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Canadian evidence-based guideline for frontline treatment of chronic lymphocytic leukemia: 2022 update

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ABSTRACT

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in North America. In 2018, the first unified national guideline in Canada was developed for the front-line treatment of CLL that helped guide treatment across the country. As an update in 2022, a group of clinical experts from across Canada came together to provide input and guidance that included new and innovative treatments and approaches that will continue to provide health care professionals with clear guidance on the first-line management of CLL. Recommendations were provided in consensus based on available evidence for the first-line treatment of CLL.

1. Introduction

Chronic lymphocytic leukemia (CLL) is the most common lymphoproliferative disorder in adults in Canada, with over 2000 patients diagnosed per year and resulting in more than 600 deaths annually [1, 2]. Most CLL patients are elderly, with a median age of 72 years at diagnosis; often these patients present with a number of comorbidities that increase the risk of morbidity and mortality from therapy [2]. As CLL is a clonally complex disease, the genetic and molecular characteristics of the CLL cells play a paramount role in deciding treatment approaches to achieve the best outcomes for patients.

The treatment of CLL has advanced significantly in the last decade but improvements are still sought to lengthen survival, improve quality of life and ideally, offer a future chance of cure [3–5]. Small molecule inhibitors have proven particularly active in CLL, including inhibitors of Bruton tyrosine kinase (BTK) (i.e. ibrutinib (IBR), acalabrutinib (ACAL), zanubrutinib (ZANU)), apoptosis regulator B-cell leukemia/ lymphoma 2 (BCL-2) inhibitor [i.e. venetoclax (V)], and phosphatidylinositol 4, 5-bisphosphate 3-kinase catalytic subunit delta (PI3Kδ) inhibitor (i.e. idelalisib). Emerging CLL therapies include doublet and triplet combinations of novel agents, bi-specific antibodies, non-covalent BTK inhibitors and cellular therapies [6–8]. With advancements in treatments, the 5-year overall survival (OS) of patients with CLL has steadily improved over time [9].

The 2018 Canadian clinician consensus guideline on first-line treatment options attempted to provide national guidance on the management of previously untreated CLL [10]. Since this publication, there have been several practice-changing clinical trials reported such that

Abbreviations: ACAL, Acalabrutinib; BCL-2, B-cell leukemia/lymphoma 2 protein; BID, Two times per day; BTK, Bruton Tyrosine Kinase; BTKi, BTK inhibitors; CIT, Chemoimmunotherapy; CLL, Chronic Lymphocytic Leukemia; CLL-IPI, CLL International Prognostic Index; CLL-TIM, CLL Treatment Infection Model; ECOG, Eastern Cooperative Oncology Group; EFS, Estimated free survival; FCR, Fludarabine, cyclophosphamide, rituximab; IBR, Ibrutinib; IGHV, Immunoglobulin heavy chain variable region; IVO, Ibrutinib + Venetoclax + Obinutuzumab; iwCLL, International workshop on CLL; LDT, Lymphocyte doubling time; NR, Not reached; Obin, Obinutuzumab; OS, Overall survival; PFS, Progression free survival; PI3Kδ, Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit delta; R, Rituximab; RCT, Randomized controlled trials; TK, Serum thymidine kinase; TLS, Tumor lysis syndrome; V, Venetoclax; VO, Venetoclax + Obinituzumab; VR, Venetoclax + Rituximab; W&W, Watch & Wait; ZANU, Zanubrutinib.

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Table 1
Clinical Trials Comparing Early Intervention versus Observation in CLL Patients.

Reference	Patient Classification	Treatment	Patients (n)	Overall Survival (%)
Herling et al., (2020), *Leukemia*[18]	Binet stage A, high-risk (at least two of four adverse prognostic markers present (TK > 10 U/L, LDT < 12 months, *IGHV* unmutated, or del11q or del17p, or trisomy 12))	FCR (6 cycles) vs. observation	800	No OS benefit: 5-yr OS FCR (82.9%) vs. 79.9% W&W
Langerbeins, P., et al. 2022, *Blood*[19]	Binet stage A CLL, 8 differently weight factors (1–6 points)*	IBR (420 mg daily up to 60 months) vs. observation	363	EFS at median 31 months: Ibrutinib (median NR) vs observation (47.8 mo)
Mayo Clinic (NCT03516617)[20]	High- or very high-risk CLL-IPI score for treatment vs. low-intermediate CLL-IPI score for observed	Arm A: ACAL (100 mg BID for 24 mo) Arm B: ACAL (100 mg BID) + Obin Arm C: observation alone	120	Results not available (trial ongoing)
PreVent-ACaLL (NCT03868722)[21]	High-risk (CLL-TIM: >65% 20-year risk) for infection and/or in need of CLL treatment within 2 years of diagnosis	ACAL (100 mg BID for 12 weeks) + V vs. Observation	212	Results not available (trial ongoing)
EVOLVE (SWOG; NCT04269902)[22]	High- or very high–risk CLL-IPI score	Early versus delayed VO	247	Results not available (trial ongoing)

Abbreviations: W&W (Watch and Wait), ACAL (Acalabrutinib), Obin (Obinutuzumab), IBR (Ibrutinib), FCR (Fludarabine, Cyclophosphamide, Rituximab), VO (Venetoclax + Obinutuzumab), CLL-IPI (CLL International Prognostic Index), TK (serum thymidine kinase), LDT (lymphocyte doubling time), *IGHV* (immunoglobulin heavy-chain variable region genes), ECOG (Eastern Cooperative Oncology Group), CLL-TIM (CLL Treatment Infection Model), EFS (estimated free survival), NR (not reached), OS (overall survival), BID (two times per day), mo (months), yr (years).
*Eight weighted factors (1–6 points): age > 60 years [1], male sex [1], ß2-microglobulin 1.7–3.5 mg/L [1] or > 3.5 mg/L [2], ECOG performance status > 0 [1], thymidine kinase > 10 U/L [2], unmutated *IGHV* [1], 11q deletion [1] and 17p deletion [6].

updated recommendations are required to incorporate new data into treatment decisions. Therefore, this guideline will provide treatment approach updates from a Canadian perspective. Small lymphocytic lymphoma is the same disease as CLL (presenting without lymphocytosis) such that these guidelines would be considered appropriate to CLL and SLL. This guideline will not address differential care in the COVID-19 setting [11].

2. Methodology

As an update to the 2018 first-line treatment guideline for CLL [10], which reviewed meta-analyses, randomized controlled trials (RCT), and single-arm prospective studies published between January 2000 and July 2017 investigating first-line treatments for CLL, this guideline extends the search from August 2017 to December 2021. This list was then narrowed to only include meta-analyses and phase 3 RCTs as this quality of data is required for funding for therapies in Canada. A manual search was performed in 2022 up until December 2022 to ensure all relevant articles meeting this definition have been included for review. Studies investigating maintenance treatments after chemo-immunotherapy were excluded. The literature search reviewed databases (MEDLINE, Pubmed, Google Scholar), using key search terms specific to CLL treatments including "chronic", "lymphocytic", "leukemia", "CLL", "first-line", and "treatment". The ClinicalTrials.gov and Cochrane Central Register of Controlled Trials Web sites were also searched for trials in progress. Publication language was restricted to English. Studies were initially screened based on title; duplicate articles and articles not publishing original research were excluded. Studies were then screened by a review of abstracts fitting the appropriate inclusion criteria (Supplemental Table 1). If abstracts fit the criteria, a complete full-text analysis was performed using similar inclusion criteria.

Lymphoma Canada coordinated the development of these guidelines and provided its support and resources throughout all facets of the Canadian clinical practice guideline creation, working closely alongside a panel of CLL experts. As an update to the 2018 guideline, research on the active surveillance approach and therapeutic regimens in the first-line setting were then compiled according to patient characteristics to illustrate new treatment options as well as effectiveness and safety. Following compilation of research in each category, information was reviewed by a national panel of CLL experts for consensus on frontline treatment recommendations for CLL patients in Canada. The National Comprehensive Cancer Network categories of evidence and consensus (Supplemental Table 2) were used to grade the level of evidence and support for the clinician recommendations for frontline treatment [12].

3. Results

A total of 4873 studies were included for review, and following exclusion of basic criteria, 79 studies remained (Supplemental Figure 1). A total of 23 studies that fit the criteria of a phase 3 trial or meta-analysis were included for analysis.

3.1. Pre-treatment Considerations

Historically, when chemotherapy and/or chemo-immunotherapy (CIT) were the only available treatment options for CLL patients, decisions on the selection of chemotherapy/CIT regimens were directed by patient age and/or comorbidities (commonly referred to as patient "fitness"). Because restrictions for age and/or fitness were used in the inclusion criteria for all Phase 3 clinical trials, these categories have been maintained within these guidelines. While age and comorbidities are less important in treatment selection today, these factors and molecular testing are still recommended to be considered, especially in patients who are candidates for CIT.

Although many different prognostic factors and scores have been validated in CLL [13,14], only two parameters, Immunoglobulin heavy chain variable region (*IGHV*) mutation status and aberrations in *TP53* [15] including deletion 17p, have proven predictive for survival outcomes and should be evaluated before treatment decision-making in all patients. Assessment of *IGHV* does not vary over time and should be performed only once. Analyses for deletion of 17p and mutations in *TP53* should both be performed prior to each treatment as they are associated with inferior responses to some therapies and influence treatment recommendations.

Recommendation:

- ***IGHV* mutation testing should be performed prior to the first treatment only**
- **Del17p and *TP53* mutation testing should be performed prior to each treatment**

3.2. Early Stage Asymptomatic CLL Patients

Nearly 80% of patients diagnosed with CLL present with early-stage asymptomatic disease and do not meet the criteria for requiring therapy according to the 2018 International Workshop on CLL guidelines

Table 2
Clinical Trials in fit CLL patients eligible for FCR with no del17p or *TP53* mutations.

Reference	Study		Patients		Median Follow-up Time	Survival	
	Phase (Name)	Treatment	n	Characteristics		PFS	OS
Leblond, V. et al. (2018), *Haematologica*[34]	Phase 3B (GREEN)	Obin, FCO, CLB-O, BO	972	Median age 65 yr, Binet stage B/C (73.3%), CIRS > 6 (19%), dep17p (5.4%), *IGHV* unmutated (51.8%)	24.5 mo	n/a	n/a
Feugier, P. et al. (2018), *Haematologica*[35]	FU Phase 3 (CLLFMP2007)	FCR vs FCA	165	Binet stage B/C, aged 18–65 yr, no del17p, *IGHV* unmutated (54.9–60.2%), CIRS < 7	76.4 mo	PFS: FCA (64.5%), FCR (60%)	OS: FCA (75.3%), FCR (85.2%)
Shanafelt, T.D., et al. (2019). *N Engl J Med*[36]	Phase 3 (ECOG1912)	IBR+R vs. FCR	529	Median age 56 years, *IGHV* unmutated (71%), del17p (0.4%), Rai stage III/IV (43.1%)	33.6 mo	3-yr PFS: IBR+R (89.4%) vs. FCR (72.9%)	3-yr OS: IBR+R (98.8%) vs. FCR (91.5%)
Kutsch, N. et al. (2020). *Hemasphere* [27]	FU Phase 3 (CLL10)	FCR vs. BR	561	Fit patients without del17p, *IGHV* unmutated (67.8% BR, 55.3% FCR), age > 70 yr (18.3% BR, 9.9% FCR), CLL-IPI (35.8% high-risk)	58.2 mo	median PFS: BR (42.3 mo) vs FCR (57.6 mo)	Median OS NR 5-yr OS: BR (80.1%), FCR (80.9%)
Hillmen, P. et al. (2021). *ASH 2021* [31]	Phase 3 (UK FLAIR)	FCR vs. IBR+R	771	Median age 62 yr, Binet stage C (45.1%), *IGHV* unmutated (53.2%), del17p (0.4%), del11q (15.4%)	52.7 mo	Median PFS: FCR (67 mo) vs IBR+R (NR)	No difference in OS between FCR and IBR+R
Eichhorst, B., et al. (2021), *ASH 2021*[32]	Phase 3 (CLL13/GAIA)	FCR/BR vs VO vs VR vs IVO	926	Median age 61 yr, Binet stage C (35.6%), *IGHV* unmutated (56%)	27.9 mo	uMRD: VR (57%), VO (86.5%), FCR (52%), IVO (92.2%)	n/a

Abbreviations: CLB (chlorambucil), Obin (Obinutuzumab), IBR (Ibrutinib), yr (years), mo (months), FCO (Fludarabine, cyclophosphamide, Ofatumumab), BO (bendamustine-obinutuzumab), Clb-O (Chlorambucil + Obinutuzumab), CIRS (Cumulative Illness Rating Score), BR (bendamustine – rituximab), R (rituximab), VR (Venetoclax+Rituximab), VO (Venetoclax+Obinutuzumab), IVO (Ibrutinib, venetoclax, obinutuzumab), CLL-IPI (CLL International Prognostic Index), FCA (fludarabine, cyclophosphamide, alemtuzumab), NR (not reached), uMRD (undetectable minimal residual disease), OS (overall survival).

(iwCLL) [16,17]. See Supplemental Table 3 for a summary of the iwCLL guidelines.

Several studies have examined early therapy for asymptomatic CLL patients who are considered to be high-risk for progression of disease, summarized in Table 1. The definition of high-risk varies between studies with no universally accepted definition of 'high risk for progression'.

Recently, the five-year follow-up of early intervention with FCR in high-risk asymptomatic patients revealed that FCR had a significantly better event-free survival (EFS) compared with observation (median not reached [NR] vs. 18.5 months respectively, $P < 0.001$) [18]. However, at this time, there was no OS benefit reported for FCR and significant toxicities (grade 3–5 adverse events in 74.4% of the population and 22% grade 3–5 infections) were observed. Therefore, the use of FCR was not recommended as an early intervention strategy. The efficacy of novel targeted therapy in comparison with observation is a topic of significant interest. The largest of these studies recently published results comparing IBR against observation in asymptomatic high-risk CLL patients as defined by the German CLL Study Group risk score [23]. With a median follow-up time of 31 months, patients receiving IBR had an improved EFS compared with observation (median NR versus 47.8 months, $P < 0.0001$) [19]. While the toxicities of IBR were manageable, the results were not interpreted as justifying a change of the current active surveillance approach. Two additional phase II/III trials are ongoing comparing the use of novel therapies for early stage asymptomatic CLL against observation [20,21]. As no study has yet demonstrated a survival or quality of life advantage to earlier intervention, we continue to recommend active surveillance in asymptomatic CLL patients.

Recommendation for early-stage asymptomatic patients:

- **Given the continued lack of an overall survival benefit for therapeutic approaches for asymptomatic early-stage CLL patients, including those at high-risk for progression, active surveillance ("Watch and Wait") is recommended (Category 1).**

3.3. Symptomatic CLL Patients

1) Patients with CLL with del17p, *TP53* mutation(s), or both

TP53 aberrations have long been recognized to confer a negative prognosis in regards to response rate, PFS and OS, particularly with chemoimmunotherapy but also with novel agents (data from the relapsed/refractory setting). No randomized clinical trial has been conducted investigating only patients with del(17p) and/or *TP53* mutated CLL; though novel agent-based therapy has consistently proven more effective than CIT in these patients [24,25].

Recommendation for patients with *TP53* aberrations (del17p and/or *TP53* mutations):

- **BTK inhibition is a highly effective continuous suppressive therapy and is the preferred therapy for CLL with *TP53* aberrations (Category 2 A).**
- **Venetoclax-Obinutuzumab has demonstrated efficacy in patients with CLL with *TP53* aberrations and is the preferred therapy for patients who would benefit from a time-limited treatment (Category 2B).**

2) Young and fit patients (FCR eligible) with CLL without del17p or *TP53* mutation(s)

For many years, the standard treatment approach for fit patients was fixed-duration chemotherapy or chemoimmunotherapy [26]. In the 2018 CLL guideline [10], the recommendation for fit younger patients without del(17p) or *TP53* mutations was FCR (level of evidence: category 1), and BR for fit elderly patients (more than 65 years of age) without del(17p) or *TP53* mutation due to its reduced toxicity levels (level of evidence: category 2 A). Though BR and FCR continue to show similar overall survival after 5-years of follow-up, FCR has an improved median PFS, particularly in younger patients up to 65 years [27]. There continues to be a good risk cohort (IGHV mutated) treated with FCR in CLL8 that are still in remission after a median follow-up of 5.9 years

which are the longest remissions recorded with chemoimmunotherapy and there is speculation that some of these patients are cured [28]. Chemoimmunotherapy thus continues to be an option for low- and intermediate-risk CLL in fit patients.

Since 2018, two studies have been reported comparing FCR to BTK inhibition with IBR + rituximab (IBR+R). The phase 3 ECOG1912 trial [29] randomized young fit CLL patients less than 70 years of age to receive IBR+R for six cycles followed by IBR until disease progression or six cycles of FCR. At a median follow-up time of 33.6 months, the 3-year PFS and OS were superior with IBR+R compared to FCR (89.4% vs. 72.9% (P < 0.001); 98.8% vs. 91.5% (*P < 0.001*) respectively). Sub-group analysis demonstrated the greatest benefit in patients with unmutated *IGHV* who had a markedly improved 3-year PFS with IBR+R compared to FCR (90.7% vs. 62.5%, *P < 0.0001*). More recent results similarly show an improved PFS in patients with mutated *IGHV* [30]. The two treatment regimens were comparable for safety with a similar incidence of grade 3 or higher adverse events (80.1% IBR+R vs. 79.7% FCR, *P = 0.013*); however, infectious complications were greater with the FCR regimen. Based on the improved efficacy and general safety of the IBR+R regimen in young and fit patients, the results of this trial led to Canadian practice change to incorporate IBR as a treatment option for young, fit patients with unmutated *IGHV* and as other data has confirmed no benefit from the addition of rituximab, ibrutinib is dosed as monotherapy. The UK FLAIR trial, another phase 3 trial with a longer median follow-up time of 52.7 months, also assessed the safety and efficacy of FCR compared to IBR+R [31]. Though the median PFS was superior with IBR+R compared to FCR at a median follow-up of 52.7 months (NR vs 67 months respectively, *P < 0.001*), no OS difference was observed. Several differences were noted between the ECOG1912 and UK FLAIR study populations with the most notable being the younger median age of 58 years in the ECOG1912 study compared to the median age of 62 years in the UK FLAIR study and the higher proportion of patients treated with novel agents at progression in the UK FLAIR study. Though the comparator was IBR +R, as several studies have demonstrated no PFS/OS benefit with the addition of R, this study is interpreted as a comparison of BTKi to FCR [25].

The less mature GAIA/CLL13 trial, evaluates frontline V-based combinations in fit CLL patients and has demonstrated a tolerable safety profile, high rates of undetectable minimal residual disease and favourable PFS data, such that VO may soon also be an available frontline treatment option for young and fit CLL patients [32]. Recently, results from the GAIA/CLL13 trial at 38.8 months median follow-up showed a superior PFS for VO vs CIT (*P < 0.0001*) [33]. Three-year PFS rates were 90.5%, 87.7%, 80.8%, and 75.5% in VO, VO+IBR, VR, and CIT (FCR for patients <65 years, BR for ≥ 65 years), while similar OS rates were observed across all treatment arms. These updated results indicate that time-limited treatment with VO or VO+IBR improves PFS compared to CIT as frontline treatment in fit patients.

A list of relevant randomized clinical trials on first-line therapeutic interventions for fit patients with CLL without *TP53* aberrations can be found in Table 2.

Recommendation for young and fit (FCR-eligible) patients without del(17p) or *TP53* mutations:

- **FCR is an effective time-limited option for patients with *IGHV*-mutated CLL (Category 1)**
- **BTK inhibition is also demonstrated to be an effective option for all CLL patients (Category 1)**
- **BTK inhibition is preferred over FCR in patients with unmutated *IGHV* (Category 2 A)**
- **Venetoclax and Obinutuzumab is a safe and effective time-limited therapy for CLL patients without *TP53* aberrations (Category 2 A)**

3) **Older and/or unfit patients (FCR-ineligible), without del17p or *TP53* mutations**

There have been a number of published studies for patients considered ineligible for FCR due to either age and/or comorbidities. Since the 2018 Canadian CLL guidelines [10], long-term follow-up results have been reported from the RESONATE-2 study investigating IBR monotherapy versus chlorambucil (CLB) monotherapy in CLL patient's ineligible for fludarabine therapy [37]. PFS and OS continue to be significantly improved with IBR monotherapy and no new safety signals have been noted. Progressive disease events on therapy are very rare with IBR (13% at 8 years), however discontinuations for adverse events are frequent (only 42% of patients remain on therapy at 8-years follow-up) [37].

The ALLIANCE A041202 trial was the first study to examine IBR compared to an intensive chemo-immunotherapy comparator [25]. This cooperative group study compared BR to IBR and IBR+R in patients 65 years and older. The 2-year PFS was superior in the IBR and IBR+R treated groups (87%, 88% respectively) compared to patients treated with BR (74%, *P < 0.001*). However, there was no difference in OS between the three groups (95% BR, 90% IBR, 94% IBR+R, *P = 0.49*). The toxicity profiles also differed between the groups, with BR having higher rates of grade ≥ 3 hematologic events (61%) compared to IBR and IBR+R (41% and 39% respectively) and IBR-containing regimens having higher rates of non-hematologic adverse events (74%) compared to BR (63%). The results of this trial also confirmed similar 2-year PFS (87% vs. 88%) and OS (90% vs. 94%, *P ≥ 0.65*) with IBR compared to IBR+R, demonstrating a lack of benefit with the addition of R to IBR.

Obinutuzumab (O) is a more effective antibody in CLL than rituximab as was confirmed in the German CLL Study Group CLL11 study [38]. Two phase 3 studies have been recently published examining O in combination with BTK inhibition in the frontline treatment of CLL. The ILLUMINATE trial [39] investigated IBR in combination with O (IBR+O) compared to CLB-O, and the ELEVATE-TN trial [40] investigated the second generation BTK inhibitor, ACAL, as monotherapy and in combination with O versus CLB-O for fludarabine-ineligible patients. The ELEVATE-TN study included previously untreated CLL patients ≥ 65 years of age or younger than 65 years with comorbidities or reduced renal function while the ILLUMINATE study additionally included younger patients with del(17p) and/or *TP53* mutations. The lack of an IBR monotherapy arm in the ILLUMINATE study makes it difficult to interpret, and no OS advantage was seen despite including patients with *TP53*-aberrant CLL who are known to do poorly with CIT. Currently available data from the ELEVATE-TN study at a median follow-up of 46.9 months demonstrates ongoing superiority of ACAL and ACAL+ O over CLB+O. Estimated 48-month PFS rates were 87% for A+O, 78% for ACAL, and 25% for CLB+O (ACAL+O vs Clb-O *P < 0.0001*; ACAL vs Clb-O *P < 0.0001*; ACAL+O vs ACAL *P = 0.0296*) [41]. Median OS was not reached in any arm and was recently reported to be significantly greater with ACAL+O compared to CLB-O [42]. Unfortunately, the study was not powered to detect a significant difference between the ACAL and ACAL+O arms (P = *0.0836*). While IBR and ACAL have not been compared directly in a frontline CLL study, a head-to-head study of ACAL vs IBR in the relapsed/refractory CLL setting demonstrated non-inferiority for PFS and reduced toxicity of ACAL over IBR [43] Notably, rates of atrial fibrillation (16% IBR vs 9.4% ACAL), hypertension and several other adverse effects all favoured ACAL over IBR as the BTK inhibitor of choice in CLL [43,44].

Another second generation BTK inhibitor, Zanubrutinib (ZANU), was investigated in previously untreated CLL patients ≥ 65 years of age or ineligible for FCR in the SEQUOIA trial [45]. At a median follow-up of 26.2 months, the median PFS was significantly longer with ZANU compared to BR (*P < 0.0001*). The phase III ALPINE trial further corroborates these results with a higher ORR and a notably prolonged PFS

Table 3
Clinical trials in CLL patient's ineligible for FCR (no del17p or *TP53* mutations).

Reference	Study		Patients		Median FU Time	Survival	
	Phase/Name	Treatment	n	Characteristics		PFS	OS
Woyach, J. et al. (2018), *N Engl J Med* [25]	Phase 3 (A041202)	BR vs. IBR vs. IBR+R	547	Median age 71 ys; del17p (6%); *TP53* mutation (10%); *IGHV* unmutated (61%), high-risk (54%)	38 mo	2-yr PFS: BR (74%), IBR (87%), IBR+R (88%)	2-yr OS: BR (95%), IBR (90%), IBR+R (94%)
Michallet, A.S. (2018), *Haematologica*[49]	Phase 3b (MABLE)	BR vs CLB-R	241	Binet stage B/C disease (91%), median age 72 yr, *IGHV* unmutated (49–60%), del17p (3–8%)	23.5 mo	Median PFS: BR (39.6 mo) vs. Clb-R (29.9 mo)	Median OS: BR (43.8 mo) vs CLB-R (NR)
Offner, F. et al. (2020), *Br J Hematol*[50]	Phase 3 (COMPLEMENT-1)	CLB-Of vs. CLB	447	Median age 69 yr, *IGHV* unmutated (56%), del17p (6%), CIRS[9], ECOG $\leq$ 2 (100%), Binet B/C (67%)	5-yr	Median PFS: Clb-Of (23.39 mo) vs Clb (14.72 mo)	Median OS: CLB-Of (NR) vs. CLB (84.67 mo) 5-yr OS: CLB-Of (68.5%) vs. CLB (65.7%)
Burger, J.A., et al. (2020), *Leukemia* [51] Barr, P.M. et al. (2021), *Blood* (59.8 mo FU)[52] Barr, P.M. et al. (2018), *Haematologica* (36-mo FU)[53] Coutre, S. et al. (2018), *Haematologica* (28.1-mo FU)[54]	Phase 3 (RESONATE-2)	IBR vs. CLB	269	Median age 72–73 yr, no del17p, Rai III-IV (44–47%), *IGHV* unmutated (57–58%), *TP53* (3–10%)	66 mo	5-yr PFS: IBR (70%), CLB (12%)	5-yr OS: IBR (83%), CLB (68%)
Al-Sawaf, O. et al. (2021), *J Clin Oncol* [47] Fischer, K. et al. (2019), *N Eng J Med* (28.1-mo FU)[38]	Phase 3 (CLL14)	VO vs. CLB-O	432	Median age 72–74 yr, *IGHV* unmutated (28.6–50%), *TP53* (10.3–14.3%), del17p (1.8%)	52.4 mo	Median PFS: Ven-O (NR), Clb-O (36.4 mo) 4-yr PFS: VO (74%), CLB-O (35.4%)	4-yr OS (VO 85.4% vs CLB-O 83.1%)
Stilgenbauer, S. et al. (2021), *Br J Hematol* [55] Stilgenbauer, S. et al. (2018), *Leukemia* (32.8-mo FU)[56]	FU Phase 3b (GREEN)	FCO, BO, CLB-O, Obin	631	Median age 68 yr, *IGHV* unmutated (55.1%), del17p (13.5%), Binet stage C (29.3%), CIRS > 6 (19.2%)	40–50 mo	Median PFS: FC-O (NR), B-O (58 mo), Obinutuzumab (30.2 mo), CLB-O (31.8 mo)	Median OS NR4-yr OS: Obinutuzumab (86%), CLB-O (79%), B-O (90%), FC-O (95%)
Sharman, J.P. et al. (2021), *ASCO 2021* [41] Sharman, J.P. et al. (2020), *Lancet* (28.3-mo FU)[40]	FU Phase 3 (ELEVATE-TN)	ACAL+Obin, ACAL, CLB+O	535	Median age 70 yr, *IGHV* unmutated IGHV (63%), del17p (9%), CIRS > 6 (8.5–16.8%), Rai stage III-IV (44–46%)	46.9 mo	Median PFS: ACAL+O (NR), ACAL (NR), CLB+O (27.8 mo) 48-mo PFS: ACAL+O (87%), ACAL (78%), CLB+O (25%)	Median OS: ACAL+O (NR), ACAL (NR), CLB+O (NR) 48-mo OS: ACAL+O (93%), ACAL (88%), CLB+O (88%)
Kater, A.P. et al. (2022), *NEJM Evid* [48]	Phase 3 (GLOW)	IBR+V + vs CLB-O	106	Median age 71 yr, *IGHV* unmutated (51.7%), *TP53* mutation (4.3%)	27.7 mo	n/a	n/a
Tam, C.S. (2022), *Lancet Oncol*[45]	Phase 3 (SEQUOIA)	ZANU, BR	479	Median age 70 yr, *IGHV* unmutated (53.4%)	26.2 mo	24-mo PFS: ZANU (85.5%), BR (69.5%)	24-mo OS: ZANU (94.3%), BR (94.6%)

Abbreviations: BR (bendamustine, rituximab), IBR (bendamustine, ibrutinib, rituximab), R (rituximab), CLB-R (chlorambucil, rituximab), CLB-Of (chlorambucil, ofatumumab), CLB (chlorambucil), CLB-O (chlorambucil, obinutuzumab), CIRS (cumulative illness rating scale), ECOG (eastern cooperative oncology group performance score), PFS (progression free survival), OS (overall survival), NR (not reached), VO (venetoclax, obinutuzumab), FCO (fludarabine, cyclophosphamide, obinutuzumab), Obin (Obinutuzumab), ACAL (acalabrutinib), V (venetoclax), ZANU (zanubrutinib), yr (years), mo (months).

with ZANU compared to IBR [46]. This study confirms the efficacy and improved toxicity profile of second generation BTK inhibitors; however, ZANU is not licensed for the treatment of CLL in Canada at the time of the publication of this article.

The CLL14 trial evaluated a CLL patient population with coexisting conditions, comparing venetoclax + O (VO) for 1-year fixed duration to CLB-O [38]. The 24-month PFS was significantly greater with VO (88.2%) compared to CLB-O (64.1%), and a significant PFS benefit was also noted in patients with unmutated *IGHV* (p-value n/a). At a median follow-up of 52.4 months, PFS continues to be superior in the VO group ($P < 0.0001$), with no difference in OS [47]. The most common grade 3–4 adverse event was neutropenia, with febrile neutropenia and infections reported in VO (5.2%, 17.5%) and CLB-O (3.7%, 15.0%) respectively [38]. VO did not have a higher frequency of tumor lysis syndrome (TLS) compared to CLB-O, which are due to numerous safety measures implemented including prophylactic treatment, weekly dose ramp-up, and initiating treatment with Obin monotherapy.

The GLOW trial assessed the combination of fixed-duration IBR with IBR+V compared to CLB-O in older and/or unfit patients [48]. With a median follow-up of 27.7 months, fixed-duration IBR+V demonstrated a superior PFS (hazard ratio= 0.216), complete remission rate, undetectable measurable residual disease and time to next treatment compared to CLB-O but no OS advantage at this time. Of importance, concerns with IBR+V are noted regarding cardiac toxicity and deaths in IBR+V arm. The IBR+V regimen has not yet been approved by Health Canada and is thus not recommended in Canada as of the time of publication.

A list of relevant randomized trials on therapeutic interventions for patient's ineligible for FCR with CLL without *TP53* aberrations can be found in Table 3.

Table 4
Expert Guide to selecting Frontline CLL therapy.

Patient/disease characteristics	Treatment	Advantages	Disadvantages	Access in Canada
Patients with del(17p) **and/or *TP53* mutation**	BTK inhibitors (IBR, ACAL	Best remission duration documented to date Favour ACAL for best side effect profile	Indefinite therapy	IBR and ACAL funded in all provinces *Preferred therapy
	VO	Improved PFS compared to CIT (no survival comparison to BTKi) Finite therapy (only 12 months)	Less durable remission compared to BTKi (cross trial comparisons only)	Only available for older/unfit patients and/or those with unmutated *IGHV* in most provinces
Young/fit patients ("FCR-eligible") with mutated *IGHV* and no *TP53* aberrations	FCR	Longest remissions documented to date and possibility of cure Finite therapy (only 6 months)	Increased risk of therapy-related myeloid malignancy and infections Many patients do not want chemotherapy	FCR funded in all provinces *Preferred therapy
	VO	Highly effective therapy with very long remissions in good risk patients	Limited long-term data compared to FCR	Not funded in Canada for young FCR-eligible patients *Preferred therapy if funded
	BTK inhibitor (ACAL)	Long remissions	Indefinite therapy Very high-cost burden for continuous therapy	Not funded in all jurisdictions due to high cost
Young/fit patients (FCR eligible) with unmutated *IGHV* and no *TP53* aberrations	ACAL	Improved PFS compared to CIT Well tolerated Questionable improvement in OS (conflicting data from 2 different studies with IBR)	Indefinite therapy High-cost burden for continuous therapy	ACAL funded in all provinces *Preferred therapy
	VO	Effective therapy expected to provide several years of treatment-free duration prior to second line therapy Finite duration (12 months)	No comparative data against BTKi No longer term data on PFS/OS in this age group PFS expected to be shorter than with BTKi (cross-trial comparison)	Variably funded in Canada for this subgroup *Preferred therapy if funded
Older or comorbid patients (FCR ineligible) with mutated *IGHV* and no *TP53* aberrations	VO	Long remissions Finite therapy of only 12 months	Frequent visits in cycle 1–2 for O loading and V ramp-up	VO funded in all provinces *Preferred therapy
	ACAL	Long remissions	Indefinite therapy Very high-cost burden for continuous therapy	Variably funded in Canada due to high costs
	CIT	Finite duration therapy	Shorter remissions than VO which is also finite duration	CIT funded in all provinces
Patients with unmutated *IGHV* (no *TP53* aberrations) who are "FCR-ineligible"	VO	Effective therapy expected to provide several years of treatment-free duration prior to second line therapy Finite duration (12 months)	PFS expected to be shorter than with continuous BTKi (cross-trial comparison)	VO funded in all provinces *Preferred therapy
	ACAL	Improved PFS compared to CIT Expected longer PFS compared to VO (cross-trial comparison)	Indefinite therapy High-cost burden for continuous therapy	
	ACAL + O	Improved OS compared to CIT	Indefinite therapy with higher cost than ACAL due to addition of O	Only funded in QC

*Preferred therapy = the preferred therapeutic option/regimen recommended for use in Canada per patient disease/characteristic group by expert opinion.

Recommendation for older or comorbid patients (FCR-ineligible) without del(17p) **or *TP53* mutation:**

- **Venetoclax + Obinutuzumab is an effective and safe time-limited therapy for CLL (Category 1)**
- **BTK inhibition (acalabrutinib, ibrutinib) is an effective and tolerable continuous CLL therapy (acalabrutinib, ibrutinib) (Category 1)**
  - o **Second generation covalent BTK inhibitors are preferred due to their improved toxicity profile (category 2 A)**
  - o **Rituximab provides no added value when combined with BTK inhibitors (category 1)**
  - o **Obinutuzumab provides improvement in PFS when combined with BTK inhibitors and can be considered if funding is available (category 2B)**

- **Chemoimmunotherapy regimens have shown inferior efficacy to targeted therapy and remain an option for patients only in limited situations (i.e. geography, funding access) (category 2 A)**

3.4. Conclusions and expert recommendations

Numerous ongoing clinical trials aim to improve upon therapeutic options and outcomes for CLL patients. Many of these studies examine novel-novel combinations, including doublet or triplet combinations, with a focus on developing effective time-limited options. The role of chemoimmunotherapy is likely to become increasingly more restricted or obsolete over time.

In addition to ongoing clinical trials, many real-world registry series are reporting data on outcomes of the sequencing of novel therapies (BTK inhibitors before BCL-2 inhibitors and the reverse). To date, there are no data to suggest a superior sequence of therapy for CLL such that individual patient considerations are required to select between available options. Given the lack of head-to-head comparison between highly effective novel therapies (ACAL, ACAL+O, VO, IBR+V), we propose the following Expert Guide to selecting therapy (Table 4).

As described in this review, there are a number of safe and effective frontline treatments options available for Canadian CLL patients. However, treatment approaches may differ across provinces based on provider preferences, patient comorbidities and proximity to a cancer center, cost and variable funding across provinces. In the future, we

suggest more research and efforts into ensuring equitable access to care given the difficulties of delivering many effective therapies (like venetoclax-based treatment) in remote settings, which is an issue that disproportionately impacts our indigenous and rural communities. Further, questions remain to be answered regarding the optimal combination and sequencing of agents, the role of MRD in duration of therapy, and the importance of genetics and clonal evolution on therapeutic decisions. There are currently numerous studies ongoing that are testing combinations to achieve deeper responses, overcome treatment resistance, and reduce toxicity and/or cost. The most promising combinations currently studied in phase 3 trials involve combination testing of venetoclax and BTKi with or without obinutuzumab. In addition, longer observation is required from earlier phase trials for improved understanding of efficacy and long-term toxicities.

There are a number of ongoing trials [57] that will provide promising information to frontline treatment combinations:

- ACE-CL-311 (NCT03836261) → FCR/BR Ven-O+Acalabrutinib (15 mo)
- CRISTALLO (NCT04285567) → FCR/BR, Ven-O (12 mo)
- FILO ERADIC (NCT04010669) → FCR, Ven+I (15 or 27 mo)
- ALLIANCE A041702 (NCT-3737981) → I-O, Ven-O + I (15 mo)
- ECOG-ACRIN EA9161 (NCT03701282) → I-O, Ven-O + I (19 mo)
- GCLLSC CLL17 (NCT04608318 (NCT0408318) → I, Ven-O (12 mo), Ven-I (15 mo)
- MAJIC (NCT05057494) → Acalabrutinib-Ven, Ven-O (14 mo)

As observed, combining targeted agents is promising, however longer follow-up is needed. The next years are anticipated to yield additional data on the combination and sequencing of drugs and to bring forth new drugs and more time-limited treatment approaches.

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Conflict of Interest Disclosures

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.leukres.2023.107016.

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