Literature Review of Safety Outcomes in Chronic Lymphocytic Leukemia (CLL): First-line (1L) Fixed Duration and Monotherapy Treatment Options in Canada

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Background

- Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in Canada[1], with an estimated 1,700 new cases in 2019 and 555 deaths in 2022.[2-4]
- CLL is a slowly progressing, chronic disease with a 5-year net survival rate of 86%[3], leading to a significant burden for patients and the healthcare system.[5]
- Currently available first-line (1L) treatment options include[6,7]:
  - Targeted treat-to-progression (TTP) monotherapy with a Bruton's tyrosine kinase inhibitor (BTKi) (acalabrutinib, ibrutinib, and zanubrutinib).
  - Targeted fixed-duration combinations (ibrutinib + venetoclax [**I+V**] and venetoclax + obinutuzumab [**V+O**]).
  - Chemoimmunotherapy (e.g., fludarabine-cyclophosphamide-rituximab [FCR], bendamustine-rituximab [BR], and chlorambucil + obinutuzumab).
- A novel targeted fixed-duration regimen, acalabrutinib + venetoclax (**A+V**), was evaluated in the AMPLIFY trial (NCT03836261)[8], which is a randomized, global, multi-centre, open-label Phase III study comparing **A+V** to investigator's choice of chemoimmunotherapy (FCR or BR) in previously untreated CLL patients.
  - The **A+V** regimen consistently demonstrated a lower within-trial incidence of grade ≥3 adverse events (AEs) than FCR or BR.[8]

Objective

This study aimed to investigate and summarize published safety profiles of current 1L CLL treatments relevant to the Canadian setting

- The use of chemoimmunotherapy has become antiquated in Canada, with near-zero utilization, while targeted fixed-duration regimens have gained preference for their ability to reduce treatment time, minimize long-term toxicity, and improve patient compliance compared to TTP regimens[7,9]; therefore, this study focuses on targeted fixed-duration therapies.

Methods

- The literature review was conducted following standard methodologies adapted from the Cochrane Handbook for Systematic Reviews of Interventions.[10]
- Studies were identified in Embase (Ovid) from 2024 to May 5, 2025, using the PICO criteria (**Table 1**) to supplement a prior global systematic literature review (SLR); screening was performed by a methodologist with support from Evidinno's proprietary AI-enabled selection tool, and any discrepancies were resolved by consensus with a second reviewer. All eligible studies were included for data extraction.
- Additionally, manual searches of publicly available European Public Assessment Reports (EPARs) for treatment combinations of interest were conducted via the EMA website (https://www.ema.europa.eu/en/medicines).

Table 1: Simplified PICOs eligibility criteria

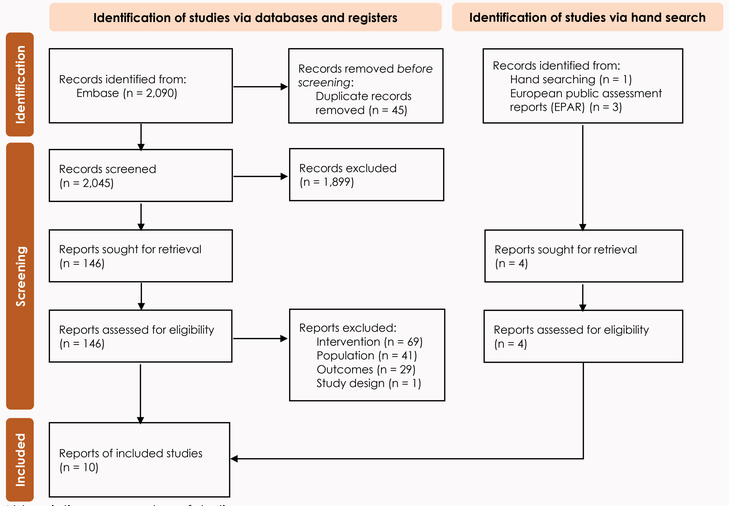
Parameter	Description
Population	Adults with CLL receiving 1L treatment
Intervention	A+V, I+V, V+O, ibrutinib monotherapy, acalabrutinib monotherapy, and zanubrutinib monotherapy
Comparator	Any treatment
Outcomes	TEAEs, TRAEs, AE-related treatment discontinuations, specific AEs of interest, and mortality
Study Design	Clinical trials, observational studies including RWE using real-world data, and systematic reviews and meta-analyses for library only
Language	English
Publication Date Limit	• 2024 - May 5, 2025 (clinical trials) • 2013 - May 5, 2025 (RWE)

Abbreviations: 1L = first-line; A+V = acalabrutinib + venetoclax; AEs = adverse events; CLL = chronic lymphocytic leukemia; I+V = ibrutinib + venetoclax; RWE = real-world evidence; TEAEs = treatment-emergent adverse events; TRAEs = treatment-related adverse events; V+O = venetoclax + obinutuzumab.

Results

- In total, 2,090 records were identified from the Embase database, of which 2,045 were screened at title/abstract screening stage following removal of duplicate records (**Figure 1**).
- After full-text screening of 146 publications, 10 publications representing 11 unique studies (one publication reported two separate clinical trials) were included:
  - 7 clinical trials
  - 4 observational studies
  - Additionally, two clinical trials were sourced from the global SLR

Figure 1: PRISMA flow diagram



Abbreviations: n = number of studies.

- In the AMPLIFY trial, **A+V** demonstrated a manageable safety profile with a lower rate of grade ≥3 treatment-emergent AEs (TEAEs) at **53.6%** and serious TEAEs at **24.7%**[8], compared with in-trial rates for **I+V** (**64.7-75.5%** grade ≥3 TEAEs; **21.7%-46.2%** serious TEAEs)[11] and **V+O** (**78.8%-80.3%** grade ≥3 TEAEs; **44.7%-49.1%** serious TEAEs).[12,13]
- The **A+V** regimen reported the lowest within-trial rate of any treatment-related AEs (TRAEs) at **79.0%** and serious TRAEs at **9.3%** based on the AMPLIFY trial[8] compared with **I+V** (**84%-95%** any TRAEs; **12.1%-24.5%** serious TRAEs)[11] and **V+O** (**89.6%** any TRAEs; **26.4%** serious TRAEs).[12]
- The **A+V** regimen was associated with improved tolerability, reporting a lower within-trial rate of treatment discontinuation due to TEAEs (AMPLIFY: **7.9%**[8]) than rates observed for **I+V** (GLOW: **19.8%**[11]) and **V+O** (CLL14: **16.0%**[12]).
- The **A+V** regimen reported low within-trial rates of cardiac events, including any-grade cardiac AEs (**9.3%**) and grade ≥3 cardiac AEs (**1.7%**)[8], while a higher incidence was reported for **I+V** (**21.7%-24.5%** any-grade cardiac AEs; **3.4%-12.3%** grade ≥3 cardiac AEs)[11] and **ibrutinib monotherapy** (**14.8%** any-grade cardiac AEs; **5.9%** grade ≥3 cardiac AEs).[14]
- Atrial fibrillation was infrequently reported for the **A+V** regimen (**0.7%** any grade; **0.3%** grade ≥3)[8], representing a potential safety advantage over ibrutinib-containing regimens, whereas higher within-trial incidences were observed with **I+V** (**5.9%-14.2%** any grade; **1.5-6.6%** grade ≥3)[11], and **ibrutinib monotherapy** (**7.4%** any grade; **2.2%** grade ≥3).[14]
- In the AMPLIFY trial[8], **A+V** demonstrated low grade ≥3 rates of anemia, neutropenia, hypertension, infections, and tumor lysis syndrome reporting within-trial rates that were similar to or lower than those observed with **I+V**[11] and notably lower than with **V+O**[12,13] (**Table 2**).
- In the AMPLIFY trial, **A+V** (an all-oral regimen) had **zero** infusion-related reactions, whereas **obinutuzumab**-containing combinations reported incidence rates of any-grade events up to **51.3%**.[13]

Table 2: Specific AEs of interest

Grade ≥3 Adverse events, n (%)	AMPLIFY – Safety population[8] Median follow-up: 40.88 months	CAPTIVATE – Safety population[11] Median follow-up: 27.9 months	GLOW – Safety population[11] Median follow-up: 27.7 months	CLL14 – Safety population[12] Median follow-up: 28.1 months	CLL13 – Safety population[13] Median follow-up: 38.8 months
	A+V (n = 291)	**I+V (n = 323)**	**I+V (n = 106)**	**V+O (n = 212)**	**V+O (n = 228)**
Anemia	11 (3.8%)	6 (1.9%)	3 (2.8%)	17 (8.0%)[15]	11 (4.8%)
Neutropenia	94 (32.3%)	110 (34.1%)	30 (28.3%)	112 (52.8%)	103 (45.2%)
Hemorrhage	3 (1.0%)	3 (0.9%)	4 (3.8%)	-	-
Hypertension	8 (2.7%)	16 (7.1%)	9 (8.5%)	6 (2.8%)	4 (1.8%)
Infection	36 (12.4%)	27 (8.4%)	16 (15.1%)	41 (19.3%)	30 (13.2%)
Infusion-related reaction	0	0	0	19 (9.0%)[15]	26 (11.4%)
Tumor lysis syndrome	1 (0.3%)	1 (0.3%)	0	-	19 (8.3%)

Abbreviations: A+V = acalabrutinib + venetoclax; I+V = ibrutinib + venetoclax; n = number of patients; V+O = venetoclax + obinutuzumab.
NOTE: These data are derived from different studies with varying designs, patient populations, AE definitions, and follow-up durations. Direct comparisons should be interpreted with caution due to methodological differences between studies.

- In the AMPLIFY trial, **A+V** had an all-cause mortality rate of **6.2%**, with more than half of the deaths related to COVID-19 rather than the treatment itself[8]; deaths due to TEAEs were **3.4%**[8] (mostly COVID-19-related). This was a lower reported within-trial incidence than **I+V** in GLOW (**6.6%**)[11] and higher than **V+O** in CLL14 (**1.9%**[12]), which was not conducted during the COVID-19 pandemic.
- Four RWE studies on 1L CLL treatment focused on **ibrutinib monotherapy**, with none evaluating combination therapies

Conclusions

- Although comparisons are limited by cross-trial heterogeneity, the **A+V** regimen consistently demonstrated lower within-trial rates of grade ≥3 AEs, serious TEAEs, and key AEs of clinical interest - including cardiac AEs, infusion-related reactions, and tumor lysis syndrome compared with other fixed duration combination therapies (**I+V** and **V+O**) available in Canada.
- Taken together, these findings support **A+V** as a potential treatment option for 1L CLL treatment, given its manageable safety profile.
- Future head-to-head trials and real-world studies will be important to validate these findings and further strengthen **A+V**'s positioning in the evolving Canadian CLL treatment landscape.

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