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Fixed-Duration First-Line Therapy For Chronic Lymphocytic Leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL) In Canada: A Canadian Expert Clinical Framework

Versha Banerji, MD, FRCPC
Isabelle Fleury, MD, FRCPC
Alina S. Gerrie, MD, MPH, FRCPC
Christopher Hillis, MD, FRCPC
Robert Puckrin, MD, FRCPC

About the Authors



Versha Banerji, MD, FRCPC

Dr. Versha Banerji obtained her MD and residency training in internal medicine and hematology at the University of Manitoba. She then completed a post-doctoral fellowship in translational research at the Harvard Cancer Centre/Dana-Farber Cancer Institute and the Broad Institute of MIT.
She is a senior scientist at the CancerCare Manitoba Research Institute, Associate Professor at the University of Manitoba, and a clinician-scientist at CancerCare Manitoba. She co-leads the chronic lymphocytic leukemia (CLL) clinic and is involved in several clinical trials and population-based treatment studies. As co-chair of the CLL research program she manages a multi-disciplinary research team in clinical, fundamental and translational research. Her own laboratory is evaluating mitochondrial bioenergetics and function as a measure of cancer cell metabolism.

Affiliations: Associate Professor, Max Rady College of Medicine, Winnipeg, Manitoba, Canada



Isabelle Fleury, MD, FRCPC

Dr. Isabelle Fleury is a hematologist and medical oncologist who worked at Maisonneuve-Rosemont Hospital before joining the CHU de Québec in 2025. She completed a bachelor's degree in microbiology and pursued a master's degree in biomedical sciences concurrently with her medical training.
She also completed a lymphoma fellowship at Hôpital Saint-Louis in Paris. She is a Clinical Associate Professor at Université Laval. She established the fellowship program in lymphoma and immune effector cells at Université de Montréal, has participated in clinical trials involving CAR-T therapies since 2015 and played a pivotal role in implementing CAR-T therapy as a standard of care in the province of Quebec since its introduction in 2019. Her primary interest is improving the care of patients with lymphoma. She is actively involved in clinical research, participating in phase I to III clinical trials.
Dr. Fleury also initiated the C3i Lymphoma Registry, which collects clinical and bioclinical data to better understand lymphoma in real-world settings.

Affiliations: Clinical Associate Professor at Université Laval, Laval, QC, Canada

About the Authors



Alina S. Gerrie, MD, MPH, FRCPC

Dr. Alina Gerrie is a hematologist and Associate Professor in the Divisions of Medical Oncology and Hematology at the University of British Columbia (UBC) and a Clinician Investigator at the Centre for Lymphoid Cancer at BC Cancer, Vancouver Centre. She completed her medical degree and internal medicine residency at the University of Toronto, followed by hematology residency at UBC. She undertook a fellowship through the Royal College Clinical Investigator Program and earned a Master of Public Health degree from Harvard University, where her research included investigating the impact of genetic abnormalities on population-level outcomes in chronic lymphocytic leukemia (CLL) patients. Dr. Gerrie is a recipient of a Michael Smith Health Professional Investigator Award and is involved in translational, clinical trial, and outcomes-based research related to leukemia and lymphoma. Other academic interests include the investigation of novel therapeutics and cellular therapy for CLL and lymphoma.

Affiliations: Associate Professor, Divisions of Medical Oncology and Hematology, Centre for Lymphoid Cancer, University of British Columbia and BC Cancer, Vancouver, BC, Canada



Christopher Hillis, MD, FRCPC

Dr. Chris Hillis is a hematologist specializing in hematologic malignancies at the Juravinski Cancer Centre and an Associate Professor at McMaster University. He is Vice President of Oncology at Hamilton Health Sciences, where he leads one of Ontario's largest integrated cancer programs, and Regional Vice President for the Hamilton Niagara Haldimand Brant Regional Cancer Program with Ontario Health-Cancer Care Ontario. He previously served as Chief of Oncology and Associate Chief Medical Information Officer, and brings expertise in cancer system leadership, quality improvement, digital transformation and clinical operations, grounded in an MSc in Quality Improvement and Patient Safety and training as a U.S. Veterans Affairs Quality Scholar. A specialist in chronic lymphocytic leukemia and myeloproliferative neoplasms, he leads a Canadian Institutes of Health Research-funded research program focused on making clinical trial outcomes more meaningful to patients with hematologic malignancies. Nationally, he has served as President of the Canadian Hematology Society and held leadership roles with the Royal College and Choosing Wisely Canada.

Affiliations: Associate Professor at McMaster University, Hamilton, ON, Canada



Robert Puckrin, MD, FRCPC

Dr. Robert Puckrin is a Hematologist and Clinician Investigator at the Arthur Child Comprehensive Cancer Centre and the University of Calgary in Calgary, Canada. His main interests are in lymphoma, stem cell transplantation, cellular therapies, bispecific antibodies, clinical trials, and real-world data.

Affiliations: University of Calgary, Calgary, AB, Canada

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Chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL) is an indolent B cell malignancy that may present with lymphocytosis, lymphadenopathy, splenomegaly, cytopenias, and/or immune complications.[1,2] In 2023, 2,030 people in Canada (excluding Nova Scotia) were diagnosed with CLL, resulting in an incidence rate of 5.2 per 100,000 population.[3] The CLL prevalence was projected to increase from 15,512 in 2020 to 19,517 in 2025, driven by rising incidence and longer survival from treatment improvements.[4]

The treatment landscape for CLL/SLL has evolved substantially with the introduction of multiple targeted therapies that differ in treatment duration, toxicity profile, and logistical complexity. This article discusses the current first-line treatment of CLL/SLL in Canada, focusing on fixed-duration (FD) treatment options that combine venetoclax with obinutuzumab, acalabrutinib, or ibrutinib, and discusses their implications for individualized treatment selection, therapeutic sequencing, and real-world implementation.

Evolution of first-line therapy

Many patients with CLL/SLL can initially be managed with active surveillance until they develop disease-related symptoms, cytopenias, significant tumour burden, or other International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria for treatment initiation.[5] Early intervention with chemoimmunotherapy (CIT) or ibrutinib has not demonstrated an overall survival (OS) benefit over active surveillance in asymptomatic, early-stage CLL.[6-8] Therefore, active surveillance remains the standard of care even in the era of targeted therapies. However, the ongoing EVOLVE trial (NCT04269902) is evaluating whether early, fixed-duration treatment with venetoclax plus obinutuzumab (VenO) improves survival in patients with high-risk CLL/SLL without indications for treatment.

Historically, CLL/SLL was treated with chemotherapy-based regimens, which later evolved into chemoimmunotherapy (CIT) with the addition of CD20-targeting antibodies (e.g. rituximab, obinutuzumab). Owing to improved understanding of disease biology, CIT has now largely been replaced by more effective targeted therapies, including covalent Bruton's tyrosine kinase inhibitors (BTKis), such as ibrutinib, acalabrutinib, and zanubrutinib, as well as the BCL-2 inhibitor venetoclax, which can be provided as monotherapies or in combination. These therapeutic advances have improved progression-free survival (PFS) compared with

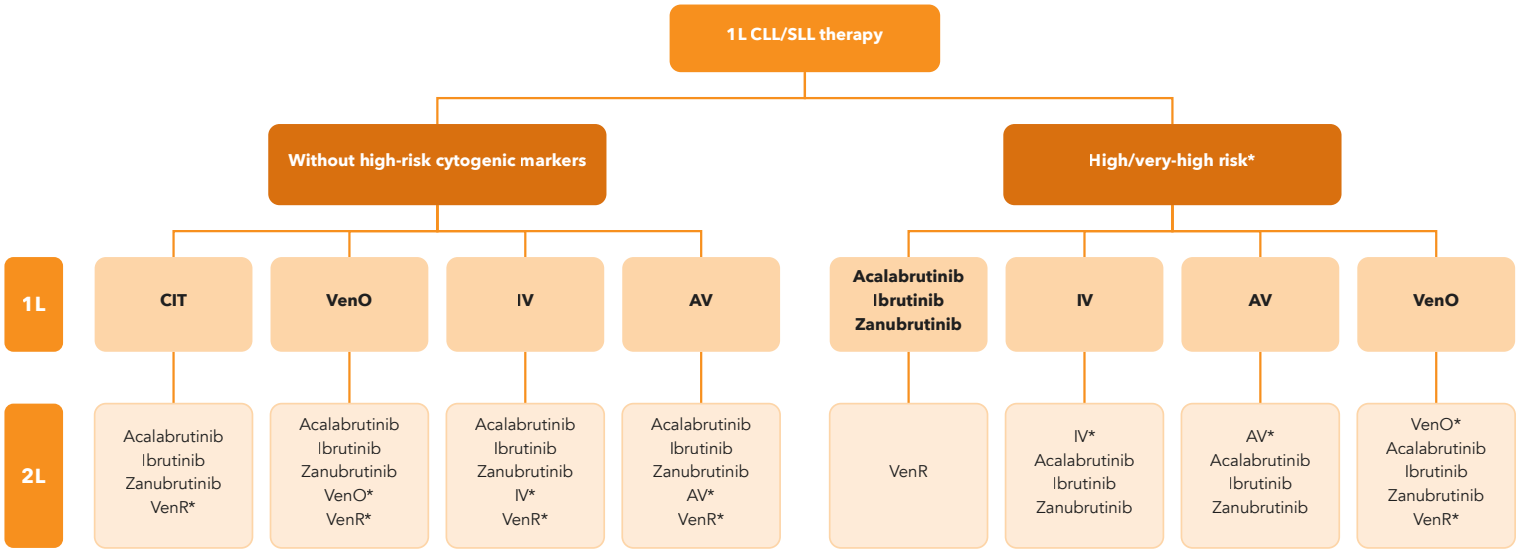


Figure 1: Provisional funding algorithm for CLL/SLL first- (1L) and second-line (2L) therapy; Figure adapted from the CDA-AMC Provisional Funding Algorithm.[57]

Abbreviations: AV: FD acalabrutinib + venetoclax; **CIT:** chemoimmunotherapy; **CLL/SLL:** chronic lymphocytic leukemia/small lymphocytic lymphoma; **FD:** fixed-duration; **IV:** FD ibrutinib + venetoclax; **VenO:** FD venetoclax + obinutuzumab; **VenR:** venetoclax + rituximab. *Venetoclax retreatment allowed if progression-free interval with previous venetoclax-based therapy is ≥12 months.

†High/very high-risk CLL include del(17p) alteration, *TP53* mutation, and unmutated *IGHV*.

CIT, and, for multiple treatments, across high and low genetic risk groups.[9-14] Long-term follow-up has also suggested improved OS compared with CIT for several of these therapies.[13,15-17] Consequently, patients with CLL/SLL treated with first-line targeted therapy now achieve survival approaching that of the age-matched general population.[18,19]

Initially, these targeted therapies were provided as continuous treatment regimens until disease progression or unacceptable toxicity. However, combination therapies were subsequently shown to produce deeper remissions, enabling fixed-duration treatment and allowing many patients to remain off therapy for several years while maintaining durable disease control.

Several of these options are now available as first-line therapy for CLL/SLL in Canada. The 2026 provisional funding algorithm from Canada's Drug Agency/L'Agence des medicaments du Canada (CDA-AMC) explicitly places the FD therapy regimens VenO, ibrutinib plus venetoclax (IV), and acalabrutinib plus venetoclax (AV) alongside continuous BTKi in the untreated CLL landscape **(Figure 1)**.

Continuous BTKi monotherapy

BTKi were initially assessed and became available for use as a continuous monotherapy until disease progression or death. The phase III trials RESONATE-2, ELEVATE-TN, and SEQUOIA have evaluated these agents as monotherapy and demonstrated improved PFS compared with chemotherapy-based regimens. The latest data from these trials revealed a 9-year PFS rate of 50% for ibrutinib, and 6-year PFS rates of 61.5% and 74% for acalabrutinib and zanubrutinib, respectively.[9,15,17] A systematic review found that the real-world effectiveness of these therapies was broadly consistent with the efficacy reported in clinical trials, albeit with short follow-up.[20]

BTKi monotherapy has demonstrated particularly favourable efficacy in patients with high-risk disease, including those with *del(17p)*/*TP53* mutations or unmutated *IGHV*, with several trials suggesting that continuous BTKi may attenuate the adverse prognostic impact of these

biomarkers.[10,17] Additionally, these oral therapies are convenient to administer and can generally be initiated without dose ramp-up or intensive monitoring. However, continuous BTKi therapy is associated with substantial cumulative drug-acquisition costs and an ongoing risk of adverse events, including arrhythmias, hypertension, and bleeding.[10,21-24] Second-generation BTKis are better tolerated than ibrutinib but do not eliminate these risks.[25,26] Prolonged treatment and cumulative toxicity may also compromise adherence. In addition, continuous BTK inhibition can lead to the emergence of resistance mutations and disease progression, precluding the use of covalent BTKis in subsequent treatment lines.[27]

Fixed-duration therapy

Fixed-duration (FD) combination therapy has been shown to result in durable remissions without the need for continuous treatment. This approach may reduce cumulative treatment-related toxicity and selective pressure, potentially delaying the emergence of resistance and preserving the option of retreatment, depending on the regimen used and the duration of remission. Whereas continuous BTKi therapy imposes a substantial financial burden on the healthcare system due to its cost and prolonged administration, FD strategies may reduce this burden by limiting treatment duration and reducing healthcare utilization associated with cumulative toxicity.[28]

The question of whether FD or continuous therapy is preferable was addressed in the CLL17 trial, which compared VenO, IV, and continuous ibrutinib in 976 patients with previously untreated CLL across a broad range of ages, fitness levels, and genetic-risk groups.[29] Three-year PFS was similar across the treatment arms (79%-81%), establishing the non-inferiority of both fixed-duration regimens to continuous ibrutinib. However, safety profiles differed, with VenO associated with higher rates of neutropenia and grade 3-5 infections, whereas the ibrutinib-containing regimens were associated with higher rates of diarrhea and cardiovascular toxicity. These findings suggest that for most patients with CLL/SLL, FD VenO and IV provide non-inferior early efficacy to continuous BTKi therapy, allowing treatment selection to be guided not by efficacy but by patient preferences, toxicity profiles, logistical complexity, treatment duration, and costs. However, longer follow-up is required to determine whether PFS non-inferiority is sustained, particularly in high-risk genetic subgroups. Any later divergence in PFS may also need to be interpreted in the context of retreatment efficacy and its effects on PFS2 and OS. Additional data are also required to clarify differences in late and cumulative toxicities and quality of life across the regimens.

Overview of fixed-duration options in first-line CLL treatment in Canada

Below we outline the evidence from clinical trials on efficacy, safety, and key features of each regimen that inform treatment selection **(Table 1)**.

Venetoclax + obinutuzumab

VenO was the first targeted FD treatment combination approved in Canada and has been evaluated in the CLL13/GAIA, CLL14, and CLL17 clinical trials.[14,29-31] These phase III trials established that 12 cycles of treatment can provide durable disease control in both younger, fit patients and older or less fit patients. For example, VenO resulted in a median PFS of 76.2 months in the CLL14 trial, and the 5-year PFS in CLL13/GAIA was 69.8%.[29-31] VenO also achieved higher rates of undetectable measurable residual disease (uMRD) than IV and ibrutinib monotherapy.[29] In Canada, funding for obinutuzumab is generally limited to the first-line setting, making VenO the principal means of accessing this agent. VenO is particularly attractive for patients with cardiovascular comorbidities or those receiving antiplatelet or anticoagulant therapy.

Despite its efficacy and overall tolerability, VenO has several limitations. The initial obinutuzumab infusions can cause infusion-related reactions (IRRs), particularly among patients with very high absolute lymphocyte counts. The regimen also requires nine intravenous infusions over six cycles, amounting to more than 30 hours of infusion-chair time and potentially limiting access for patients who live far from an infusion centre. In addition, obinutuzumab causes B-cell depletion and is associated with infections and impaired vaccine responsiveness. In CLL17, infection-related mortality was numerically higher with VenO than with the other regimens: of 22 deaths in the VenO arm, 12 were attributed to infection.[29] CLL14 also unexpectedly reported a higher incidence of second primary malignancies with VenO than with CIT (14.2% versus 8.4%).[30] Conversely, their incidence was lower with VenO than with CIT in CLL13, potentially reflecting differences in patient populations and baseline immune competence.[31] These safety signals

require further investigation to clarify their clinical significance and help identify patients for whom VenO is most appropriate.

Ibrutinib + venetoclax

IV was the first entirely oral, once-daily, FD targeted regimen available in Canada. This combination has been evaluated in several studies, including the phase II CAPTIVATE and phase III CLL17 and GLOW trials, with five-year PFS rates of 60%-67% following 15 cycles of treatment.[13,19,29,32,33] In GLOW, IV significantly improved both PFS and OS compared with CIT, whereas a significant OS benefit has not yet been demonstrated in trials of VenO.[13] IV is an attractive option for many patients because it is an entirely oral regimen that avoids intravenous infusions and associated chair time, although the requirement to take seven tablets daily during combination therapy may be burdensome for some. In CLL17, IV was also associated with lower rates of grade ≥3 infections (25.1% vs. 34.9%) than VenO, and VenO was associated with IRRs (39.7%).[29] Furthermore, the three-cycle ibrutinib lead-in provides effective debulking, eliminating the risk of tumour lysis syndrome (TLS) in most patients and simplifying the venetoclax ramp-up.

The principal limitation of IV is the toxicity associated with the first-generation BTKi ibrutinib. In CLL17, IV was associated with higher rates of diarrhea (47.2% [grade ≥3: 1.3%] for IV vs. 27.1% [grade ≥3: 1.7%] for VenO) and cardiovascular toxicity than VenO (cardiovascular toxicity: 23.8% [grade ≥3: 7.3%] for IV vs. 13.9% [grade ≥3: 4.4%] for VenO).[13,29] In GLOW, IV was also associated with increased early treatment-related mortality compared with CIT, including four cardiac or sudden deaths during treatment.[32] These findings underscore the importance of careful patient selection and support avoiding this regimen in patients with significant underlying cardiovascular disease.

Acalabrutinib + venetoclax

The AV regimen is a second all-oral FD option for first-line CLL/SLL that recently became funded in Canada. The efficacy of this regimen has been demonstrated in the AMPLIFY trial, with improved PFS compared to CIT (median follow-up 40.8 months; hazard ratio: 0.33; 95% confidence interval: 0.18-0.56; p<0.001).[34] The AV combination also had an improved estimated 36-month OS of 94.1% versus 85.9% for CIT. As a second-generation BTKi, acalabrutinib has demonstrated lower rates of cardiovascular toxicity and bleeding than ibrutinib in a head-to-head trial.[21] Although AV and IV have not been compared directly, cross-trial comparisons also suggest lower rates of cardiovascular toxicity (9.3% in AMPLIFY vs. 23.8% in CLL17 for IV) and diarrhea (32.6% in AMPLIFY vs. 45.9% for IV in CLL17) with AV.[29,34] These comparisons should be interpreted cautiously, however, given differences between the study populations, including the younger population enrolled in AMPLIFY.

There is some concern that AV may be less potent than IV given the lower peripheral blood uMRD rate reported in AMPLIFY than in CLL17 (uMRD in peripheral blood for AV 26.8% to 38% vs. 47.2% for IV in CLL17).[29,34,35] Potential explanations include the shorter duration of AV treatment (14 vs. 15 cycles) and pharmacokinetic differences that may result in lower venetoclax exposure with AV than with IV; however, whether these factors meaningfully affect clinical outcomes remains unknown. At the currently available follow-up, PFS appears broadly comparable across regimens: 3-year PFS 76.5% for AV vs. 79.4% for IV in CLL17 and 3.5-year PFS of 74.6% in GLOW.[13,29,34] Further data are needed to establish the long-term outcomes of AV, and its efficacy in patients with *del17p/TP53* mutations as well as in older or unfit patients who were not represented in AMPLIFY.

Patient selection and risk stratification

In Canada, the current CDA-AMC provisional funding algorithm **(Figure 1)** lists multiple therapeutic options without prioritizing one over another. However, several factors may be considered to guide selection of the most appropriate therapy for an individual patient, including age and fitness, disease biology, tumour burden, comorbidities, concomitant medications, mobility, and available social support, all of which may influence treatment selection and monitoring requirements. The patient's preferences and priorities should also be incorporated through shared decision-making.

Important biomarkers for CLL risk include *del17p/TP53* aberrations, *IGHV* mutation status, and complex karyotype.[36] *IGHV* mutation status tends not to vary over time; therefore, testing is recommended only prior to the first treatment. *TP53* mutation testing and fluorescence in situ hybridization (FISH) for *del(17)* should be

performed before each line of treatment in patients without previously documented *TP53* aberrations, as *TP53* aberrations are associated with poor responses to some therapies and therefore impact treatment decision-making. However, access to genetic risk testing varies between Canadian provinces and should be improved.

Most international guidelines recommend continuous BTK inhibition for patients with *TP53*-aberrant CLL/SLL, reflecting the durable disease control observed with extended follow-up, exemplified by 6-year PFS rates of 64% and 56% with first-line zanubrutinib and acalabrutinib, respectively, in patients with *del(17p)* CLL/SLL.[9,17,37-39] Nevertheless, subgroup analyses from CAPTIVATE and CLL14 demonstrate that FD IV and VenO remain active in this high-risk population, providing a median PFS of approximately 4 years.[30,40] Although CLL17 showed numerically higher 3-year PFS with ibrutinib than FD therapy in *TP53*-aberrant CLL, no randomized evidence has yet demonstrated an OS advantage with either strategy.[29] Treatment duration and sequencing should, therefore, inform shared decision-making. Fixed-duration therapy may be a reasonable alternative to continuous BTKi therapy for selected patients with *TP53*-aberrant disease who value time off treatment and are comfortable with a potentially shorter initial remission but with the possibility of retreatment or initiation of a continuous BTKi at progression.

While continuous BTK inhibition appears to mitigate the adverse prognostic impact of unmutated *IGHV*, this is less well established with fixed-duration therapies. CLL17 confirmed

Trial	Treatment regimen	Logistics	Study population	Efficacy
CLL13/GAIA[31]	VenO	O: 6 cycles Ven: 12 cycles	Fit patients; no *del17p/TP53* aberrations included	5-yr PFS: 69.8% Unmutated/mutated *IGHV*: 59.0%/82.9%
CLL14[14,30]	VenO	O: 6 cycles Ven: 12 cycles	11.8% *del17p/TP53* aberrations; 59.8% unmutated *IGHV*	9-yr PFS: 26% Unmutated *IGHV*/no *TP53* mutations: 9-yr PFS 79.2 months Mutated *IGHV*/*TP53* mutations: 9-yr PFS 49.0 months
CLL17[29]	VenO	O: 6 cycles Ven: 12 cycles	7.6% *del17p/TP53* aberrations; 56.5% unmutated *IGHV*	3-yr PFS: 81.1% Unmutated/mutated *IGHV*: 75.8%/87.6% *TP53* mutations: 62.0%
CAPTIVATE[33,40]	IV	Ibru: 15 cycles Ven: cycles 4-15	≤70 years	5.5-yr PFS: 66% With/without *TP53* aberrations: 36%/70% Unmutated/mutated *IGHV*: 55%/79% 5.5-yr OS: 97%
CLL17[29]	IV	Ibru: 15 cycles Ven: cycles 4-15	7.6% *del17p/TP53* mutations; 56.5% unmutated *IGHV*	3-yr PFS: 79.4% Unmutated/mutated *IGHV*: 78.9%/80.0% *TP53* mutations: 69.0% 3-yr OS: 96.0% Overall response: 88.5%
GLOW[13,32]	IV	Ibru: 15 cycles Ven: cycles 4-15	No *TP53* aberrations	3.5-yr PFS: 74.6% Unmutated/mutated *IGHV*: 69.8%/90.0% 3.5-yr OS: 87.5%
AMPLIFY[34]	AV	Acala: cycles 1-14 Ven: cycles 3-14	No *TP53* aberrations; 57.4% unmutated *IGHV*	3-yr PFS: 76.5% 3-yr OS: 94.1% Overall response: 92.8%

Table 1: Clinical trials investigating FD regimens for first-line CLL/SLL [13,14,29-34]

Abbreviations: Acala: acalabrutinib; **AV:** acalabrutinib plus venetoclax; **AEs:** adverse events; **Ibru:** ibrutinib; **IV:** ibrutinib plus venetoclax; **mos:** months; **O:** obinutuzumab; **OS:** overall survival; **PFS:** progression-free survival; **SEAs:** serious adverse events; **SPM:** second primary malignancies; **Ven:** venetoclax; **VenO:** venetoclax plus obinutuzumab; **yr:** year.

the non-inferiority of VenO and IV to continuous ibrutinib among patients with unmutated *IGHV* at 3 years.[29] However, longer-term data from other trials indicate that patients with unmutated *IGHV* experience shorter remissions after VenO or IV than those with mutated *IGHV*. Nevertheless, outcomes for the unmutated *IGHV* subgroup remain favourable, with a median PFS of approximately 5 years in CLL14 and GLOW.[13,30] Moreover, patients who relapse after FD therapy may not require immediate retreatment, extending the median time to next treatment to more than 6 years in this subgroup.[40] Thus, both continuous BTKi therapy and FD regimens are valid options for patients with unmutated *IGHV*.

Patients with a high tumour burden are at increased risk of TLS, which should be considered when planning 1L treatment, particularly when BCL-2i are used (see venetoclax ramp-up section). Feasibility of this monitoring may vary based on the patient's geographical location (distance to the treatment/monitoring centre) and age and fitness level (ability to travel regularly to the centre for monitoring).

Patient preferences should also shape CLL/SLL treatment management decision-making. Patients may have a strong preference for continuous BTKi treatment for its convenience and simplicity or the psychological reassurance that the disease is being treated. Others may prefer an FD approach as it offers treatment-free intervals with a lower likelihood of cumulative toxicity. For others, their comorbidities, concurrent medications, geographical location, and logistical challenges may determine the treatment of choice. AV may be favoured over IV due to its improved cardiovascular safety profile. The choice between AV and VenO should be individualized to each patient, depending on the anticipated toxicities and their comorbidities (e.g. cardiovascular toxicities, bleeding history, anticoagulant, infection history, infusion reaction risk), personal preferences (e.g. oral versus intravenous, chair time), ease of access (e.g. distance to an infusion centre), and considerations around obinutuzumab funding.

Venetoclax ramp-up implementation

While most of the adverse events (AEs) associated with venetoclax are considered tolerable and manageable, venetoclax has potent pro-apoptotic effects that can cause rapid tumour cell death, potentially leading to TLS.[41] TLS risk is influenced by tumour burden, particularly lymph node size and lymphocytosis, as well as renal function and the venetoclax dose. Assessment of tumour burden and baseline laboratory parameters is therefore recommended to determine TLS risk before treatment. A repeat of computed tomography (CT) imaging after debulking may be helpful in high-risk patients to facilitate outpatient venetoclax ramp-up.

Venetoclax-associated TLS was observed primarily in early-phase trials that used higher starting doses.[42] A 5-week dose-escalation schedule was subsequently introduced to mitigate this risk by gradually reducing tumour burden, beginning at 20 mg daily in week 1 and increasing to 400 mg daily by week 5. Together with appropriate monitoring and prophylaxis, including adequate hydration and uric acid-lowering therapy, this ramp-up strategy has markedly reduced the incidence of TLS.

TLS risk is further reduced through lead-in therapy with four doses of obinutuzumab in VenO or two to three cycles of a BTKi in IV and AV, which decreases tumour burden before venetoclax initiation, resulting in a small percentage of patients in the high-risk category.[32,34,43] Consequently, venetoclax-associated TLS is exceedingly uncommon with FD regimens. No cases of TLS were reported with IV in CAPTIVATE or GLOW, and only one occurred with AV in AMPLIFY, an approximately tenfold lower incidence than with chemoimmunotherapy.[32,44] In CLL14, only three patients (1.4%) in the VenO arm developed laboratory TLS, with no cases of clinical TLS; all events occurred before venetoclax initiation and were attributed to obinutuzumab.[45] These findings confirm that the risk of venetoclax-associated TLS after obinutuzumab or BTK inhibitor lead-in therapy is minimal.

Although the risk of TLS historically necessitated a complex dose ramp-up with intensive laboratory monitoring and several blood tests per week, the exceedingly low incidence of venetoclax-associated TLS under current protocols supports simplifying monitoring to reduce the burden on patients and healthcare systems and improve treatment access while maintaining safety. Emerging Canadian experience supports evaluating protocolized simplification in appropriately selected patients. In Alberta, for example, ramp-up monitoring has been

streamlined to include prophylactic allopurinol, oral hydration, and a single set of outpatient TLS laboratory tests after each weekly dose increase, which can be collected at most community hospitals. A coordinated multidisciplinary approach remains essential, particularly for patients who live far from the treatment centre.

Other safety and tolerability considerations

To help improve implementation of FD regimens, safety and tolerability should be considered. The risk of obinutuzumab infusion reactions can be mitigated through prophylactic medications, dividing the first 1,000 mg dose over two days, and slowing the first infusion rate; the second infusion can then proceed at an increased rate in patients who did not have IRRs to the first infusion. A real-world Manitoba study showed that for patients treated with obinutuzumab starting at a rate of 6 mg/hr on day 1, after which the rate is doubled every hour to a maximum rate of 24 mg/hr, led to fewer severe IRRs (6%) than were observed in the CLL11 clinical trial (20%).[46]

Other toxicities associated with FD therapy can be mitigated through supportive care and appropriate dose modification. For example, granulocyte colony-stimulating factor may be used to manage neutropenia in patients receiving VenO. When dose reduction is required in a combination regimen, the agent most likely responsible for the toxicity and relevant pharmacokinetic interactions should be considered. In patients receiving IV who develop diarrhea or neutropenia, venetoclax should generally be reduced first because ibrutinib may increase venetoclax exposure approximately two-fold.[47,48]

Sequencing after fixed-duration therapy

One major question that remains largely unanswered is what the best sequencing of therapy is when patients relapse after first-line FD therapy with VenO or BTKi plus venetoclax. Based on accumulating evidence from the trials CAPTIVATE, CLL13, ReVenG, and MURANO, as well as real-world studies, many patients can be successfully retreated after FD therapy, depending on time to relapse.[19,31,49,50] However, it remains unknown whether there is a difference in clinically relevant resistance after FD venetoclax-based therapy compared with continuous BTKi therapy, which may depend on regimen and retreatment strategy.

In an exploratory analysis of the CLL13/GAIA trial, 112 patients who received a venetoclax-based regimen in the first line had a 2-year treatment-free survival of 77.9-100% with a BTKi-based regimen, a venetoclax-based regimen, or a combination of the two, compared with 27.8%

Study	1L regimen	Requiring 2L treatment (n)	Efficacy 2L treatment
CLL13/GAIA	Venetoclax-based (VenR, VenO, IVO)	112	TFS2: BTKi: 77.9% Venetoclax: 81.4% Venetoclax + BTKi: 100% CIT: 27.8%
CAPTIVATE	IV	64	ORR: Ibrutinib (n=25): 76% (28.4 mos follow-up) IV (n=11): 82% (15.2 mos follow-up) 2-yr PFS/OS ibrutinib: 91%/96% 1-yr PFS/OS IV: 100%/100%
GLOW	IV	8	Response ibrutinib (n=3): 1 CR, 2 PR

Table 2: Efficacy of 2L regimens after FD 1L therapy

Abbreviations: 1L: first-line; **2L**: second-line; **BTKi:** Bruton's tyrosine kinase inhibitor; **CIT:** chemoimmunotherapy; **CR:** complete response; **IV:** ibrutinib + venetoclax; **IVO:** ibrutinib + venetoclax + obinutuzumab; **FD:** fixed-duration; **mos:** months; **ORR:** overall response rate; **OS:** overall survival; **PFS:** progression-free survival; PR: partial response; **TFS2:** 2-year treatment-free survival; **VenO:** venetoclax + obinutuzumab; **yr:** year.

with CIT **(Table 2)**.[31] Venetoclax-based regimens were more commonly chosen when patients had a longer time to relapse from first-line treatment. In CAPTIVATE, 64 patients with progressive disease after IV were retreated in the second line, with 25 receiving ibrutinib and 11 receiving IV.[40] The ORR was 76% and 82% for ibrutinib and IV retreatment, respectively, with 2-year PFS of 91% and 1-year PFS of 100%. A preliminary analysis from the ReVenG trial demonstrated high response rates (100%; n=15) and rates of undetectable measurable residual disease (uMRD; 85%; n=13) in patients retreated with VenO after a first-line venetoclax-based regimen.[50] Another retreatment study is the ongoing phase II study MAVRiC, which investigates FD AV in patients with relapsed CLL after 1L treatment with FD BTKi plus BCL2i with or without obinutuzumab (NCT07024706).

These limited data suggest that retreatment with a BTKi, venetoclax, or their combination after VenO or IV might be successful. Although no similar data yet exist for AV, the pan-Canadian Oncology Drug Review Expert Review Committee (pERC) and clinical experts suggested that retreatment with AV may be considered at the clinicians' discretion. The current CDA-AMC provisional funding algorithm **(Figure 1)** suggests that FD venetoclax-based retreatment in the second line is only available to patients previously treated with that same regimen, provided that relapse occurred ≥12 months after the end of 1L treatment. These funding decisions, however, are arbitrary and not based on scientific evidence. The 12-month rule has not been established by clinical trial data, nor has the rule on retreatment only with the same regimen as used in 1L. Further research is needed to define optimal treatment sequencing and determine how time to relapse, resistance mutations, and other factors can guide the selection of second-line therapy.

Practical implementation in Canadian practice

A retrospective analysis of 2024 Alberta data evaluated 1L treatment selection in CLL/SLL.[51] FD therapy was used in 51% of cases (n=75), predominantly VenO because IV was not yet funded, while continuous BTKi therapy was used in 44% of cases (n=65). A discussion of more than one therapeutic option was documented in 64% of cases (n=94), underscoring the importance of shared decision-making. Continuous BTKi treatment was selected more frequently for patients with *del17p/TP53* mutations (84%), those older than 75 years (66%), and those living more than 100 km from an obinutuzumab infusion centre (70%). Other factors included patient preferences regarding the treatment duration and logistical considerations. These findings suggest that older patients and those living farther from infusion centres face barriers to FD regimens, such as VenO. Expanding community-based infusion capacity, increasing access to all-oral regimens, and simplifying venetoclax ramp-up protocols may improve equitable access to FD therapy in Canada.

Improving the implementation of these FD regimens as first-line therapy for CLL/SLL requires several considerations. There is a need to improve access to these regimens across Canada and ensure their timely implementation. Although access to infusion centres, pharmacy support, and laboratory monitoring may differ between academic and community settings, IV and AV provide infusion-free options that can be administered regardless of geographic setting. Moreover, simplified venetoclax ramp-up monitoring and debulking with either obinutuzumab or a BTKi substantially reduces the risk of TLS. Together, these strategies support safe treatment delivery in the inpatient setting at both academic and community centres in urban and rural areas.

Further, improvements to care and accessibility for more patients may be achieved through telemedicine and multidisciplinary shared-care models in which community physicians, pharmacists, and/or nurses collaborate with academic centre-associated hematologists/oncologists and/or pharmacists to ensure adequate follow-up, where needed. In addition, social workers, patient coordinators, and/or financial counsellors may be helpful in coordinating and assisting the patient with planning for travel, lodging, and challenges related to drug access. Clear protocols for each of these situations may help implementation in the community setting.

Future directions and unmet needs

Triplet therapy

Triplet therapy consisting of a BCL-2i, a BTKi, and a CD20 antibody is also being assessed and may become available in future **(Table 3)**. Since all three therapy classes have distinct mechanisms of action, triple therapy may improve efficacy and

response durability; however, it may come at the cost of increased toxicity, making the risk-benefit ratio relative to fixed-duration doublets uncertain.

The combination of venetoclax, ibrutinib, and obinutuzumab (IVO; up to 36 cycles) was assessed in the CLL13/GAIA trial, where it was compared with VenO (12 cycles) and CIT (6 cycles).[31] The 5-year PFS for IVO was significantly higher than for VenO and CIT (81.3%), but there was no difference in OS. The highest rates of cardiac events and early treatment discontinuations were observed in the IVO group (13.9% vs. 6.1% for VenO; 11.7% vs. 3.9% due to AE), which negatively impacted PFS.

The AMPLIFY trial included an arm assessing AVO, which resulted in an ORR of >92% and a 36-month PFS of 83.1%, compared with 76.5% for AV, with uMRD in 95% of patients with AVO versus 40% with AV.[34] The PFS from AVO was similar in patients with unmutated and mutated *IGHV* status. However, AVO was associated with more toxicity, resulting in discontinuation of acalabrutinib in 13.7% of cases (7.6% for AV) and dose reductions in 20.8% of cases (14.1% for AV). The rate of severe AEs was 38.4%, and AVO was associated with higher rates of grade ≥3 infections. Deaths from any cause were reported in 37 patients in the AVO group (12.9%, mainly due to infections) with a numerically worse estimated 36-month OS (87.7%/94.1% for AVO/AV).

Continued follow-up of these studies may provide insight into which patient populations benefit from a triple regimen and whether the potential additional toxicity is warranted. CLL16 is a phase 3 trial assessing AVO in patients with

Trial ID	NCT link	Regimen(s) tested	Comparator arm	Population	Primary outcome	Status
MAJIC (Phase III)	NCT05057494	AV	VenO	Treatment-naive CLL/SLL	PFS	Active, fully accrued
BGB-11417-301 (Phase III)	NCT06073821	SZ	VenO	Treatment-naive CLL	PFS; uMRD rate	Active, fully accrued
BGB-11417-304 (Phase III)	NCT07277231	SZ	AV	Treatment-naive CLL	PFS; uMRD rate	Accruing
EA9161 (Phase III)	NCT03701282	IVO	IO	Treatment-naive CLL	PFS	Active, fully accrued
CLL16 (Phase III)	NCT05197192	AVO	VenO	Treatment-naive high-risk CLL (*del17p/TP53*-mutated, complex karyotype or unmutated *IGHV*)	PFS	Recruiting/ active
BRAVE (Phase II)	NCT06524375	Venetoclax added to ongoing cBTKi (1L) to achieve uMRD and allow treatment break	-	1L CLL on cBTKi	uMRD rate by EOCT	Active, fully accrued
SPRUCE-TN (Phase II)	NCT06367374	SZ (MRD-guided, up to 2 years)	-	Treatment-naive CLL/SLL	4-yr PFS	Not yet recruiting
A042302 (Phase III)	NCT07321652	MRD-guided SZ	Continuous zanubrutinib	Older, treatment-naïve CLL/SLL	PFS	Recruiting
BRUIN CLL-313 (Phase III)	NCT05023980	Continuous pirtobrutinib	CIT	Treatment-naive CLL/SLL	PFS	Active, fully accrued

Table 3: Ongoing Phase II and III trials for 1L CLL/SLL

Abbreviations: 1L: first-line; **AO:** acalabrutinib + obinutuzumab; **AV:** acalabrutinib + venetoclax; **AVO:** acalabrutinib + venetoclax + obinutuzumab; **BTKi:** Bruton's tyrosine kinase inhibitor; **CIT:** chemoimmunotherapy; **CLL/SLL:** chronic lymphocytic leukemia/small lymphocytic lymphoma; **EOCT:** end of combination treatment; **IO:** ibrutinib + obinutuzumab; **IV:** ibrutinib + venetoclax; **IVO:** ibrutinib + venetoclax + obinutuzumab; **PFS:** progression-free survival; **SZ:** sonrotoclax + zanubrutinib; **uMRD:** undetectable minimal residual disease; **VenO:** venetoclax + obinutuzumab; **VenR:** venetoclax + rituximab; yr: year; **ZV:** zanubrutinib + venetoclax.

high genetic risk CLL (NCT05197192) to determine whether a triplet improves PFS over the control arm of VenO.

Next-generation agents

Several next-generation drugs are in the clinical pipeline for 1L treatment of CLL/SLL. Pirtobrutinib is the first noncovalent BTKi being assessed in 1L CLL **(Table 3)**. The BRUIN phase III trial assesses continuous pirtobrutinib versus CIT, and early results indicate a PFS benefit with the BTKi, as well as non-inferior response rates but favourable toxicity compared to ibrutinib.[52,53] Combinations with venetoclax and obinutuzumab are in earlier stages of clinical development. A next-generation BCL-2i is sonrotoclax, currently being assessed in combination with zanubrutinib as a doublet and with zanubrutinib and obinutuzumab as a triplet, all in early clinical assessment. The CELESTIAL TNCLL 1 and 2 phase III trials investigate sonrotoclax + zanubrutinib and compare it to VenO or AV (NCT06073821; NCT07277231). In addition, immunotherapies are currently assessed in relapsed/refractory CLL settings after targeted therapies but may move into development for 1L treatment when proven successful. This may include therapies such as CD20XCD3 bispecifics (e.g, epcoritamab) and CD19-directed chimeric antigen receptor (CAR)-T cell therapy.

MRD as predictor of duration of therapy

A current question that remains largely unanswered is whether uMRD can guide treatment duration and improve clinical outcomes in CLL/SLL. Although MRD is prognostic in some settings, including after VenO or CIT, this relationship is not consistent across regimens. In AMPLIFY, AV achieved superior PFS compared with CIT despite lower uMRD rates, while CLL17 demonstrated similar PFS across ibrutinib-containing arms despite differences in uMRD rates.[29,34] Few studies have directly compared MRD-guided treatment strategies with current standards of care. In FLAIR, 66.2% of patients receiving IV had uMRD in bone marrow within 2 years (compared to 0.0% in the ibrutinib group and 48.3% in the CIT group), and MRD-guided IV improved outcomes compared with CIT and ibrutinib, with a 5-year PFS of 93.9% for IV versus 79.0% for ibrutinib and 58.1% for CIT.[54] However, the applicability of this approach is limited by the complexity of MRD testing, the prolonged duration of therapy administered, and the lack of direct comparison with established FD-targeted regimens. The role of MRD-guided therapy may be further clarified by the ongoing MAJIC trial, which compares MRD-guided AV with MRD-guided VenO, and the CLL18/MOIRAI trial, which compares FD VenO with FD pirtobrutinib plus venetoclax (PV) and MRD-guided PV.[55,56]

Practical take-home principles

- Time-limited FD therapy of a venetoclax-based regimen, such as VenO, IV, or AV, is now a standard 1L option for CLL/SLL
- Continuous BTKi therapy has the most mature evidence for durable disease control in high-risk *TP53*-aberrant CLL; FD therapy remains a reasonable individualized option, although remission duration may be shorter
- The choice between FD therapy regimens should be individualized based on toxicity profile, treatment logistics, and the patient's preferences
- Access to FD therapy can be improved with all-oral options and simplification of venetoclax ramp-up monitoring, given the minimal risk of TLS with current regimens
- MRD may be prognostic and may serve as a biomarker for therapy duration but requires further study before it can be used routinely to guide treatment decisions
- Implementation logistics should be considered when choosing regimen for 1L treatment
- Treatment sequencing should be considered when selecting a 1L therapy, as the choice of 1L treatment may influence options in the 2L setting

Conclusion

FD venetoclax-based therapy has taken an increased role in first-line treatment of CLL/SLL. A FD treatment approach limits treatment exposure and provides a treatment-free interval. Access varies between Canadian provinces, but barriers to FD treatment may be overcome by expanded availability of all-oral options and simplified venetoclax ramp-up monitoring. Therefore, various factors should be considered when choosing a 1L FD regimen, including safety profile, reimbursement, logistics, and patient preferences. Ongoing trials will shed light on patient selection criteria, therapy duration and sequencing, and may introduce novel therapies and combinations into the clinic.

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