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ORIGINAL RESEARCH ARTICLE

A Probabilistic Cost-Effectiveness Analysis of Venetoclax and Obinutuzumab as a First-Line Therapy in Chronic Lymphocytic Leukemia in Canada

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Abstract

Background Venetoclax is a first-in-class targeted therapy option that is an inducer of apoptosis in chronic lymphocytic leukemia (CLL) cells. The open-label phase III CLL14 clinical trial showed that venetoclax combined with obinutuzumab (VEN+O) is superior to obinutuzumab combined with chlorambucil in newly diagnosed patients with CLL. The aim of this study was to assess the health economic value of VEN+O for the frontline treatment of CLL in Canada from a publicly funded healthcare system perspective.

Methods A partitioned survival analyses model was developed including three health states: progression free, progressed, and death. A cycle length of 28 days and a time horizon of 10 years was assumed. VEN+O treatment for a fixed duration of 12 months was compared to obinutuzumab combined with chlorambucil, fludarabine plus cyclophosphamide plus rituximab, bendamustine plus rituximab, chlorambucil plus rituximab, ibrutinib, and acalabrutinib. The population in the model included both unfit and overall frontline CLL patients, two subgroups were also assessed (patients with del17p/TP53 mutations and patients without del17p/TP53 mutations). Survival data extrapolated from the CLL14 trial were used to populate the model. Uncertainty was assessed via one-way sensitivity analyses, probabilistic analyses, and scenario analyses.

Results Based on the probabilistic analyses, unfit frontline CLL patients receiving VEN+O were estimated to incur costs of Canadian dollars ($) 217,727 [confidence interval (CI) $170,725, $300,761] (del17p/TP53: $209,102 [CI $159,698, $386,190], non-del17p/TP53: $217,732 [CI $171,232, $299,063]) and accrue 4.96 [CI 4.04, 5.82] quality-adjusted life-years (del17p/TP53: 3.11 [CI 2.00, 4.20], non-del17p/TP53: 5.04 [CI 4.05, 5.92]). Obinutuzumab combined with chlorambucil, bendamustine plus rituximab, chlorambucil plus rituximab, and ibrutinib accrued lower quality-adjusted life-years and higher costs and as such, VEN+O was the dominant treatment option. The full incremental analysis showed that acalabrutinib was more expensive and more efficacious compared with VEN+O with an incremental-cost-effectiveness-ratio of $2,139,180/quality-adjusted life-year versus VEN+O and not a cost-effective option in Canada. Probabilistic analyses show that at a willingness to pay of $50,000/quality-adjusted life-year gained, VEN+O has the greatest probability of being cost effective.

Conclusions VEN+O is a cost-effective treatment option for unfit frontline CLL patients and provides value for money to healthcare payers.

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Key Points for Decision Makers

Fixed-duration treatment, such as that offered by venetoclax plus obinutuzumab, has the potential of reducing the substantial health and economic burden of frontline chronic lymphocytic leukemia.

This cost-effectiveness model shows that, for frontline unfit patients with chronic lymphocytic leukemia, venetoclax plus obinutuzumab as a 12-month fixed-duration treatment offers lower projected costs and more quality-adjusted life-years gained versus relevant treatments, except acalabrutinib, which was not cost effective (incremental cost-effectiveness ratio of $2,139,180/quality-adjusted life-year versus venetoclax plus obinutuzumab).

At a threshold of $50,000/quality-adjusted life-year gained, venetoclax plus obinutuzumab provides value for money to Canadian jurisdictions compared with existing funded treatments in Canada.

1 Introduction

Chronic lymphocytic leukemia (CLL) is a clonal disease of unknown etiology and is the most common type of leukemia reported in adults living in Western countries [1]. Chronic lymphocytic leukemia manifests as the uncontrolled growth of B lymphocytes, which accumulate in the blood, bone marrow, lymph nodes, and spleen [2]. The incidence of CLL in the Western world is estimated at 4.2 per 100,000 persons per year and increases by more than ten-fold with age [3]. In Canada, yearly incidence varies between 5.0 and 8.0 per 100,000 persons [4, 5], translating into over 1700 new CLL cases in 2016 and about 600 deaths in 2017 [6].

Chronic lymphocytic leukemia is more common with advanced age, with a median age of diagnosis between 67 and 72 years. Therefore, the majority of patients with CLL also have clinically relevant co-existing medical conditions [7]. The fitness of patients, defined by age and the Cumulative Illness Rating Scale measuring patient comorbidity, has been defined as a key prognostic factor for CLL survival [9]. Important disease-related risk factors influencing CLL prognosis and treatment pathway include the deletion of the short arm of chromosome 17 (del17p) and/or mutations in the tumor suppressor gene *TP53* (m*TP53*), the mutation status of the immunoglobulin heavy-chain variable region (IGVH), b2-microglobulin level, and CLL clinical stage [2, 8]. Presence of del17p/m*TP53* indicates a poor prognosis, with resistance to conventional chemoimmunotherapy and median overall survival (OS) of 2–5 years. Overall survival and duration of remissions are also shorter for unmutated IGVH patients owing to a higher risk of genetic instability [3].

The frontline treatment options for patients with CLL (1L CLL) vary with patients' prognostic risk factors. For patients with a non-del17p/m*TP53* status, treatment options depend on the fitness level. Patients aged < 65 years with a Cumulative Illness Rating Scale score < 6, defined as 'fit' patients, usually receive fludarabine combined with cyclophosphamide and rituximab (FCR). Patients aged > 65 years with multiple comorbidities, commonly defined as 'unfit', cannot tolerate FCR treatment because of the high toxicity and infection rates associated primarily with fludarabine [9]. For the FCR-ineligible previously untreated patients with CLL, obinutuzumab (Gazyvaro® [G]) combined with chlorambucil (GClb) has been considered an effective regimen [3, 10, 11]. Other treatment options for the FCR-ineligible 1L CLL patients include bendamustine and rituximab (BR), chlorambucil and rituximab (Clb+R), and ibrutinib (Ibr). Patients with a del17p/m*TP53* status usually have a poor prognosis even after FCR therapy, hence the usual treatments are based on novel inhibitors such as Ibr, which is currently the most frequently used regimen out of the funded novel inhibitors in Canada.

Venetoclax (VEN) is a first-in-class oral selective inhibitor of BCL-2 anti-apoptotic protein that is overexpressed in approximately 95% of patients with CLL. Its unique targeted mechanism of action and fixed treatment duration distinguish it from other available therapies [12]. The recent open-label, phase III, CLL14 clinical trial (NCT02242942) results demonstrated an acceptable safety profile of VEN in combination with obinutuzumab (VEN+O), for the treatment of previously untreated patients with CLL with co-existing medical conditions (unfit patients) [7, 13]. In all patients and across all the major prognostic subgroups analyzed, VEN+O also showed a consistently superior treatment profile compared with the standard of care GClb [7]. Health Canada has issued a notice of compliance for VEN+O for the 1L treatment of patients with previously untreated CLL [14].

The health and economic burden of previously untreated CLL is substantial and increasing over time, leading to both considerable decreases in quality of life for 1L CLL patients and high lifetime costs to the healthcare system and caregivers [15]. Randomized controlled trial data suggest that various therapeutic options for 1L CLL are associated with improved efficacy in both unfit and a combination of unfit and fit populations. Nonetheless, the increased number of therapeutic options for patients with CLL requires formal comparisons of efficacy, safety, and economic burden to effectively treat 1L CLL patients.

The objective of the current study was to assess the cost effectiveness of VEN+O for the treatment of 1L CLL patients compared to current and future treatment options in Canada. The model has been parametrized to be consistent with Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines. It also aligns with the National Institute of Health and Care Excellence (NICE) economic evaluation guidelines and the decision analytic modeling best practice recommendations from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

2 Methods

A systematic literature review (SLR) was conducted in September 2020 to identify studies assessing the cost effectiveness of 1L CLL treatment options [16]. The SLR identified 17 full-text articles and 27 abstracts [5, 17–59]. Most published models followed a Markov or semi-Markov model. Other modeling approaches were discrete-event simulations or microsimulation models, whereas more recent models adopted a partitioned survival analysis (PartSA) approach.

2.1 Model Structure

The current analysis employed a PartSA model for two main reasons. First, recent pan-Canadian Oncology Drug Review (pCODR) appraisals of CLL treatments have primarily used PartSA models [60–63]. Second, the PartSA model allows for a clear linkage between the clinical efficacy data from the pivotal trial and the clinical data used in the model.

The PartSA methodology was used to estimate and extrapolate progression-free survival (PFS), post-progression survival (PPS), time to next treatment (TTNT), and OS for up to a 10-year time horizon. Patient distribution among health states (PFS, PPS, and dead) and over time were estimated using the extrapolated survival curves alongside an area-under-the-curve analysis. The model cycle length was 28 days and a half-cycle correction was also applied. It was assumed that the age-adjusted and sex-adjusted mortality hazard rates of patients with CLL were not lower than age-adjusted and sex-adjusted all-cause mortality rates of the general population. To enable a cost-effectiveness analysis, specific utility values and cost profiles were attributed to the different health states of the model.

2.2 Patient Population and Treatment Interventions

The patient population base-case characteristics, including age and sex distributions, were informed by the CLL14 trial population (Table 1). The present study considered two populations, the unfit as the base case and the overall 1L CLL (fit and unfit patients) as a scenario. The unfit 1L CLL population was further subdivided into four subgroups based on del17p/TP53 and IGVH mutation status. The treatment comparators of VEN+O for the 1L CLL unfit patient population were GClb, BR, Clb+R, Ibr, and acalabrutinib monotherapy. For the overall 1L CLL patient population, in addition to all the comparators, VEN+O was also compared to FCR. For all the unfit subgroups, the treatment comparator was GClb, except in the case of the del17p/TP53 subgroup, where Ibr was also used.

2.3 Model Inputs

The model inputs were either identified from the economic and clinical SLRs, estimated from the CLL14 trial, or elicited from clinical experts during an advisory board. Ten local clinical experts validated the model structure and inputs, facilitated by an economic expert. Given the nature of a probabilistic model, expert responses on eight survey questions were used to calculate mean resource use responses along with variances and standard errors. Specifically, health-related quality of life, cost, resource use, and previous economic model data were identified from the economic SLR. Whenever possible, model inputs were informed from Canadian-specific sources and databases. Background mortality was estimated from the latest Canadian life tables published by Statistics Canada [64].

2.3.1 Treatment Efficacy

The primary measures of clinical effectiveness for the 1L CLL treatments were from the CLL14 trial data and included PFS, OS, TTNT, and time on treatment (ToT) curves for VEN+O and GClb treatment arms. The observed survival curves of VEN+O and GClb in the CLL14 trial were parameterized (a) to estimate outcomes beyond the observed trial period, (b) to allow synthesis of outcomes with data from external comparators, and (c) to facilitate a probabilistic analysis. The parameterization methods were guided by the NICE technical support documentation [65]. The dependent and independent models explored included exponential, Weibull, Gompertz, log-normal, log-logistic, gamma, and generalized-gamma distributions. Additionally, spline 1–3 knot models based on the hazards, odds, and probit (or normal) scale were also fitted to the observed time-to-event data. The internal validity of the models was investigated using statistical measures of fit (Akaike's Information Criterion and the Bayesian Information Criterion), followed by a visual fit inspection. To assess the clinical plausibility and external validity, landmark survival values were discussed

Table 1 Baseline patient characteristics from the CLL14 trial

	VEN+O (*N* = 216)		GClb (*N* = 216)		Overall	
Age (years)						
N	216		216		432	
Median	71		72		72	
Minimum-maximum	41-89		41-89		41-89	
Sex						
N	216		216		432	
Male	146	67.6%	143	66.2%	289	66.9%
Female	70	32.4%	73	33.8%	143	33.11%
Region						
N	216		216		432	
Australia/New Zealand	32	14.8%	32	14.8%	64	14.8%
Central and Eastern Europe	57	26.4%	63	29.1%	120	27.8%
Latin America	13	6.0%	10	4.6%	23	5.3%
US/Canada/Central America	21	9.7%	23	10.6%	44	10.2%
Western Europe	93	40.7%	88	43.1%	181	41.9%
Race						
N	216		216		432	
American Indian or Alaskan native	0	0%	1	0.5%	1	0.2%
Black or African American	1	0.5%	3	1.4%	4	0.9%
Native Hawaiian or other Pacific Islander	3	1.4%	0	0%	3	0.7%
Unknown	20	9.3%	18	8.3%	38	8.8%
White	192	88.9%	194	89.8%	386	89.4%
ECOG						
N	216		215		431	
0	89	41.2%	103	47.9%	192	44.5%
I	99	45.8%	87	40.5%	186	43.2%
II	27	12.5%	25	22.6%	52	12.1%
III	1	0.5%	0	0.0%	1	0.2%
CIRS score category						
N	216		216		432	
≤ 6	30	13.9	39	18.1%	69	16%
> 6	186	86.1%	177	81.9%	363	84%
TP53 mutated and/or 17p deletion						
N	172		161		333	
Yes	24	14%	22	13.7%	46	13.8%
No	148	86%	139	86.3%	287	86.2%
IGVH mutation status						
N	216		216		432	
Mutated	76	38%	83	39.9%	159	36.8%
Not evaluable	3	1.5%	2	1.0%	5	1.2%
Unmutated	121	60.5%	123	59.1%	244	56.5%
Missing sample	16	7.4%	8	3.7%	24	5.6%

CLL chronic lymphocytic leukemia, *CIRS* Cumulative Illness Rating Scale, *del17p/TP53* deletion of the short arm of chromosome 17 and/or mutations in the tumor suppressor gene TP53, *ECOG* Eastern Cooperative Oncology Group, *GClb* Gazyvaro (obinutuzumab) plus chlorambucil, *IGVH* immunoglobulin heavy-chain variable region, *VEN+O* venetoclax plus obinutuzumab

with clinical experts and cross-validated with external sources.

The sample of patients with the del17p/TP53 mutation is small. To maximize the predictive power of the CLL14 data, del17p/TP53 was included as a covariate in the time-to-event modeling and the impact of del17p/TP53 status on the scale of the survival curves was estimated. Similarly, to assess the differential effect of IGVH mutation on survival outcomes, IGVH mutation status was included as a covariate in the independent and dependent modeling approaches of OS, PFS, and TTNT to enable parametrization of the survival outcomes of the two subgroups.

A clinical SLR was conducted to inform indirect treatment comparisons (ITC) between VEN+O and the comparators outside the CLL14 trial. Indirect treatment comparisons were made using network meta-analysis (NMA) methods. Two sets of NMAs were performed: unfit only 1L CLL and overall 1L CLL [66]. Hazard ratios (HRs) were generated versus VEN+O for two outcomes (PFS and OS). These NMAs were updated to include acalabrutinib (Tables S1 and S3 of the Electronic Supplementary Material [ESM]). The NMA feasibility assessment had identified heterogeneity in GClb dosing and Clb treatment duration across trials. A scenario analysis was run to adjust for this heterogeneity in the NMA (Table S2 of the ESM). The analysis was not used in the base case because the results favored VEN+O and would introduce further uncertainty in the analysis.

In the del17p/TP53 population, two naïve comparisons and one matching-adjusted indirect comparison (MAIC) was conducted for VEN+O versus Ibr monotherapy [67, 68]. The PFS and OS HRs from the naïve comparison using Mato et al. [67] were combined with the VEN+O PFS and OS curves, respectively, to generate the individual survival curves for Ibr. The naïve comparison using Mato et al. was used in the base case because the results were powered by a larger sample size [16]. All parameter estimations for the treatment effects were performed using maximum likelihood using the R package flexsurv [69].

2.3.2 Model Validation

The OS outcomes from the CLL14 trial were immature for both treatment arms. Due to this and as the proportional hazards assumption could not be rejected, dependent modeling was the most appropriate option. To account for the immature OS data and to explore the validity of the OS CLL14-based extrapolations, PPS curves were generated based on 5-year follow-up data from the GClb arm of the CLL11 trial comparing GClb to Clb+R [70]. During the advisory board, the CLL11 trial was highlighted as a relevant external data source, as GClb was one of the included treatment arms and the trial population inclusion criteria were comparable to CLL14.

Comparing survival estimates with real-world data [71–74] showed that long-term survival estimates matched better with the relative than with the absolute real-word-based survival values. Brenner et al. [71] for instance, indicate that the absolute 10-year survival in the 1L CLL population in the USA was between 28 and 35%, and the relative between 46 and 55%, whereas the landmark 10-year OS survival prediction from the CLL14 trial data ranged from 57 to 77% in both trial arms (Table S4 of the ESM). Such discrepancies originate from the fact that available real-world data pertain to a treatment era in which efficacious treatment options were lacking. More recent studies indicate higher 10-year OS estimates of 51–64% [72, 73]. Following the exploration of alternative approaches, including validation with external data sources, and consultations with clinical and economic experts, it was concluded that the CLL14 trial was the most appropriate source of evidence for base-case OS predictions. Therefore, the dependent model using the exponential distribution was employed in the base-case scenario, while we assumed no difference in OS between VEN+O and GClb. The latter is a conservative assumption because the CLL14 trial shows that patients progressed slower in the VEN+O arm and post-first-relapse patients were salvaged quite quickly in the CLL14 trial.

For PFS and TTNT survival curves, the proportional hazards assumption was rejected. Therefore, independent models were used to extrapolate beyond the trial duration. The landmark PFS and TTNT estimates from the extrapolations were discussed with clinical experts, who recommended a log-logistic distribution for PFS as the base-case option. However, uncertainty remained in the TTNT extrapolations because of limited follow-up data. Similar to the OS projections, the GClb arm from the CLL11 trial was used as a source for external validation. The 5-year TTNT in the CLL11 trial was 49%, comparable to the CLL14-based extrapolations that varied between 52 and 60% (Table S5 of the ESM). The independent log-logistic distribution also provided the best-fitting distribution for the TTNT extrapolations.

Patients in the VEN+O and GClb treatment arms followed a fixed treatment duration. To inform treatment costs, the number of patients remaining on treatment per cycle length up until the fixed treatment duration point from the CLL14 trial was estimated. Time on treatment was estimated based on discontinuation of therapy using censoring pegged to OS. Due to a fixed treatment duration, no extrapolations of the ToT curve were required. For comparators outside the CLL14 trial, PFS curves were used to determine the number of patients on treatment per cycle.

2.3.3 Modeling Beyond First-Line Therapy

To inform the number of patients receiving subsequent treatment following VEN+O or GClb, the estimated differences between the OS and TTNT from the CLL14 curves were used. For comparators outside the CLL14 trial, the difference between their own OS and PFS curves were used to inform the respective number of patients receiving subsequent treatment. To inform the duration that patients remain on subsequent treatment, previously published data collected from a targeted literature search were used [12, 75–80]. To be conservative, the lowest duration on subsequent treatment between the modeled and the literature values was incorporated in the model. See Box 1 in the ESM for further details on the approach to modeling subsequent treatments.

2.3.4 Utility Values and Adverse Events

Health state utilities and adverse event (AE) disutilities were derived from the SLR. Utilities from CLL14 were deemed to be clinically implausible by clinical and economic experts as they were higher than the age-adjusted general population utilities. Therefore, utility values for pre-progression and post-progression states were derived from the most recent NICE submission for 1L CLL trials for obinutuzumab (TA343 and TA174, see Table S8 in the ESM) [32, 81–83], and were also adjusted for age-related deterioration as recommended by the NICE Decision Support Unit [65].

Adverse event disutility values and duration estimates were used to assess the impact of AEs on quality-adjusted life-years (QALYs). The parameters for each AE were sourced from previous NICE technology appraisals and the literature (see Table S9 in the ESM) [84–89]. For VEN+O and GClb, the incidence of AEs was informed from CLL14. Neutropenia, febrile neutropenia, pneumonia, sepsis, and thrombocytopenia were the most common serious AEs. Grade 3–4 AEs with at least a 2% difference in the rate between the treatment arms were also included. For other comparators, the most recent publications (including NICE appraisals) with the longest follow-up data were used to inform respective AE incidence (Table S6 of the ESM). In accordance with other oncology models, AEs were assumed to occur within the first cycle. Because of a lack of granular data, the same approach was also taken for treat-to-progress regimens (e.g., Ibr and acalabrutinib), which was a conservative assumption.

2.3.5 Cost and Resource Use Data

Total costs consisted of CLL active treatment (drug and administration) costs, routine care and monitoring costs, treatment-specific monitoring costs, costs related to AEs, disease progression, and end-of-life care and were taken from various sources (Table S7 of the ESM). All costs were inflated to 2020 Canadian dollars using the healthcare component of the consumer price index [90].

2.4 Model Analyses

The key outcomes of the cost-effectiveness analysis were total life-years (LYs), QALYs, and costs over a 10-year time horizon, as well as incremental LYs, QALYs, costs and incremental cost-effectiveness ratios (ICERs), representing the cost or per QALY gained. Analysis was conducted using a pan-Canadian healthcare system perspective. The overall analytic structure includes both a probabilistic and deterministic model. Consistent with CADTH guidelines, the base-case analysis results were derived using the probabilistic model. In the probabilistic analyses, a simulation of a certain number of iterations generated a mean output with associated upper and lower confidence intervals (CIs). For each individual iteration, the model parameters were simultaneously sampled from pre-defined distributions: the gamma distribution was selected for cost parameters, the beta distribution (bound between 0 and 1) for utilities and proportions, and log-normal distributions for hazard ratios. The method of Hatswell et al. [91] suggested that 1000 iterations were enough to generate stable results, but the base-case outcomes were generated from 5000 iterations to adhere to CADTH guidelines. Outcomes and costs were discounted at 1.5% per year [92].

2.5 Sensitivity Analyses

Variables for which values were uncertain were tested in a one-way sensitivity analysis (OWSA). The OWSA was conducted based on a pairwise comparison between two treatments examining the impact of different model parameter values (i.e., based upon the 95% CI) on incremental costs, incremental QALYs, and ICERs. Using the net monetary benefit approach, the probability of each treatment being cost effective at different willingness-to-pay (WTP) levels was investigated in a cost-effectiveness acceptability curve (CEAC). Last, extensive scenario analyses were conducted to examine the impact on outcomes of alternative modeling assumptions or alternative data sets (e.g., utility values).

3 Results

3.1 Incremental Costs and QALYs

Table 2 presents the per-patient costs across the different categories. All comparators resulted in higher costs than VEN+O. For treat to progression-based regimens, the high costs were

Table 2 Overview of total costs per patient over a 10-year time horizon (discounted) for unfit and total 1L CLL per treatment in the base-case scenario

Treatment	Total drug acquisition (mean, CI)	Total drug administration (mean, CI)	Total disease management (mean, CI)	One-time drug, administration, monitoring (mean, CI)	Subsequent treatment (mean, CI)	Adverse events (mean, CI)	Terminal care (mean, CI)	Total costs (mean, CI)
Unfit 1L CLL								
Venetoclax + O	$116,456 [116,290, 116,504]	$1541 [1255, 1853]	$12,892 [11,056, 14,917]	$2679 [2173, 3245]	$43,625 [0, 126,262]	$7072 [6022, 8215]	$33,462 [27,308, 40,500]	$217,727 [170,725, 300,761]
Chlorambucil + G	$42,911 [42,893, 42,926]	$1536 [1250, 1848]	$9706 [8612, 10,909]	$2380 [1938, 2867]	$216,126 [140,420, 280,089]	$6169 [5203, 7232]	$33,459 [27,288, 40,458]	$312,287 [238,878, 377,036]
Bendamustine + R	$47,116 [42,734, 49,396]	$2890 [2379, 3434]	$8372 [6855, 10,396]	$0	$296,520 [263,935, 332,539]	$10,738 [9349, 12,292]	$33,583 [27,400, 40,638]	$399,219 [365,934, 434,779]
Chlorambucil + R	$23,614 [21,431, 24,818]	$661 [556, 771]	$7690 [6234, 9117]	$0	$312,131 [275,886, 351,569]	$2937 [2369, 3564]	$33,681 [27,531, 40,720]	$380,713 [343,567, 420,473]
Ibrutinib	$494,503 [312,860, 667,868]	$0	$10,637 [8385, 13,102]	$0	$196,091 [98,311, 224,029]	$1200 [750, 1757]	$33,586 [27,454, 40,625]	$736,017 [568,143, 877,908]
Acalabrutinib	$759,631 [653,420, 820,574]	$0	$14,045 [11,934, 16,438]	$0	$60,761 [0, 174,736]	$1097 [731, 1526]	$33,263 [27,158, 40,205]	$868,797 [790,648, 897,489]
Unfit 1L CLL with del17p/TP53								
Venetoclax + O	$109,842 [101,752, 111,291]	$1488 [1211, 1802]	$7880 [5473, 10,385]	$2686 [2201, 3242]	$44,910 [0, 223,608]	$7081 [6040, 8222]	$35,217 [28,756, 42,522]	$209,102 [159,698, 386,190]
Chlorambucil + G	$40,133 [39,689, 40,462]	$1390 [1136, 1675]	$5300 [3720, 6935]	$2376 [1948, 2851]	$241,456 [31,450, 378,296]	$6179 [5198, 7280]	$35,253 [28,730, 42,666]	$330,698 [121,425, 468,799]
Ibrutinib	$474,485 [217,752, 712,464]	$0	$8,590 [3961, 12,632]	$0	$64,905 [0, 187,644]	$1206 [756, 1,758]	$34,977 [28,422, 42,467]	$584,164 [289,477, 824,664]
Unfit 1L CLL without del 17p/TP53 mutation								
Venetoclax + O	$116,850 [116,664, 116,899]	$1544 [1253, 1852]	$13,144 [11,348, 15,187]	$2,691 [2,195, 3,229]	$43,021 [0, 125,887]	$7060 [6016, 8223]	$33,422 [27,199, 40,342]	$217,732 [171,232, 299,063]
Chlorambucil + G	$43,188 [43,171, 43,203]	$1546 [1254, 1854]	$10,032 [8908, 11,272]	$2,379 [1,942, 2,868]	$202,380 [138,408, 267,174]	$6161 [5163, 7262]	$33,420 [27,233, 40,371]	$299,105 [231,978, 363,546]
Unfit 1L CLL with IGVH mutation								
Venetoclax + O	$116,827 [116,531, 116,897]	$1545 [1248, 1875]	$12,891 [10,991, 14,983]	$2682 [2168, 3228]	$39,682 [0, 120,137]	$7072 [6047, 8202]	$33,481 [27,170, 40,431]	$214,180 [170,650, 297,474]
Chlorambucil + G	$43,160 [43,135, 43,183]	$1547 [1250, 1877]	$9614 [8468, 10,874]	$2381 [1939, 2865]	$201,001 [125,028, 272,734]	$6166 [5215, 7277]	$33,475 [27,127, 40,381]	$297,343 [219,378, 368,492]
Unfit 1L CLL without IGVH mutation								
Venetoclax + O	$116,806 [116,410, 116,893]	$1540 [1254, 1842]	$12,157 [10,276, 14,208]	$2680 [2172, 3229]	$25,900 [0,119,327]	$7068 [5999, 8192]	$33,821 [27,674, 40,743]	$199,972 [168,674, 293,279]
Chlorambucil + G	$43,157 [43,127, 43,181]	$1542 [1255, 1845]	$8640 [7569, 9816]	$2379 [1931, 2864]	$251,848 [171,248, 309,490]	$6174 [5206, 7274]	$33,821 [27,701, 40,681]	$347,562 [266,777, 405,857]

Table 2 (continued)

Treatment	Total drug acquisition (mean, CI)	Total drug administration (mean, CI)	Total disease management (mean, CI)	One-time drug, administration, monitoring (mean, CI)	Subsequent treatment (mean, CI)	Adverse events (mean, CI)	Terminal care (mean, CI)	Total costs (mean, CI)
Total 1L CLL								
Venetoclax + O	$116,456 [116,297, 116,504]	$1541 [1254, 1853]	$12,881 [11,088, 14,904]	$2680 [2192, 3227]	$45,562 [0, 126,498]	$7066 [6013, 8195]	$33,465 [27,332, 40,359]	$219,651 [171,178, 301,957]
Chlorambucil + G	$42,911 [42,893, 42,925]	$1536 [1251, 1846]	$9705 [8629, 10,900]	$2380 [1924, 2867]	$216,421 [146,280, 279,487]	$6154 [5180, 7211]	$33,463 [27,334, 40,353]	$312,570 [240,486, 375,887]
Fludarabine, cyclophosphamide, and rituximab	$27,984 [26,659, 28,683]	$700 [598, 812]	$9148 [6801, 11,495]	$0	$265,362 [111,639, 317,331]	$5113 [4301, 5978]	$33,887 [27,653, 40,896]	$342,195 [191,837, 393,956]
Bendamustine + R	$47,798 [44,607, 49,457]	$2931 [2441, 3451]	$8591 [6743, 10,497]	$0	$293,547 [255,626, 331,416]	$10,725 [9315, 12,267]	$33,669 [27,523, 40,595]	$397,262 [359,673, 435,116]
Chlorambucil + R	$23,702 [21,566, 24,859]	$664 [558, 777]	$7731 [6259, 9159]	$0	$311,823 [274,668, 352,136]	$2933 [2366, 3544]	$33,699 [27,532, 40,701]	$380,551 [343,213, 421,597]
Ibrutinib	$516,272 [345,933, 680,639]	$0	$10,909 [8749, 13,151]	$0	$195,213 [99,232, 222,612]	$1200 [761, 1773]	$33,535 [27,453, 40,517]	$757,129 [603,315, 889,470]
Acalabrutinib	$758,664 [653,144, 820,298]	$0	$14,016 [11,914, 16,272]	$0	$61,337 [0, 175,441]	$1098 [730, 1562]	$33,274 [27,242, 40,150]	$868,388 [786,237, 897,537]

1L frontline, *CI* confidence interval, *CLL* chronic lymphocytic leukemia, *del17p/TP53* deletion of the short arm of chromosome 17 and/or mutations in the tumor suppressor gene TP53, *G* Gazyvaro, *IGVH* immunoglobulin heavy-chain variable region, *O* obinutuzumab, *R* rituximab, *VEN* venetoclax

driven by the high drug acquisition costs that were accrued for these comparators. For non-treat to progression-based comparators, the high costs were driven by the subsequent treatment costs that were accrued because of the larger proportion of patients remaining in the PPS period compared with VEN+O.

Table 3 shows the 10-year expected per-patient LYs (undiscounted) and QALYs (discounted), averaged across the 5000 simulations, by the pre-progression and post-progression periods, AE disutilities, and by treatment for the unfit and the overall 1L CLL patient population. Acalabrutinib accrued the highest health gains at 5.27 [95% CI 4.25, 6.25] QALYs, followed by VEN+O, and GClb, with 4.96 [95% CI 4.04, 5.82] and 4.75 [95% CI 4.03, 5.45] QALYs, respectively. VEN+O accrued most of its QALYs during the progression-free stage, reflecting the improved PFS for VEN+O compared with other treatments. For unfit 1L CLL patients with the del17p/TP53 mutation, Ibr accrued 0.26 more QALYs and was $375,061 more expensive than VEN+O. For the IGVH mutation subgroup, VEN+O resulted in higher QALYs and less costs compared with GClb.

3.2 Cost-Effectiveness Analysis Results

Figure 1 presents the cost-effectiveness frontier for the different treatments of the base-case unfit 1L CLL patient population included in the model. The figure shows that VEN+O is on the frontier with acalabrutinib. Acalabrutinib is not cost effective and compared with VEN+O shows an ICER of $2,139,180 per QALY.

Table 4 presents the full incremental analysis for the unfit and overall 1L CLL population and the subgroups included in the analyses. When comparing to Ibr for the del17p/TP53 subgroup, Ibr accrued more QALYs but also incurred more costs than VEN+O. For all other subgroups, VEN+O was dominant.

3.3 Sensitivity Analyses on the Unfit 1L CLL Population

The OWSA demonstrates that variances in the OS and PFS hazard ratios from the NMA and from the unadjusted comparison have the biggest influence on key model results

Table 3 Overview of total LYs, QALYs, and disutilities for unfit and total 1L CLL per treatment in the base-case scenario

Treatment	PFS LYs (mean, CI)	PPS LYs (mean, CI)	Total LYs (mean, CI)	PFS QALYs (mean, CI)	PPS QALYs (mean, CI)	AE disutilities (mean, CI)	Total QALYs (mean, CI)
Unfit 1L CLL							
Venetoclax + O	7.15 [6.26, 7.79]	1.17 [0.28, 2.18]	8.32 [7.67, 8.75]	4.36 [3.37, 5.30]	0.61 [0.14, 1.15]	− 0.0029 [− 0.0036, − 0.0023]	4.96 [4.04, 5.82]
Chlorambucil + G	3.63 [3.21, 4.08]	4.70 [3.96, 5.32]	8.32 [7.71, 8.74]	2.29 [1.79, 2.81]	2.46 [1.86, 3.07]	− 0.0024 [− 0.0030, − 0.0019]	4.75 [4.03, 5.45]
Bendamustine + R	2.38 [1.17, 4.19]	5.72 [3.75, 7.14]	8.10 [7.16, 8.78]	1.52 [0.74, 2.67]	3.03 [1.90, 4.10]	− 0.0041 [− 0.0049, − 0.0034]	4.55 [3.71, 5.33]
Chlorambucil + R	1.79 [1.11, 2.69]	6.13 [4.44, 7.38]	7.92 [6.38, 8.81]	1.16 [0.69, 1.78]	3.27 [2.20, 4.25]	− 0.0011 [− 0.0014, − 0.0008]	4.42 [3.39, 5.33]
Ibrutinib	4.84 [3.01, 6.60]	3.25 [0.90, 5.37]	8.10 [6.49, 8.86]	3.00 [1.83, 4.28]	1.71 [0.47, 2.94]	− 0.0001 [− 0.0002, − 0.0001]	4.71 [3.65, 5.61]
Acalabrutinib	8.13 [6.95, 8.79]	0.56 [0.00, 1.75]	8.68 [7.94, 8.90]	4.98 [3.85, 6.09]	0.29 [0.00, 0.92]	− 0.001 [− 0.001, 0.000]	5.27 [4.25, 6.25]
Unfit 1L CLL with del17p/TP53							
Venetoclax + O	4.22 [2.70, 5.70]	0.91 [NA, 3.04]	5.13 [3.38, 6.77]	2.63 [1.62, 3.68]	0.49 [NA, 1.66]	− 0.0029 [− 0.0036, − 0.0023]	3.11 [2.00, 4.20]
Chlorambucil + G	1.49 [0.93, 2.28]	3.57 [1.66, 5.44]	5.06 [3.22, 6.84]	0.97 [0.58, 1.51]	1.94 [0.88, 3.07]	− 0.0024 [− 0.0030, − 0.0019]	2.90 [1.86, 4.00]
Ibrutinib	4.65 [2.08, 7.06]	0.92 [NA, 4.09]	5.57 [2.37, 8.26]	2.88 [1.29, 4.52]	0.49 [NA, 2.24]	− 0.0001 [− 0.0002, − 0.0001]	3.37 [1.47, 5.03]
Unfit 1L CLL with non-del17p/TP53 mutation							
Venetoclax + O	7.33 [6.45, 7.97]	1.13 [0.30, 2.11]	8.46 [7.90, 8.81]	4.45 [3.46, 5.40]	0.59 [0.15, 1.14]	− 0.0029 [− 0.0035, − 0.0023]	5.04 [4.05, 5.92]
Chlorambucil + G	3.88 [3.42, 4.34]	4.58 [3.90, 5.18]	8.46 [7.91, 8.80]	2.44 [1.88, 2.99]	2.39 [1.83, 2.99]	− 0.0024 [− 0.0024, − 0.0019]	4.83 [4.10, 5.53]
Unfit 1L CLL with IGVH mutation							
Venetoclax + O	7.21 [6.21, 7.88]	1.03 [0.13, 2.12]	8.24 [7.59, 8.68]	4.39 [3.37, 5.35]	0.54 [0.07, 1.11]	− 0.0029 [− 0.0036, − 0.0023]	4.92 [3.97, 5.83]
Chlorambucil + G	3.58 [3.14, 4.02]	4.67 [3.96, 5.30]	8.25 [7.63, 8.68]	2.26 [1.73, 2.78]	2.44 [1.86, 3.03]	− 0.0024 [− 0.0030, − 0.0019]	4.70 [3.96, 5.39]
Unfit 1L CLL without IGVH mutation							
Venetoclax + O	6.74 [5.61, 7.52]	1.06 [0.00, 2.37]	7.80 [6.95, 8.48]	4.11 [3.12, 5.05]	0.56 [0.002, 1.25]	− 0.0029 [− 0.0036, − 0.0023]	4.66 [3.71, 5.54]
Chlorambucil + G	2.89 [2.48, 3.32]	4.91 [3.98, 5.71]	7.88 [6.94, 8.49]	1.84 [1.40, 2.28]	2.59 [1.91, 3.26]	− 0.0024 [− 0.0030, − 0.0019]	4.42 [3.69, 5.15]
Total 1L CLL							
Venetoclax + O	7.14 [6.22, 7.81]	1.19 [0.30, 2.22]	8.33 [7.69, 8.75]	5.19 [3.97, 6.24]	0.70 [0.17, 1.33]	− 0.0029 [− 0.0036, − 0.0023]	5.89 [4.71, 6.82]

Table 3 (continued)

Treatment	PFS LYs (mean, CI)	PPS LYs (mean, CI)	Total LYs (mean, CI)	PFS QALYs (mean, CI)	PPS QALYs (mean, CI)	AE disutilities (mean, CI)	Total QALYs (mean, CI)
Chlorambucil + G	3.63 [3.20, 4.06]	4.70 [3.94, 5.32]	8.33 [7.69, 8.74]	2.73 [2.07, 3.33]	2.79 [2.12, 3.47]	− 0.0024 [− 0.0030, − 0.0019]	5.52 [4.66, 6.29]
Fludarabine + cyclophosphamide + R	3.64 [2.12, 5.46]	3.92 [1.10, 6.17]	7.57 [5.31, 8.83]	2.73 [1.54, 4.16]	2.34 [0.63, 3.84]	− 0.0016 [− 0.0020, − 0.0013]	5.07 [3.56, 6.26]
Bendamustine + R	2.73 [1.57, 4.29]	5.23 [3.01, 6.90]	7.96 [6.19, 8.85]	2.07 [1.14, 3.27]	3.13 [1.74, 4.39]	− 0.0041 [− 0.0049, − 0.0034]	5.20 [3.92, 6.24]
Chlorambucil + R	1.84 [1.15, 2.77]	6.06 [4.36, 7.31]	7.91 [6.39, 8.81]	1.42 [0.83, 2.16]	3.65 [2.48, 4.80]	− 0.0011 [− 0.0014, − 0.0008]	5.07 [3.90, 6.11]
Ibrutinib	5.06 [3.35, 6.73]	3.14 [0.91, 5.11]	8.20 [6.66, 8.87]	3.74 [2.34, 5.17]	1.86 [0.53, 3.16]	− 0.0001 [− 0.0002, − 0.0001]	5.60 [4.33, 6.59]
Acalabrutinib	8.12 [6.96, 8.79]	0.56 [0.00, 1.76]	8.68 [7.87, 8.90]	5.93 [4.44, 7.17]	0.33 [0.00, 1.06]	− 0.001 [− 0.001, 0.000]	6.26 [4.94, 7.31]

1L frontline, *AE* adverse event, *CI* confidence interval, *CLL* chronic lymphocytic leukemia, *del17p/TP53* deletion of the short arm of chromosome 17 and/or mutations in the tumor suppressor gene TP53, *IGVH* immunoglobulin heavy-chain variable region, *LYs* life-years, *NA* not applicable, *PFS* progression-free survival, *PPS* post-progression survival, *QALYs* quality-adjusted life-years, *R* rituximab

across all comparisons, including the subgroup analyses for with and without del17p/TP53. Tornado plots for incremental costs and incremental QALYs, for all pairwise comparisons of VEN+O versus GClb (all populations) or Ibr (for del17p/TP53 subgroup), can be found in the Figs. S1–6 of the ESM.

As shown in Fig. 2, PA results following 5000 iterations remained stable and in accordance with the deterministic results conveying that the dominance of VEN+O over GClb and most other comparators is robust. The total cost and QALY estimates were comparable between the deterministic and PA. Cost estimates revealed higher uncertainty (<5% for all other interventions) compared with the QALY estimates (≤4% both intervention and comparator treatment arms). The CEAC shows that at $50,000 WTP threshold, VEN+O has an over 90% probability of being cost effective (Fig. 3).

Scenario analyses are presented in Tables 5 and 6. Despite variations in expected costs and expected QALYs, during pairwise comparisons, VEN+O remained dominant over all four treatment comparators (apart from vs acalabrutinib) across almost all the scenarios. The three exceptions were the scenario assuming a 5-year time horizon, applying the PPS CLL11 data, and applying alternative HRs from the NMA. In the first two scenarios, VEN+O was predicted to cost $311,691 and $316,165/QALY gained compared to GClb, respectively. When applying Clb dosing-adjusted HRs from the NMA, VEN+O was dominant versus all comparators including acalabrutinib. Reducing discount rates improved incremental QALYs for the comparators that accrued lower QALYs than VEN+O. Changing utility values had a large impact on the incremental QALYs but did not alter conclusions. Finally, relaxing the assumption of difference in OS between VEN+O and GClb did not significantly alter expected costs or QALYs relative to the base case.

4 Discussion

The identification of effective 1L CLL treatments with limited toxicity that can be tolerated by older or unfit patients remains a challenge in the management of newly diagnosed FCR-ineligible CLL patients. This study estimated the health economic impact of VEN+O in the frontline treatment of CLL in Canada. The CLL14 trial demonstrated that VEN+O improved PFS in previously untreated CLL older and less fit patients when compared with chemoimmunotherapy, GClb. The results showed the improved treatment potential of VEN+O translated into improved long-term health outcomes in CLL patients ineligible for FCR. VEN+O showed better economic outcomes as it was more clinically effective and less costly than most comparators owing to its fixed treatment duration. A probabilistic

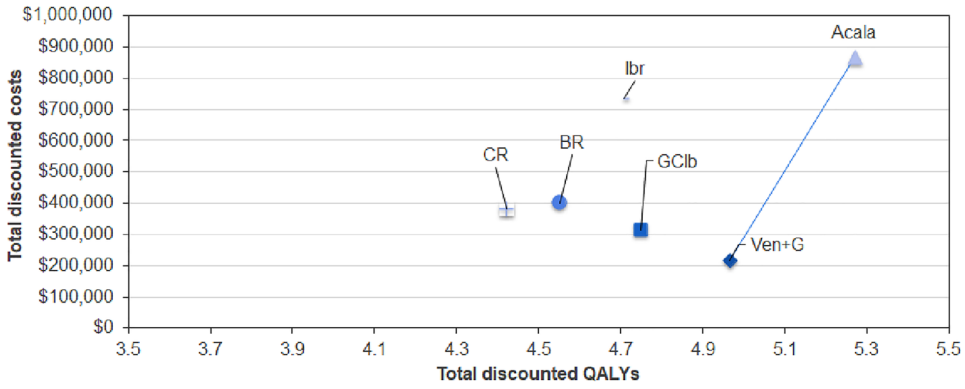

Fig. 1 Cost-effectiveness frontier for the unfit frontline chronic lymphocytic leukemia population. *Acala* acalabrutinib, *BR* bendamustine plus rituximab, *Clb* chlorambucil, *CR* chlorambucil plus rituximab, *GClb* Gazyvaro (obinutuzumab) plus chlorambucil, *Ibr* ibrutinib, *QALYs* quality-adjusted life-years, *Ven+G* venetoclax plus Gazyvaro (obinutuzumab)

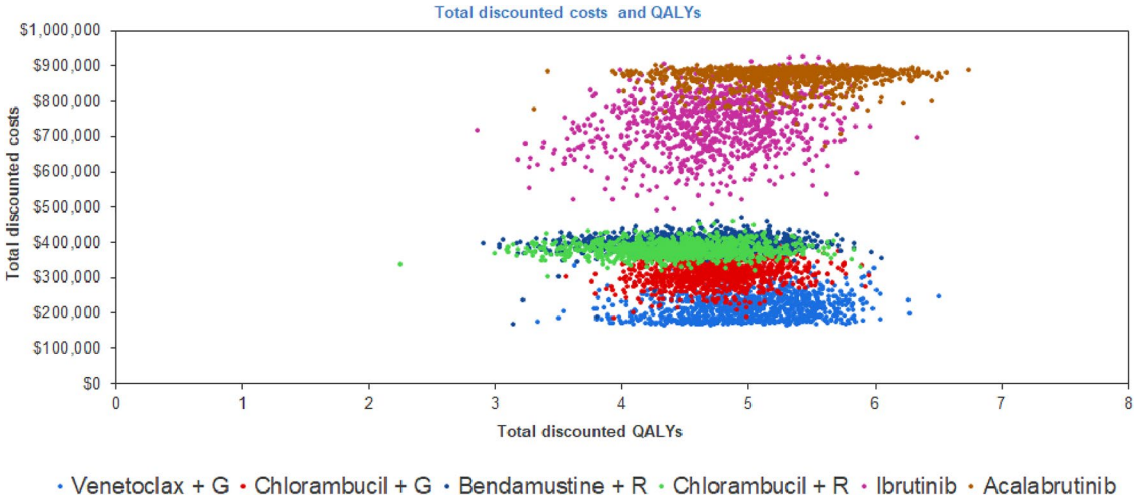

Fig. 2 Cost-effectiveness plane (unfit frontline chronic lymphocytic leukemia). *G* Gazyvaro (obinutuzumab), *QALYs* quality-adjusted life-years, *R* rituximab

analysis showed that at a WTP of approximately $50,000 per QALY, VEN+O had an over 90% probability of being the most cost-effective treatment. This was acknowledged by CADTH in the final recommendation on VEN+O in 1L CLL, which mentioned a 97% probability that VEN+O is cost effective at a WTP of $50,000 per QALY. At the time of submission, acalabrutinib was not yet recommended by CADTH [93].

VEN+O consistently showed better outcomes for PFS compared with all comparators across the total and the unfit 1L CLL population including the IGVH mutated population, except compared to acalabrutinib for the unfit and total 1L CLL patient population and compared to Ibr for the patient population with the del17p/TP53 mutation. The OWSA and several scenario analyses conveyed the robustness of the results. Within the scenario analysis where Clb dosing-adjusted HRs were used, VEN+O remained the dominant treatment option across all comparators including acalabrutinib.

For the unfit 1L CLL population, the best source of evidence for the VEN+O arm and the GClb arm was utilized from the CLL14 trial. Demonstrating robust evidence for the cost effectiveness of VEN+O for the treatment of 1L CLL patients was challenging for two reasons. First, the CLL14 trial data were still immature because the median OS was not reached in both treatment arms, while median PFS was only reached for GClb and not for VEN+O. Second, data limitations exist for the comparator study versus Ibr for the del17p population.

In the absence of mature data from the CLL14 patient population, long-term OS results are uncertain. To validate the extrapolated results from the CLL14 patient population,

Table 4 Full incremental analyses result for 1L CLL and subgroups

Treatment	Total costs	Total QALYs gained	Incremental costs	Incremental QALYs gained	Mean ICER (vs VEN+O)	Frontier analysis results for base-case population
Unfit 1L CLL						
VEN + O	$217,727	4.96	–	–	–	On frontier
Chlorambucil + G	$312,287	4.75	$94,560	− 0.215	–	Strictly dominated by VEN+G
Chlorambucil + R	$380,713	4.42	$162,986	− 0.542	–	Strictly dominated by VEN+G, chlorambucil+G
Bendamustine + R	$399,219	4.55	$181,492	− 0.414	–	Strictly dominated by VEN+G, chlorambucil+G
Ibrutinib	$736,017	4.71	$518,290	− 0.256	–	Strictly dominated by VEN+G, chlorambucil+G
Acalabrutinib	$868,797	5.27	$651,070	0.304	$2,139,180	$2,139,180
Unfit 1L CLL with del17p/TP53						
VEN + O	$209,102	3.11	–	–	–	On frontier
Chlorambucil + G	$330,698	2.90	$121,596	− 0.209	–	Strictly dominated by VEN+G
Ibrutinib	$584,164	3.37	$375,061	0.257	$1,458,423	$1,458,423
Unfit 1L CLL with non-del17p/TP53 mutation						
VEN + O	$217,732	5.04	–	–	–	NA
Chlorambucil + G	$299,105	4.83	$81,373	− 0.207	–	NA
Unfit 1L CLL with IGVH mutation						
VEN + O	$214,180	4.92	–	–	–	NA
Chlorambucil + G	$297,343	4.70	$83,163	− 0.218	–	NA
Unfit 1L CLL without IGVH mutation						
VEN + O	$199,972	4.66	–	–	–	NA
Chlorambucil + G	$347,562	4.42	$147,590	− 0.242	–	NA
Total 1L CLL						
VEN + O	$219,651	5.89			–	On frontier
Chlorambucil + G	$312,570	5.52	$92,919	− 0.369	–	Strictly dominated by VEN+G
FCR	$342,195	5.07	$122,543	− 0.821	–	Strictly dominated by VEN+G, chlorambucil+G
Chlorambucil + R	$380,551	5.07	$160,900	− 0.815	–	Strictly dominated by VEN+G, chlorambucil+G
Bendamustine + R	$397,262	5.20	$177,611	− 0.690	–	Strictly dominated by VEN+G, chlorambucil + G
Ibrutinib	$757,129	5.60	$537,478	− 0.290	–	Strictly dominated by VEN+G
Acalabrutinib	$868,388	6.26	$648,737	0.371	$1,748,296	$1,748,296

1L frontline, *CLL* chronic lymphocytic leukemia, *del17p/TP53* deletion of the short arm of chromosome 17 and/or mutations in the tumor suppressor gene TP53, *FCR* fludarabine plus cyclophosphamide plus rituximab, *G* Gazyvaro (obinutuzumab), *ICER* incremental cost-effectiveness ratio, *IGVH* immunoglobulin heavy-chain variable region, *NA* not applicable, *O* obinutuzumab, *QALYs* quality-adjusted life-years, *R* rituximab, *VEN* venetoclax

the 5-year follow-up data from the CLL11 trial were incorporated within a scenario. The CLL11 serves as a conservative scenario as the post-progression period has limited innovative treatment regimens that were provided to the CLL14 trial population. Therefore, the OS estimates from CLL11 are likely underestimated given the current treatment landscape and poorly fit the VEN+O as well as the GClb treatment arms in CLL14.

5 Conclusions

This study supports that VEN+O is an effective fixed-duration treatment option for the treatment of unfit 1L CLL patients demonstrating potential cost savings for Canadian jurisdictions compared with existing funded treatments in Canada. This is in line with the recently released CADTH CLL provisional funding algorithm used to provide advice

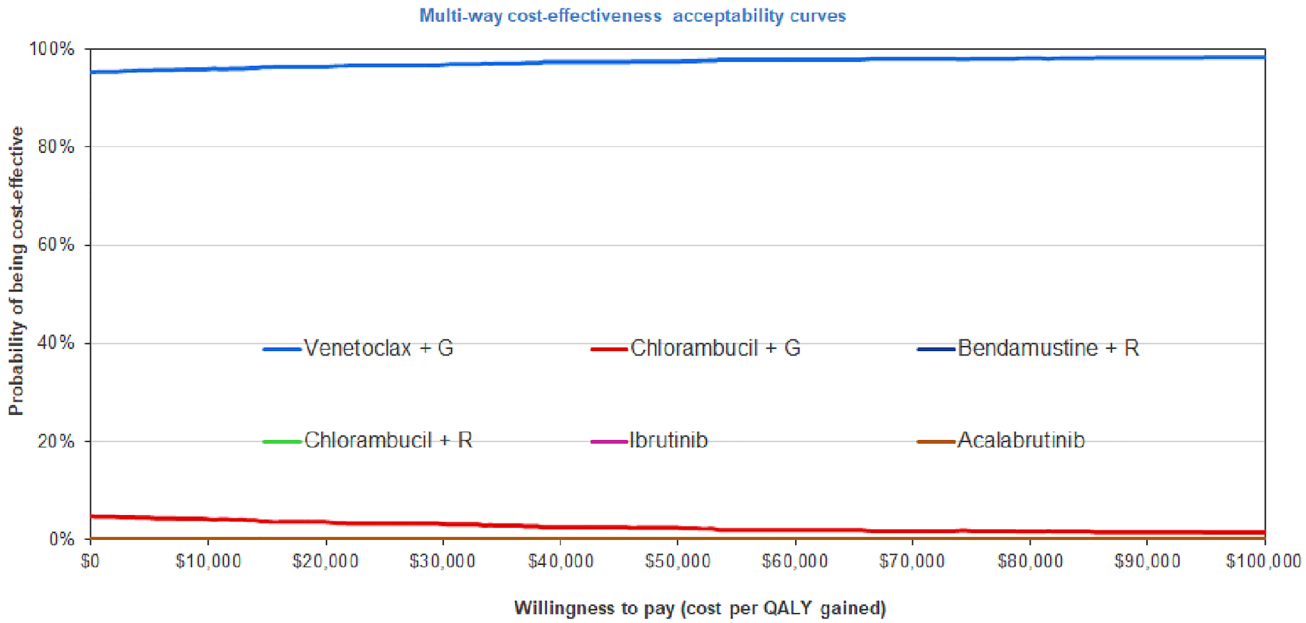

Fig. 3 Cost-effectiveness acceptability curves (unfit frontline chronic lymphocytic leukemia). *G* Gazyvaro (obinutuzumab), *QALY* quality-adjusted life-year, *R* rituximab

Table 5 Scenario analysis frontline CLL unfit population (1/2)

	GClb			BR			Clb+R		
	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER
Base case	− $94,560	0.215	Dominant	− $181,492	0.414	Dominant	− $162,986	0.542	Dominant
Discount rate, costs: 0%, QALYs: 0%	− $108,698	0.229	Dominant	− $187,694	0.441	Dominant	− $167,189	0.577	Dominant
Time horizon: 5 years	$25,449	0.082	$311,691	− $140,701	0.179	Dominant	− $141,722	0.234	Dominant
Time horizon: 15 years	− $135,063	0.297	Dominant	− $159,634	0.613	Dominant	− $140,886	0.820	Dominant
Time horizon: 20 years	− $124,344	0.367	Dominant	− $148,096	0.797	Dominant	− $129,432	1.066	Dominant
Time horizon: lifetime (~ 30 years)	− $116,747	0.422	Dominant	− $141,993	0.936	Dominant	− $123,230	1.246	Dominant
Drug wastage included	− $93,755	0.211	Dominant	− $184,118	0.407	Dominant	− $164,433	0.535	Dominant
Utility (from CLL14 trial) Pre-progression utility = 0.829	− $92,764	0.706	Dominant	− -$179,289	1.080	Dominant	− $160,819	1.291	Dominant
CLL11	$45,475	0.144	$316,165	− $225,815	0.517	Dominant	− $207,655	0.716	Dominant
OS distribution—Exponential	− $91,042	0.219	Dominant	− $177,374	0.404	Dominant	− $158,799	0.529	Dominant
Using NMA outcomes adjusted for Clb dosing	− $93,397	0.210	Dominant	− $162,518	1.743	Dominant	− $140,733	1.855	Dominant

The CLL11 scenario is based on the deterministic analysis, not on the probabilistic analysis

BR bendamustine and rituximab, *CLL* chronic lymphocytic leukemia, *Clb* chlorambucil, *Clb+R* chlorambucil and rituximab, *GClb* Gazyvaro (obinutuzumab) plus chlorambucil, *ICER* incremental cost-effectiveness ratio, *NMA* network meta-analysis, *OS* overall survival, *QALYs* quality-adjusted life-years

Table 6 Scenario analysis frontline chronic lymphocytic leukemia unfit population (2/2)

	Ibr			Acala		
	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER
Base case	− $518,290	0.256	Dominant	− $651,070	− 0.304	South-west quadrant of the CE plane
Discount rate, costs: 0%, QALYs: 0%	− $549,304	0.273	Dominant	− $699,827	− 0.328	South-west quadrant of the CE plane
Time horizon: 5 years	− $326,012	0.086	Dominant	− $309,818	− 0.103	South-west quadrant of the CE plane
Time horizon: 15 years	− $566,086	0.437	Dominant	− $885,168	− 0.561	South-west quadrant of the CE plane
Time horizon: 20 years	− $580,734	0.611	Dominant	− $1,024,344	− 0.904	South-west quadrant of the CE plane
Time horizon: lifetime (−30 years)	− $581,779	0.743	Dominant	− $1,103,235	− 1.451	South-west quadrant of the CE plane
Drug wastage included	− $516,420	0.253	Dominant	− $650,278	− 0.301	South-west quadrant of the CE plane
Utility (from CLL14 trial) Pre-progression utility = 0.829	− $516,504	0.573	Dominant	− $649,566	− 0.446	South-west quadrant of the CE plane
CLL11	− $388,651	0.386	Dominant	− $537,527	− 0.837	South-west quadrant of the CE plane
OS distribution Treatment effect Exponential	− $514,939	0.251	Dominant	− $648,815	− 0.290	South-west quadrant of the CE plane
Using NMA outcomes adjusted for Clb dosing	− 356,159	1.509	Dominant	− $509,062	0.208	Dominant

Acala acalabrutinib, *CE* cost-effectiveness, *Clb* chlorambucil, *Ibr* ibrutinib, *ICER* incremental cost-effectiveness ratio, *Inc.* including, *NMA* network meta-analysis, *OS* overall survival, *QALYs* quality-adjusted life-years

to the Canadian public-participating drug programs on implementation issues in CLL, which raised the concept of affordability as an important factor to consider when assessing the relative place in therapy for the different treatment options in the first-line setting [94].

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Declarations

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Availability of data and material Input data for the generation of the results are available in this article and its Electronic Supplementary Material. Additional datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. The MS Excel model cannot be shared because of confidentiality reasons.

Code availability Not applicable.

Authors' 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 and Pharmerit, an OPEN Health Company participated in the design, study conduct, analysis and interpretation of data, as well as the writing, review, and approval of the manuscript.

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