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Is Continuous Therapy Becoming Finite? The Evolving Landscape of CLL Treatment in 2026

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Introduction

The front-line treatment landscape for chronic lymphocytic leukemia (CLL) is rapidly evolving, with several new therapeutic options emerging. Traditionally, chemoimmunotherapy (CIT) formed the foundation of front-line treatment. However, over the past decade, targeted therapies have transformed the management of CLL, replacing CIT as the backbone of front-line treatment.

Table 1 summarizes pivotal trials that have advanced CLL treatment.

As a result of these advances, clinicians now have multiple highly effective frontline options. The challenge is no longer selecting the most efficacious regimen but rather selecting the optimal strategy for each individual patient. To address this evolving landscape, this review highlights current evidence and key practical considerations shaping frontline CLL management in Canada.

Trial	Regimen	Duration	Population	High-risk patients included?	Median Follow-up	Progression-Free Survival
Amplify[13]	Acalabrutinib + venetoclax or acalabrutinib + venetoclax + obinutuzumab or CIT	Fixed-duration	≥18 yr and ECOG PS 0–2	No	40.8 mo	Est. 36 mo, 76.5% for acalabrutinib + venetoclax; 83.1% for acalabrutinib + venetoclax + obinutuzumab; 66.5% for CIT
ALLIANCE[3]	Ibrutinib or ibrutinib + rituximab or BR	Continuous	≥65 yr	Yes	55 mo	Estimated 48 mo, 47% for BR; 76% for ibrutinib; 76% for ibrutinib + rituximab
CLL13/GAIA[10]	Venetoclax + obinutuzumab or venetoclax + obinutuzumab + ibrutinib or venetoclax + rituximab or CIT (FCR for pts ≤65 yr; BR for pts >65 yr)	Fixed-duration	≥18 yr and ECOG PS 0–2 and CIRS ≤6 or a single score of 4 or lower	No	63.8 mo	Est. 60 mo, 69.8% for venetoclax + obinutuzumab; 81.3% for venetoclax + obinutuzumab + ibrutinib; 57.4% for venetoclax + rituximab; 50.7% for CIT
CLL14[9]	Venetoclax + obinutuzumab or Clb-O	Fixed-duration	≥65 yr, or CIRS >6, or creatinine clearance <70 mL/min	Yes	76.4 months	Est. 72 mo, 76.2 mo (53.1%) for venetoclax + obinutuzumab; 36.4 mo (21.7%) for Clb-O
CLL17[17]	Ibrutinib or venetoclax + obinutuzumab or ibrutinib + venetoclax	Continuous vs. Fixed-duration	≥18 yr	Yes	34.2 mo	Est. 36 mo, 81.1% for venetoclax–obinutuzumab; 81.0% for ibrutinib; 79.4% for ibrutinib-venetoclax
ELEVATE-TN[5]	Acalabrutinib +/- obinutuzumab or Clb-O	Continuous	≥65 yr, or 18-65 yr with comorbidities (CIRS >6 or creatinine clearance 30–69 mL/min)	Yes	74.5 mo	Est. 72 mo, 78.0% for acalabrutinib-obinutuzumab; 61.5% for acalabrutinib; 17.2% for Clb-O
GLOW[11]	Ibrutinib-venetoclax or Clb-O	Fixed-duration	≥65 yr or CIRS >6 or creatinine clearance <70 mL/min	No	46 mo	Est. 42 mo, 74.6% for ibrutinib + venetoclax; 24.8% for Clb-O
RESONATE-2[2]	Ibrutinib or Clb-O	Continuous	≥65 yr	No	9.6 yr	Est. 8.9 yr for ibrutinib vs. 1.3 yr for Clb-O
SEQUOA[6]	Zanubrutinib vs. BR	Continuous	≥65 or ≥18 yr + comorbidities	No	61.2 mo	Est. 60 mo, 75.8% for zanubrutinib; 40.1% for BR

Table 1. Pivotal Trials in Front-line CLL Management; *courtesy of Stephanie Craig, MD and Shannon Murphy, MD.*

Abbreviations: BR: Bendamustine-rituximab; **CIRS:** Cumulative Illness Rating Scale; **CIT:** chemoimmunotherapy; **Clb-O:** chlorambucil-obinutuzumab; **ECOG PS:** Eastern Cooperative Oncology Group Performance Score; **est:** estimated; **FCR:** fludarabine, cyclophosphamide, and rituximab; **mo:** months; **pts:** patients; **yr:** years.

Risk Stratification in the Targeted Therapy Era: What Still Matters?

While historically numerous prognostic markers informed risk stratification in CLL, their relevance has evolved as the field has transitioned toward targeted therapies. In the modern era, molecular disease characteristics, particularly immunoglobulin heavy chain variable region (*IGHV*) mutational status and the presence of del(17p) and/or *TP53* aberrations, have emerged as the most clinically relevant predictors of outcome. In contrast, traditional factors, such as clinical stage and age, now play a more limited role in treatment decisions.[1]

Unmutated IGHV is associated with more aggressive disease and inferior overall survival (OS), particularly in the CIT era. Similarly, del(17p)/*TP53* aberrations remain one of the strongest adverse prognostic factors, historically associated with poor response to CIT and inferior outcomes. Importantly, targeted therapies have significantly improved outcomes in these high-risk groups, with multiple phase III trials demonstrating superior efficacy compared with CIT, reinforcing the role of molecular and cytogenetic characteristics in guiding front-line treatment selection.[1]

Front-line Treatment Strategies in CLL

Continuous Bruton's Tyrosine Kinase Inhibitor (BTKi) Therapy: The Foundation of Modern Therapy

Continuous BTKi therapy remains a cornerstone of front-line CLL management. This approach was established by ibrutinib, the first-in-class agent, which showed durable efficacy across multiple trials. The RESONATE-2 trial provides the longest phase III follow-up data for any targeted CLL therapy. In the final analysis, with a median follow-up of 9.6 years, front-line ibrutinib demonstrated a median progression-free survival (PFS) of 8.9 years compared with 1.3 years for chlorambucil. This benefit was largely preserved in high-risk subgroups, with a median PFS of 8.4 years with ibrutinib versus 0.7 years with chlorambucil.[2] Similarly, follow-up from the ALLIANCE A041202 trial demonstrated continued efficacy in patients with and without high-risk aberrations, with superior PFS for ibrutinib-containing regimens compared with bendamustine-rituximab (BR).[3]

In current practice, the second-generation BTKis acalabrutinib and zanubrutinib have largely replaced ibrutinib due to improved safety profiles and lower discontinuation rates.[4] The ELEVATE-TN trial compared acalabrutinib-obinutuzumab and acalabrutinib monotherapy to chlorambucil-obinutuzumab (Clb-O) in patients ≥65 years, or 18–65 years with comorbidities. At a median follow-up of 74.5 months, acalabrutinib-containing regimens demonstrated superior PFS compared to Clb-O (78.0% for acalabrutinib-obinutuzumab vs. 61.5% for acalabrutinib vs. 17.2% for Clb-O), irrespective of *IGHV* or TP53 status.[5] The SEQUOIA study similarly demonstrated superior PFS for zanubrutinib over BR with an estimated 60-month PFS rate of 75.8% and 40.1% in zanubrutinib- and BR-treated patients, respectively.[6]

While no phase III trials have directly compared ibrutinib with second-generation BTKis in previously untreated patients, evidence in the relapsed/refractory setting supports second-generation agents as the standard of care. The ALPINE and ELEVATE-RR trials demonstrated improved tolerability with second-generation BTKis, with the ALPINE trial additionally showing superior PFS for zanubrutinib, supporting their preferential use.[7,8]

Fixed-Duration Venetoclax-Obinutuzumab

Ushering in the era of fixed-duration targeted therapy, venetoclax-obinutuzumab (VenO) was the first targeted fixed-duration treatment combination, proving to be well-tolerated while achieving deep and durable remissions in previously untreated patients.

Its efficacy has been demonstrated across multiple phase III randomized trials in both fit and unfit populations. Established in the CLL14 trial, the VenO regimen demonstrated a substantial improvement in outcomes, with a median PFS of 76.2 months compared with 36.4 months for Clb-O. Notably, the 6-year time-to-next-treatment (TTNT) rate was 65.2%, indicating that nearly two-thirds of patients remained free of subsequent therapy for more than 5 years after completing a single year of treatment. While outcomes were best in low-risk patients, those with del(17p)/*TP53* aberrations still demonstrated a median PFS and TTNT of 51.9 months and 57.3 months, respectively.[9]

The Phase III GAIA/CLL13 trial also showed that VenO outperformed CIT, with superior PFS in fit patients without *TP53* aberrations (5-year PFS 69.8% vs. 50.7%). Importantly, patient-reported outcomes from CLL13 showed more rapid and clinically meaningful improvements in quality of life with VenO, likely reflecting the advantages of fixed-duration treatment and reduced treatment-related symptoms.[10]

VenO has been reimbursed in Canada since 2022 and is established as a front-line standard of care for CLL. A substantial body of evidence supports its efficacy as a fixed-duration regimen, offering durable remissions and clinically meaningful treatment-free intervals.

Ibrutinib-Venetoclax: The First All-Oral Fixed-Duration Doublet

Building on the success of fixed-duration venetoclax-based therapy, the combination of ibrutinib and venetoclax (Ibr–Ven) represents the first all-oral, fixed-duration regimen combining BTK and BCL-2 inhibition as an alternative treatment strategy. This combination has regulatory approval in Canada and is currently publicly reimbursed in select provinces. The Ibr-Ven regimen was evaluated against Clb-O in the randomized phase III GLOW trial, which included patients without del(17p)/*TP53* aberrations who were ≥65 years old, or those younger with comorbidities. At a median follow-up of 46 months, Ibr-Ven demonstrated a significant PFS advantage, with an estimated 42-month PFS of 74.6% versus 24.8% with Clb-O. This benefit was consistent across subgroups, including older patients, those with comorbidities, and *IGHV* mutational status.[11] Similarly, in younger, fit patients treated with Ibr–Ven, the phase II CAPTIVATE trial demonstrated a 5.5-year PFS rate of 70% among patients without high-risk mutations, at a median follow-up of 68.9 months.[12]

Next-Generation Doublet: Acalabrutinib-venetoclax

For patients seeking an all-oral, fixed-duration approach but for whom cardiac history may limit the use of ibrutinib-based regimens, acalabrutinib–venetoclax (AV) may be an attractive alternative. As a second-generation BTKi, acalabrutinib provides a more favourable cardiac safety profile while maintaining the convenience of a chemotherapy-free, time-limited approach. Based on the phase III AMPLIFY trial, AV is the newest fixed-duration, all-oral doublet approved in Canada. In this study, the 3-year PFS for AV was 76.5%, compared with 83.1% for AV plus obinutuzumab and 66.5% for CIT in previously untreated patients with CLL without del(17p)/*TP53* aberrations. Notably, OS at 36 months was highest in the AV arm, despite higher rates of undetectable measurable residual disease (MRD) in the triplet arm, likely reflecting increased toxicity with the addition of obinutuzumab.[13]

From a practical standpoint, access remains a key limitation. While approved by Health Canada, AV is currently under review for reimbursement by the Canadian Drug Agency for use, and access is currently dependent on private insurance or special access pathways.

Chemoimmunotherapy: The End of an Era?

In Canada, CIT remains available and funded but plays a small role in contemporary front-line CLL management. Although fludarabine, cyclophosphamide, and rituximab (FCR) can produce durable remissions in select younger patients with favourable-risk disease, this benefit is offset by long-term toxicity, including an increased risk of second primary malignancies, and by the availability of more effective targeted options.[14] Phase III trials such as ECOG-E1912, FLAIR, AMPLIFY, and GAIA/CLL13 have shown that targeted therapies can outperform FCR with a more acceptable safety profile, while acknowledging that neither comparator regimen perfectly mirrors modern clinical practice.[10,13,15,16] Outcomes with CIT are particularly poor in patients with *TP53* aberrations or unmutated *IGHV*, further limiting its applicability.[5,6,9-11] Given broad Canadian access to front-line targeted therapies, CIT is best viewed as largely obsolete, reserved only for rare situations where targeted agents are inaccessible.

Fixed-Duration vs. Continuous Therapy: Defining the Optimal Approach

Perhaps the most relevant question in front-line CLL management today is not which therapy is most effective, but rather how long to treat. Fixed-duration and continuous treatment strategies have each demonstrated remarkable efficacy, yet until recently, no randomized trial had directly compared them. The CLL17 trial provided the first head-to-head comparison, randomizing treatment-naïve patients to fixed-duration VenO or Ibr-Ven versus continuous ibrutinib. At a median follow-up of 34.2 months, both fixed-duration arms demonstrated noninferior PFS compared with continuous ibrutinib, with 3-year PFS rates

of approximately 80% across all arms. However, outcomes among high-risk subgroups were more nuanced. Patients with *TP53* aberrations and complex karyotype appeared to derive greater benefit from continuous BTKi therapy, although these findings are limited by small numbers and a relatively short follow-up. Conversely, fixed-duration therapy performed particularly well in *IGHV*-mutated disease, with no clear disadvantage in unmutated *IGHV*.[17] While fixed-duration strategies offer the appeal of time-limited therapy with durable remissions for many patients, continuous BTKi therapy may remain preferable for select high-risk populations until more mature data are available.

Putting it All Together: A Shift Toward Individualized Care

As multiple targeted strategies demonstrate comparable disease control in front-line CLL, treatment selection has shifted from an efficacy-driven decision to an individualized one, incorporating several key factors (**Figure 1**).

Molecular disease characteristics remain a key driver of front-line treatment selection. Current evidence suggests that patients with del(17p)/*TP53* aberrations derive more durable disease control with continuous BTKi–based strategies or BTKi–venetoclax combinations than with VenO alone. In contrast, patients with mutated *IGHV* often experience favourable outcomes with fixed-duration venetoclax-based regimens, supporting their use in individuals seeking a time-limited approach.

Beyond disease characteristics, patient-specific factors further influence treatment selection. BTKis carry increased risks of atrial fibrillation, hypertension, and bleeding, warranting caution in patients with pre-existing cardiac disease or those requiring anticoagulation. While fixed-duration BTKi–venetoclax combinations limit cumulative BTKi exposure and cardiovascular events often improve after treatment cessation, cardiac toxicity may still occur during the active treatment period. In patients for whom even time-limited BTKi exposure poses unacceptable risk, a venetoclax-based strategy without a BTKi may be preferred. Venetoclax-based regimens, however, carry their own risks, including an increased susceptibility to tumour lysis syndrome (TLS), particularly in patients with renal impairment, and higher rates of neutropenia. Patient preferences further shape decision-making, as some patients prioritize the predictability of a time-limited approach and the potential for treatment-free intervals, whereas others favour the simplicity and psychological reassurance of continuous oral therapy.

Logistical factors and economic considerations can also influence treatment selection. Continuous BTKi therapy offers the convenience of oral-only administration and easier treatment initiation, without the need for intravenous infusions or intensive laboratory monitoring. In contrast, VenO requires intravenous obinutuzumab infusions and close laboratory monitoring to mitigate TLS risk. From an economic perspective, continuous therapies impose a considerable financial burden on the Canadian healthcare system due to their high costs and indefinite administration. Fixed-duration regimens may alleviate this burden by reducing cumulative treatment expenditures and resource utilization, offering a more sustainable care model without compromising clinical outcomes.[18]

Future Directions: Emerging Therapies and Evolving Strategies

As the CLL treatment landscape continues to evolve, novel agents are being explored in the front-line setting. Pirtobrutinib, a highly selective, noncovalent BTKi, is currently approved, though not funded, in Canada for relapsed/refractory CLL after at least two prior lines of therapy. Recent phase III data suggest a potential role in earlier lines of therapy. In treatment-naïve CLL, pirtobrutinib achieved better 24-month PFS than BR[19] and had a noninferior overall response rate to ibrutinib with favourable early PFS trends.[20] Both trials demonstrated a favourable safety profile, with lower rates of atrial fibrillation, hypertension, and treatment discontinuation in the pirtobrutinib groups.[19,20] These findings support the potential expansion of pirtobrutinib into earlier lines of therapy.

Beyond novel agents, MRD-guided strategies represent another emerging frontier, offering the potential to individualize treatment duration based on depth of response. Although included in international guidelines, adoption in Canadian clinical practice remains limited and largely confined to use in clinical trials and specialized centres.

Decision Point	Favours Continuous Therapy	Favours Finite-based Therapy
Disease Biology	Patients with *TP53*/del(17p) aberrations; concerns about durability of finite therapy	Mutated *IGHV*; standard-risk biology
Patient Preference	Reassurance of continuous therapy	Treatment-free interval
Patient Comorbidities		
Cardiac	Prefer second-generation BTKi if used	Pre-existing cardiac history present
Renal	Pre-existing renal dysfunction	No pre-existing renal dysfunction
Bleeding/Anticoagulation	Caution with BTKi therapy	Preferred in patients requiring anticoagulation or increased bleed risk
Infection	No neutropenia risk	Neutropenia risk
Logistics	Avoids infusion requirements and TLS ramp-up; advantageous for patients living remotely	Preferred if long-term adherence a concern
Economic burden	Lower upfront resource utilization but higher long-term costs	Higher upfront resource utilization but long-term cost savings

Figure 1. Fixed-Duration vs. Continuous Therapy in Front-line CLL: A Comparative Framework; *courtesy of Stephanie Craig, MD and Shannon Murphy, MD.*

Abbreviations: IGHV: immunoglobulin heavy chain variable region; **BTKi:** Bruton's tyrosine kinase inhibitor; **TLS:** tumour lysis syndrome

Conclusion

In summary, the front-line treatment paradigm of CLL continues to evolve, leading to substantial improvements in PFS and OS for patients. While continuous therapy may not be finite, the key decision is no longer simply what works, but rather what is best for the individual patient, underscoring the importance of a shared decision-making approach. This approach must thoughtfully integrate disease biology, patient comorbidities, treatment preferences, and practical considerations to optimize patient outcomes.

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