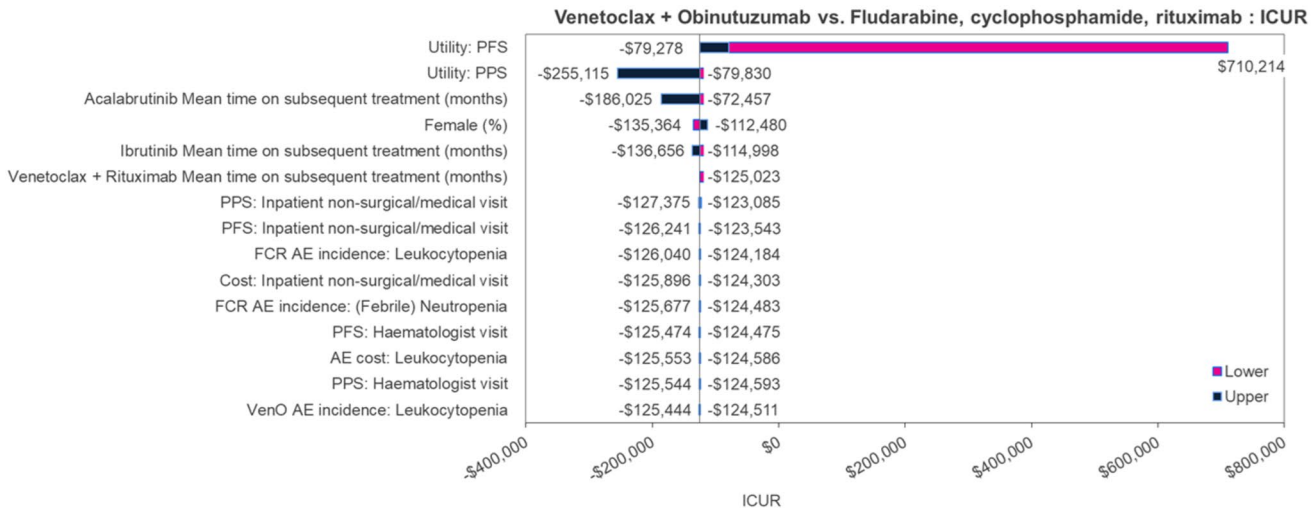

Fig. 2 Tornado plot ICUR: VEN + O vs FCR.

utility values for both health states. Tornado diagrams for all other comparisons (VEN + I, ACA, IBR, ZANU) are provided in Fig. S3 (A–D) in the ESM.

As can be seen in Fig. 4, the PSA results are in line with the conclusions of the base case analysis as the majority of simulations for each comparator are in the same quadrant as their respective base case result. Figure 5 displays the CEAC, which shows that VEN + O has an 87% probability of being cost effective compared with comparators at a CA$50,000/QALY WTP threshold. Treatments with a zero percent probability of being cost effective (IBR, ACA, ZANU) are not displayed in Fig. 5.

3.4 Scenario Analyses Results

The results for all scenario analyses are displayed in Tables S9 to S18 in the ESM and are consistent with the base-case results. As illustrated, VEN + O remains cost effective for all scenarios: dominant versus IBR and ZANU, dominant or with an ICUR at or below CA$26,221/QALY versus FCR, an ICUR at or below CA$24,789/QALY versus BR, and an ICUR versus VEN + I and ACA that lies in the south-west quadrant at values substantially above a WTP threshold of CA$50,000/QALY.

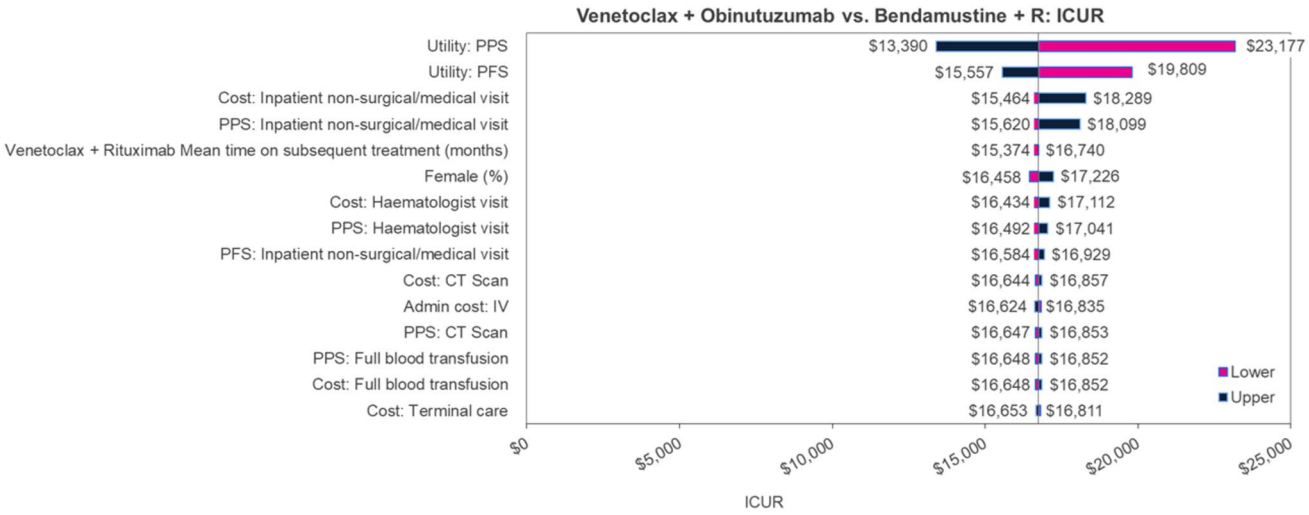

Fig. 3 Tornado plot ICUR: VEN + O vs BR.

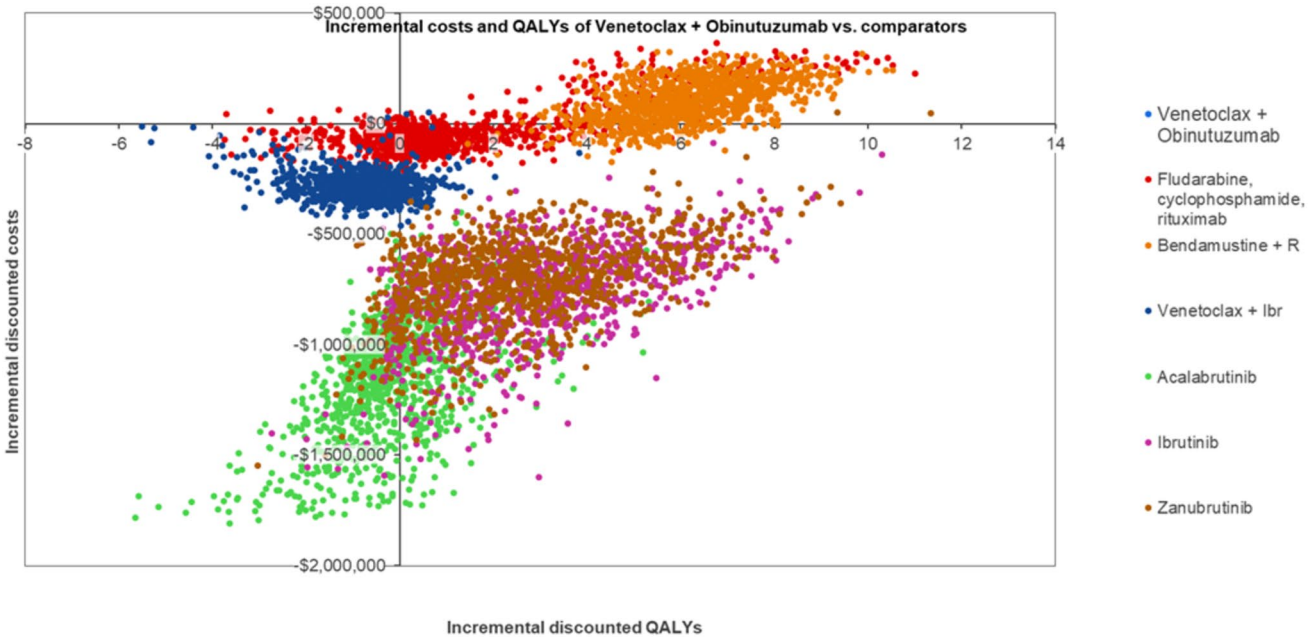

Fig. 4 Incremental cost-effectiveness scatter plot for VEN + O vs all comparators.

4 Discussion

This study evaluates the economic impact of introducing VEN + O to the Canadian health care system for the treatment of previously untreated fit CLL patients. In the CLL13 trial, VEN + O showed superior PFS compared with FCR and BR. This study shows that these results translated into long-term health gains versus FCR and BR. In addition, an NMA was conducted to evaluate the treatment efficacy for treatments not assessed in CLL13 (i.e., VEN + I, ACA, IBR, ZANU). There were no significant differences between these treatments for PFS and OS.

VEN + O was associated with favorable outcomes versus all comparators. Model results show that VEN + O was associated with the second-lowest total costs (after BR). In terms of QALYs, VEN + O accrued substantially more QALYs than BR, FCR, IBR, and ZANU, was associated with similar QALYs compared with ACA, and slightly lower QALYs

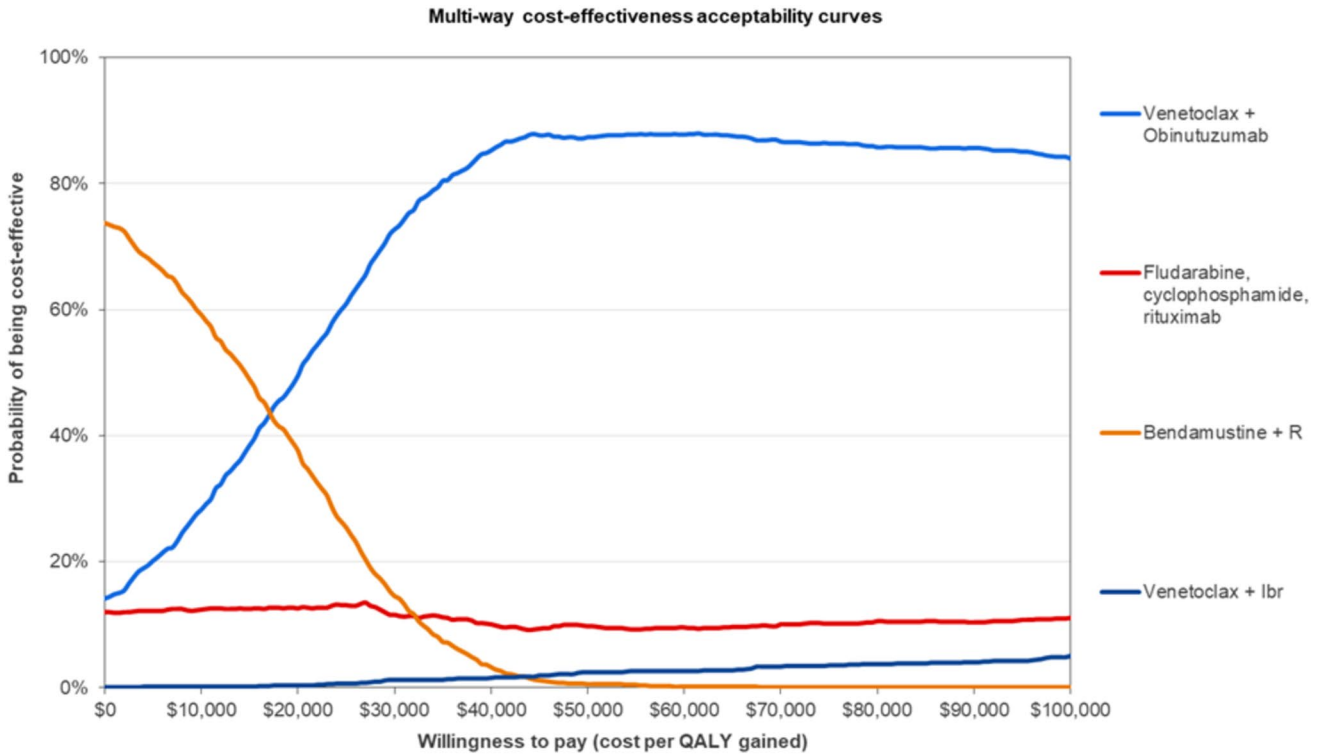

Fig. 5 Cost-effectiveness acceptability curves for all treatments.

compared with VEN + I. As a result, VEN + O dominates FCR, IBR, and ZANU. It could be assumed that VEN + O would likely also dominate ACA considering a similar efficacy between BTKis (IBR, ZANU, and ACA), but this could not be shown in this analysis due to the uncertainty of the NMA results. VEN + I was relatively comparable in terms of clinical benefit compared with VEN + O, and was associated with a small QALY gain but an increase in costs. As such, the ICUR versus VEN + I is in the south-west quadrant and is substantially above a CA$50,000/QALY threshold at CA$347,762/QALY, indicating that VEN + O is also cost effective versus VEN + I. VEN + O was cost effective versus BR at an ICUR of CA$16,621/QALY.

The OWSA shows that the main drivers for incremental costs are utilities for the PFS and PD health states, HRs for PFS and OS, and mean time on subsequent treatments. The outcomes of the PSA are in line with the base-case analysis suggesting model stability and demonstrate that at a WTP threshold of CA$50,000/QALY, VEN + O has an 87% probability of being cost effective. Furthermore, various scenario analyses were performed. In all of these scenarios, VEN + O remains cost effective with all ICUR values below a threshold of CA$50,000/QALY, or in the case of ICURs in the south-west quadrant, ICUR values higher than CA$50,000/QALY.

This economic evaluation has notable strengths. Efficacy data are based on high quality clinical trials and resulting survival estimates have been validated by Canadian clinical experts. Furthermore, data on costs and resource use are estimated from Canadian data and validated with Canadian clinical experts.

A limitation of this analysis is that in the CLL13 trial, patients treated with BR were older than 65 years, whereas patients treated with FCR were aged 65 years or younger. This creates a potential bias as survival for BR might be underestimated and survival for FCR might be overestimated compared with VEN + O and all other treatments. This is shown in Fig. S1B, which depicts the OS for BR and FCR. A potential solution would have been to pool the BR and FCR populations, but this would have resulted in a 'mixed treatment' for which any results would be difficult to interpret. Also, since FCR is a very relevant comparator in the patient group under study for the Canadian situation, pooling was not considered to be valid. It should be noted that longer survival for BR would have likely resulted in a less favorable ICUR for BR, as this would have resulted in more costs for subsequent treatment (since patients live longer).

Secondly, quality-of-life data was not available from the CLL13 study, necessitating the use of literature. To address this limitation, utility values which were used in

multiple previous NICE health technology assessment submissions have been incorporated in this analysis. Moreover, as can be seen from the OWSA results, the model results are sensitive to variations in utility values. It should be noted though that large variations in the OWSA due to changes in utility values are a result of the utility value for the PD health state exceeding that of the PFS health state, which is clinically implausible.

Thirdly, the NMA included both fit and unfit CLL patients in the network because of limited data availability. Although this heterogeneity in fitness could bias results, a network meta-regression could not be performed due to the small number of studies eligible for inclusion in the NMA. Nevertheless, the inclusion of unfit patients in the NMA was necessary to enable comparison to all relevant comparators. The impact on treatment effects of including unfit patients is uncertain. As relative effects are used in the NMA, an imbalance in treatment effect modifiers (not prognostic factors) could bias results. However, the impact this has on the final results depends on how an effect modifier influences treatment response for both arms within a randomized controlled trial. It was considered whether stratification of outcomes according to age would be preferred; however, this greatly reduced the sample sizes for some of the studies included and resulted in the exclusion of relevant comparators. As can be seen from Table 1, many CrIs are wide and included one (especially for OS), indicating no significant difference between treatments. Thus, although this may have influenced point estimates, it is less likely that CrIs will drastically narrow with one falling outside of the CrIs. The wide CrIs also cause uncertainty in the model results, which were investigated in the PSA in which the uncertainty around the PFS and OS HRs was taken into account. As reflected in the PSA results, the model results remained robust and the conclusions of the analysis did not change.

Fourthly, due to the lack of TTNT and ToT data for VEN + I, ACA, IBR, and ZANU, the model uses PFS as a proxy to estimate these values, which may introduce bias in the subsequent treatment costing for these therapies. However, in the scenario analysis where subsequent treatment costs were excluded, it was found that this exclusion had no significant impact on the ICURs versus these particular treatments.

Lastly, real-world evidence of CLL treatments for the population under study is not available yet. Although treatment efficacy data in this study is based on high quality clinical trials and has been validated by Canadian clinical experts, the generalizability of the results of this study to clinical practice are, as is the case for all clinical trials, subject to a certain level of uncertainty.

5 Conclusion

This analysis shows that VEN + O, a drug with a 12-month fixed treatment duration, is a cost-effective option for previously untreated fit patients with CLL in Canada. The analysis was conducted from a Canadian public healthcare payer perspective, and demonstrated potential health benefits and cost savings for VEN + O when compared with relevant treatments (BTKis, VEN + I, and chemoimmunotherapies). This conclusion is supported by extensive sensitivity and scenario analyses.

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Declarations

Conflict of interest A.G., N.P.R., S.B., and B.S.M. are employees of AbbVie. Employees of AbbVie may hold equity. S.K. is an employee of PIVINA and C.V. is the managing director of PIVINA Consulting Inc., a company that has served as a consultant to AbbVie and has received research funding from AbbVie. G.W., L.B. and G.R. are employees of OPEN Health, which served as a consultant to AbbVie and has received research funding from AbbVie. C.O. has received research funding from AbbVie, Roche, AstraZeneca, Janssen, Beigene, and Merck and has served as a consultant to AbbVie, Astrazeneca, Beigene, Janssen, Roche, and Merck. V.B. has received research funding from CIHR, CancerCare Manitoba, University of Manitoba, AstraZeneca, and Eli Lilly. V.B. has contracts with Beigene, AbbVie, and Janssen related to the CLL Unit, and has served as a consultant to AbbVie, Janssen, AstraZeneca, Merck, Eli Lilly, and Beigene.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Data availability Data reported in this manuscript are available within the article and its supplementary materials. Additional data may be requested by contacting AbbVie.

Code availability Code may be requested by contacting AbbVie.

Author contributions All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published. AbbVie, OPEN Health, and PIVINA Consulting Inc. participated in the design, study conduct, analysis and interpretation of data, as well as the writing, review, and approval of the manuscript. C.O. and V.B. were involved in study conception and design, data interpretation and revision of the manuscript.

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