A Probabilistic Cost-Effectiveness Analysis of Venetoclax and Obinutuzumab as a First-Line, 12-Month, Fixed Duration Therapy in Chronic Lymphocytic Leukemia in Canada

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OBJECTIVE

To assess the cost effectiveness of venetoclax in combination with obinutuzumab (Ven+O) for the treatment of previously untreated (1L) chronic lymphocytic leukemia (CLL) in Canada from a publicly funded healthcare system perspective

CONCLUSIONS

This study supports that Ven+O is a cost-effective fixed duration treatment option for the treatment of unfit 1L CLL patients demonstrating potential cost-savings for Canadian jurisdictions compared to existing funded treatments in Canada

This is in line with the recently released CADTH CLL provisional funding algorithm used to provide advice 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[14]

INTRODUCTION

- CLL is a clonal disease of unknown etiology. In Canada, yearly incidence varies between 5.0–8.0 per 100,000 persons,[1,2] translating into over 1700 new CLL cases in 2016 and about 600 deaths in 2017[3]
- CLL is more common with advanced age, median age of diagnosis ranges between 67–72 years old. The fitness of patients has been defined as a key prognostic factor for CLL survival[4]
- 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 (mTP53), the mutation status of the immunoglobulin heavy-chain variable region (IGVH), b2-microglobulin level and CLL clinical stage[5,6]
- Venetoclax (Ven) is a first-in-class, oral, selective inhibitor of BCL-2 anti-apoptotic protein that is overexpressed in approximately 95% of CLL patients. Its unique targeted mechanism of action and fixed treatment duration distinguish it from other available therapies[7]
- The open-label Phase 3 CLL14 clinical trial (NCT02242942) results demonstrated an acceptable safety profile of Ven+O, for the treatment of 1L CLL patients with co-existing medical conditions (unfit patients).[8,9] In all patients and across all the major prognostic subgroups analyzed, Ven+O showed a consistent superior treatment profile compared to the standard of care obinutuzumab + chlorambucil (O+Clb).

METHODS

Population of interest and treatment interventions

- The population of interest for this study were patients considered "unfit" for chemotherapy. The unfit 1L CLL population was further subdivided in 4 subgroups based on del17p/TP53 and IGVH mutation status
- The treatment comparators of Ven+O for the 1L CLL unfit patient population, were O+Clb, bendamustine + rituximab (BR), chlorambucil + rituximab (Clb+R), ibrutinib (Ibr) and acalabrutinib monotherapy. For all the unfit subgroups the treatment comparator was O+Clb, except in the case of the del17p/TP53 subgroup, where Ibr was also used

Trial data

- The primary measures of clinical effectiveness for the 1L CLL treatments in the CEM were drawn from the CLL14 trial data and included PFS, OS, TTNT, and time on treatment (ToT) curves for Ven+O and O+Clb treatment arms

Modeling approach

- A partitioned survival analyses (PartSA) model was developed with 3 health states: progression free (PFS), progressed (PPS), and dead. A cycle length of 28 days and a time horizon of 10 years was used for the model
- 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
- It was assumed that the age- and sex-adjusted mortality hazard rates of CLL patients were not lower than those 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
- Uncertainty was assessed via 1-way sensitivity analyses, probabilistic analyses (PA), and scenario analyses

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 (ad-board). 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

Treatment efficacy

- The observed survival curves of Ven+O and O+Clb in the CLL14 trial were parameterized and used to estimate outcomes beyond the observed trial period and allow synthesis of outcomes with data from external comparators
- As the sample of patients with the del17p/TP53 mutation is small, del17p/TP53 was included as a covariate in time to event modeling to maximize the predictive power of the CLL14 data. Similarly, 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 2 subgroups
- A clinical SLR was conducted to inform indirect treatment comparisons (ITC) between Ven+O and the comparators outside the CLL14 trial and were made using network meta-analysis (NMA) methods. Hazard ratios (HRs) were generated vs Ven+O for 2 outcomes (PFS and OS). These NMAs were updated to include acalabrutinib
- In the del17p/TP53 population 2 naïve comparisons and 1 matching-adjusted indirect comparison (MAIC) was conducted for Ven+O vs Ibr monotherapy.[10,11] The PFS and OS HRs from the naïve comparison using Mato et al[10] were combined with the Ven+O PFS and OS curves respectively to generate the individual survival curves for Ibr. The naïve comparison using Mato was used in the base case since the results were powered by a larger sample size[12]

Model analyses and sensitivity analyses

- The key outcomes of the cost-effectiveness analysis were total life years (LYs), quality-adjusted life-years (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 per QALY gained
- Analysis was conducted from a publicly funded healthcare system perspective. Consistent with CADTH guidelines, the base case analysis results were derived using the probabilistic model. Based on CADTH guidelines, a 1.5% discount rate was applied to the cost and effects outcomes[13]
- In the PA a simulation of 5000 iterations generated a mean output with associated upper and lower confidence intervals

RESULTS

- All comparators resulted in higher costs than Ven+O, with acalabrutinib-based regimens accruing the highest costs (**Table 1**). For treat to progression-based regimens the high costs were driven by the high drug acquisition costs that were accrued for these comparators. For non-treat to progression-based regimens the high costs were driven by the subsequent treatment costs which were accrued due to the larger proportion of patients remaining in the PPS period compared to Ven+O
- Acalabrutinib accrued the highest health gains at 5.27 [95% CI: 4.25, 6.25] QALYs, followed by Ven+O, and O+Clb, 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 to other treatments. For unfit 1L CLL patients with del17p/TP53 mutation subgroup, 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 to O+Clb (all, **Table 2**)

Table 1. Overview of Total Costs per Patient over a 10-year Time Horizon (Discounted) for Unfit Patients per Treatment in Base Case Scenario

Treatment	Total drug acquisition	Total drug administration	Total disease management	One-time drug, administration, monitoring	Subsequent treatment	Adverse events	Terminal care	Total costs
Unfit 1L CLL								
Venetoclax + O	$116,456	$1,541	$12,892	$2,679	$43,625	$7,072	$33,462	$217,727
	[116,290; 116,504]	[1,255, 1,853]	[11,056, 14,917]	[2,173, 3,245]	[0, 126,262]	[6,022, 8,215]	[27,308, 40,500]	[170,725, 300,761]
Chlorambucil + O	$42,911	$1,536	$9,706	$2,380	$216,126	$6,169	$33,459	$312,287
	[42,893, 42,926]	[1,250, 1,848]	[8,612, 10,909]	[1,938, 2,867]	[140,420, 280,089]	[5,203, 7,232]	[27,288, 40,458]	[238,878, 377,036]
Bendamustine + R	$47,116	$2,890	$8,372	$0	$296,520	$10,738	$33,583	$399,219
	[42,734, 49,396]	[2,379, 3,434]	[6,855, 10,396]		[263,935, 332,539]	[9,349, 12,292]	[27,400, 40,638]	[365,934, 434,779]
Chlorambucil + R	$23,614	$661	$7,690	$0	$312,131	$2,937	$33,681	$380,713
	[21,431, 24,818]	[556, 771]	[6,234, 9,117]		[275,886, 351,569]	[2,369, 3,564]	[27,531, 40,720]	[343,567, 420,473]
Ibrutinib	$494,503	$0	$10,637	$0	$196,091	$1,200	$33,586	$736,017
	[312,860, 667,868]		[8,385, 13,102]		[98,311, 224,029]	[750, 1,757]	[27,454, 40,625]	[568,143, 877,908]
Acalabrutinib	$759,631	$0	$14,045	$0	$60,761	$1,097	$33,263	$868,797
	[653,420, 820,574]		[11,934, 16,438]		[0, 174,736]	[731, 1,526]	[27,158, 40,205]	[790,648, 897,489]
Acalabrutinib + O	$830,685	$1,780	$14,355	$0	$32,538	$3,545	$33,235	$916,139
	[736,802, 870,830]	[1,450, 2,142]	[12,247, 16,729]		[0, 134,690]	[2,827, 4,347]	[27,203, 40,142]	[844,935, 941,959]
Unfit 1L CLL with del17p/TP53								
Venetoclax + O	$109,842	$1,488	$7,880	$2,686	$44,910	$7,081	$35,217	$209,102
	[101,752, 111,291]	[1,211, 1802]	[5,473, 10,385]	[2,201, 3,242]	[0, 223,608]	[6,040, 8,222]	[28,756, 42,522]	[159,698, 386,190]
Chlorambucil + O	$40,133	$1,390	$5,300	$2,376	$241,456	$6,179	$35,253	$330,698
	[39,689, 40,462]	[1136, 1675]	[3,720, 6,935]	[1,948, 2,851]	[31,450, 378,296]	[5,198, 7,280]	[28,730, 42,666]	[121,425, 468,799]
Ibrutinib	$474,485	$0	$8,590	$0	$64,905	$1,206	$34,977	$584,164
	[217,752, 712,464]		[3,961, 12,632]		[0, 187,644]	[756, 1,758]	[28,422, 42,467]	[289,477, 824,664]
Unfit 1L CLL without del 17p/TP53 mutation								
Venetoclax + O	$116,850	$1,544	$13,144	$2,691	$43,021	$7,060	$33,422	$217,732
	[116,664, 116,899]	[1,253, 1,852]	[11,348, 15,187]	[2,195, 3,229]	[0, 125,887]	[6,016, 8,223]	[27,199, 40,342]	[171,232, 299,063]
Chlorambucil + O	$43,188	$1,546	$10,032	$2,379	$202,380	$6,161	$33,420	$299,105
	[43,171, 43,203]	[1,254, 1,854]	[8,908, 11,272]	[1,942, 2,868]	[138,408, 267,174]	[5,163, 7,262]	[27,233, 40,371]	[231,978, 363,546]
Unfit 1L CLL with IGVH mutation								
Venetoclax + O	$116,827	$1,545	$12,891	$2,682	$39,682	$7,072	$33,481	$214,180
	[116,531, 116,897]	[1,248, 1,875]	[10,991, 14,983]	[2,168, 3,228]	[0, 120,137]	[6,047, 8,202]	[27,170, 40,431]	[170,650, 297,474]
Chlorambucil + O	$43,160	$1,547	$9,614	$2,381	$201,001	$6,166	$33,475	$297,343
	[43,135, 43,183]	[1,250, 1,877]	[8,468, 10,874]	[1,939, 2,865]	[125,028, 272,734]	[5,215, 7,277]	[27,127, 40,381]	[219,378, 368,492]
Unfit 1L CLL without IGVH mutation								
Venetoclax + O	$116,806	$1,540	$12,157	$2,680	$25,900	$7,068	$33,821	$199,972
	[116,410, 116,893]	[1,254, 1,842]	[10,276, 14,208]	[2,172, 3,229]	[0,119,327]	[5,999, 8,192]	[27,674, 40,743]	[168,674, 293,279]
Chlorambucil + O	$43,157	$1,542	$8,640	$2,379	$251,848	$6,174	$33,821	$347,562
	[43,127, 43,181]	[1,255, 1,845]	[7,569, 9,816]	[1,931, 2,864]	[171,248, 309,490]	[5,206, 7,274]	[27,701, 40,681]	[266,777, 405,857]

Table 2. Overview of Total Life Years, QALYs, and Disutilities for Unfit Patients per Treatment in Base Case Scenario

Treatment	PFS LYs	PPS LYs	Total LYs	PFS QALYs	PPS QALYs	AE Disutilities	Total QALYs
Unfit 1L CLL							
Venetoclax + O	7.15	1.17	8.32	4.36	0.61	-0.0029	4.96
	[6.26, 7.79]	[0.28, 2.18]	[7.67, 8.75]	[3.37, 5.30]	[0.14, 1.15]	[-0.0036, -0.0023]	[4.04, 5.82]
Chlorambucil + O	3.63	4.70	8.32	2.29	2.46	-0.0024	4.75
	[3.21, 4.08]	[3.96, 5.32]	[7.71, 8.74]	[1.79, 2.81]	[1.86, 3.07]	[-0.0030, -0.0019]	[4.03, 5.45]
Bendamustine + R	2.38	5.72	8.10	1.52	3.03	-0.0041	4.55
	[1.17, 4.19]	[3.75, 7.14]	[7.16, 8.78]	[0.74, 2.67]	[1.90, 4.10]	[-0.0049, -0.0034]	[3.71, 5.33]
Chlorambucil + R	1.79	6.13	7.92	1.16	3.27	-0.0011	4.42
	[1.11, 2.69]	[4.44, 7.38]	[6.38, 8.81]	[0.69, 1.78]	[2.20, 4.25]	[-0.0014, -0.0008]	[3.39, 5.33]
Ibrutinib	4.84	3.25	8.10	3.00	1.71	-0.0001	4.71
	[3.01, 6.60]	[0.90, 5.37]	[6.49, 8.86]	[1.83, 4.28]	[0.47, 2.94]	[-0.0002, -0.0001]	[3.65, 5.61]
Acalabrutinib	8.13	0.56	8.68	4.98	0.29	-0.001	5.27
	[6.95, 8.79]	[0.00, 1.75]	[7.94, 8.90]	[3.85, 6.09]	[0.00, 0.92]	[-0.001, 0.000]	[4.25, 6.25]
Acalabrutinib + O	8.43	0.31	8.73	5.20	0.16	-0.001	5.36
	[7.40, 8.87]	[0.00, 1.35]	[8.02, 8.91]	[4.03, 6.32]	[0.00, 0.69]	[-0.002, -0.001]	[4.28, 6.38]
Unfit 1L CLL with del17p/TP53							
Venetoclax + O	4.22	0.91	5.13	2.63	0.49	-0.0029	3.11
	[2.70, 5.70]	[NA, 3.04]	[3.38, 6.77]	[1.62, 3.68]	[NA, 1.66]	[-0.0036, -0.0023]	[2.00, 4.20]
Chlorambucil + O	1.49	3.57	5.06	0.97	1.94	-0.0024	2.90
	[0.93, 2.28]	[1.66 5.44]	[3.22, 6.84]	[0.58, 1.51]	[0.88, 3.07]	[-0.0030, -0.0019]	[1.86, 4.0]
Ibrutinib	4.65	0.92	5.57	2.88	0.49	-0.0001	3.37
	[2.08, 7.06]	[NA, 4.09]	[2.37, 8.26]	[1.29, 4.52]	[NA, 2.24]	[-0.0002, -0.0001]	[1.47, 5.03]
Unfit 1L CLL with non-del 17p/TP53 mutation							
Venetoclax + O	7.33	1.13	8.46	4.45	0.59	-0.0029	5.04
	[6.45, 7.97]	[0.30, 2.11]	[7.90, 8.81]	[3.46, 5.40]	[0.15, 1.14]	[-0.0035, -0.0023]	[4.05, 5.92]
Chlorambucil + O	3.88	4.58	8.46	2.44	2.39	-0.0024	4.83
	[3.42, 4.34]	[3.90, 5.18]	[7.91, 8.80]	[1.88, 2.99]	[1.83, 2.99]	[-0.0024, -0.0019]	[4.10, 5.53]
Unfit 1L CLL with IGVH mutation							
Venetoclax + O	7.21	1.03	8.24	4.39	0.54	-0.0029	4.92
	[6.21, 7.88]	[0.13, 2.12]	[7.59, 8.68]	[3.37, 5.35]	[0.07, 1.11]	[-0.0036, -0.0023]	[3.97, 5.83]
Chlorambucil + O	3.58	4.67	8.25	2.26	2.44	-0.0024	4.70
	[3.14, 4.02]	[3.96, 5.30]	[7.63, 8.68]	[1.73, 2.78]	[1.86, 3.03]	[-0.0030, -0.0019]	[3.96, 5.39]
Unfit 1L CLL without IGVH mutation							
Venetoclax + O	6.74	1.06	7.80	4.11	0.56	-0.0029	4.66
	[5.61, 7.52]	[0.00, 2.37]	[6.95, 8.48]	[3.12, 5.05]	[0.002, 1.25]	[-0.0036, -0.0023]	[3.71, 5.54]
Chlorambucil + O	2.89	4.91	7.88	1.84	2.59	-0.0024	4.42
	[2.48, 3.32]	[3.98, 5.71]	[6.94, 8.49]	[1.40, 2.28]	[1.91, 3.26]	[-0.0030, -0.0019]	[3.69, 5.15]

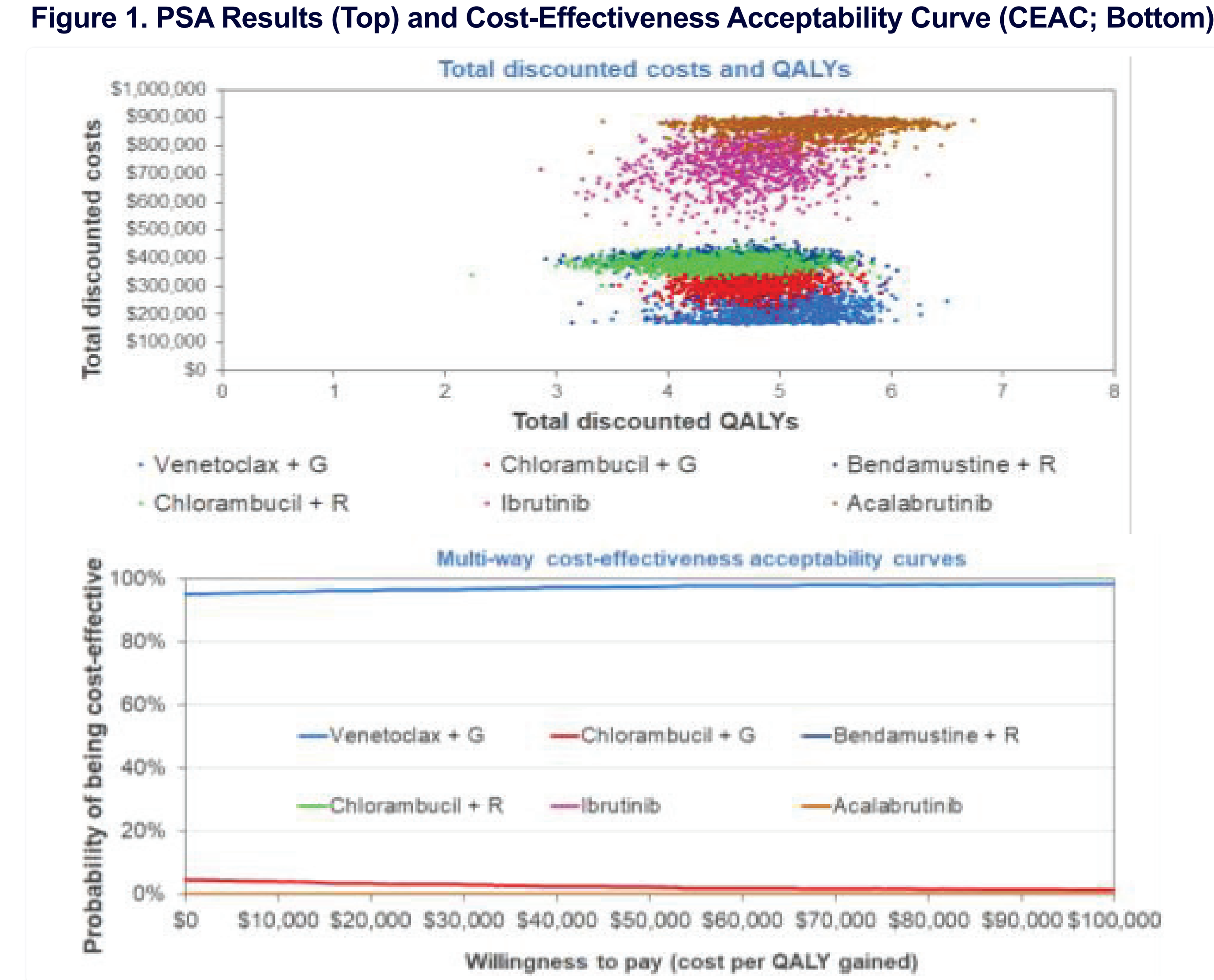
Table 3. Full Incremental Analyses Result for Unfit Patients

Treatment	Total Costs	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 + O	$312,287	4.75	$94,560	-0.215	—	Strictly dominated by Ven+O
Chlorambucil + R	$380,713	4.42	$162,986	-0.542	—	Strictly dominated by Ven+O, GClb
Bendamustine + R	$399,219	4.55	$181,492	-0.414	—	Strictly dominated by Ven+O, GClb
Ibrutinib	$736,017	4.71	$518,290	-0.256	—	Strictly dominated by Ven+O, GClb
Acalabrutinib	$868,797	5.27	$651,070	0.304	$2,139,180	$2,139,180
Acalabrutinib + O	$916,139	5.36	$698,412	0.395	$1,768,650	$1,768,650
Unfit 1L CLL with del17p/TP53						
Ven+O	$209,102	3.11	—	—	—	On frontier
Chlorambucil + O	$330,698	2.90	$121,596	-0.209	—	Strictly dominated by Ven+O
Ibrutinib	$584,164	3.37	$375,061	0.257	$1,458,423	$1,458,423
Unfit 1L CLL with non-del 17p/TP53 mutation						
Ven+O	$217,732	5.04	—	—	—	NA
Chlorambucil + O	$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 + O	$347,562	4.42	$147,590	-0.242	—	NA

Sensitivity analysis

- The PA results remained stable and in accordance with the deterministic results conveying that the dominance of Ven+O over O+Clb and most other comparators is robust. The total cost and QALYs estimates were comparable between the deterministic and PA.
- The CEAC shows that at a $50,000 WTP threshold, Ven+O has over 90% probability of being cost-effective.

Figure 1. PSA Results (Top) and Cost-Effectiveness Acceptability Curve (CEAC; Bottom)



DISCUSSION

- Ven+O showed better economic outcomes as it is more clinically effective and less costly than most comparators due to its fixed treatment duration. Ven+O consistently showed better outcomes for PFS compared to all comparators across the unfit 1L CLL population including the IGVH mutated-population, except compared to acalabrutinib for the unfit population and compared to Ibr for the del17p/TP53 mutated patient population. In the absence of mature data from the CLL14 study, long-term OS results are uncertain

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