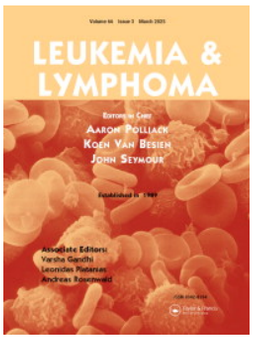

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REVIEW ARTICLE

Clinical trials in early-stage CLL: what has been learned and what's next?

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ABSTRACT

More than 80% of newly diagnosed chronic lymphocytic leukemia (CLL) patients present with asymptomatic, early-stage CLL. Of these, only 30–50% progress to advanced stage with reduced survival, while the rest may never require treatment. According to the 2018 International Workshop on CLL (iwCLL) guidelines, patients who do not meet the criteria for treatment initiation should only be treated within the context of clinical trials, as data demonstrating an overall survival benefit in early-stage CLL are still awaited. Risk stratification through continually advancing prognostic models can assist in identifying high-risk patients for early, risk-adapted treatment within clinical trials. Currently, new targeted therapies with high efficacy and lower toxicity are available in early intervention trials. This review (1) explores the development of prognostic models for identifying high-risk patients, (2) examines the design of early intervention trial, (3) summarizes the outcomes of early intervention trials, particularly in the context of targeted therapies, and (4) highlights ongoing clinical trials involving targeted treatments.

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Introduction

Chronic lymphocytic leukemia (CLL) is one of the most common malignant lymphoid diseases in adults in the Western world with up to 19,000 new cases diagnosed per year in the United States [1]. It is often discovered incidentally due to lymphocytosis during a routine complete blood count. Some patients have a slow-progressing disease that does not require treatment for many years. In contrast, some patients have an aggressive form of the disease that requires treatment shortly after diagnosis and may later transform into an aggressive lymphoma, known as Richter's transformation [2]. Nowadays, patients with early-stage, asymptomatic CLL who do not meet the 2018 International Workshop on CLL (iwCLL) criteria to initiate therapy are managed with an observational strategy ('watch and wait'), where treatment is deferred until it progresses and becomes symptomatic [3]. Although CLL typically progresses slowly, early-stage CLL remains a critical period in disease management.

There have been significant advances in the treatment of symptomatic CLL, leading to a substantial expansion of the available drug options, including both fixed-duration and continuous treatment with pathway inhibitors, and recently the approval of the first CAR T-cell therapy lisocabtagene maraleucel by the Food and Drug Administration (FDA).

The oral covalent BTK inhibitors (BTKis) – ibrutinib, acalabrutinib, and zanubrutinib – which are designed to target and inhibit BTK, have been approved for CLL treatment in many countries around the world. BTK is a crucial part of the B-cell receptor signaling pathway, which plays a crucial role in the pathogenesis of B-cell malignancies including CLL, Waldenstrom's macroglobulinemia (WM), mantle cell lymphoma (MCL) and marginal zone lymphoma (MZL), driving abnormal proliferation and survival. Non-covalent BTKis like pirtobrutinib and nemtabrutinib have alternative mechanisms of binding to BTK than covalent BTKi, and therefore offer a therapeutic alternative for patients with B-cell malignancies, including those who have been intolerant to, or experienced disease progression during treatment with a covalent BTKi. Idelalisib and duvelisib, which target phosphatidylinositiol-3-kinase (PI3K) in the B-cell receptor signaling pathway, are approved in the treatment of CLL and predominantly applied in the relapsed/refractory setting. The BCL-2 antagonist venetoclax in combination with obinutuzumab is approved as time-limited treatment in frontline CLL. New treatment strategies offer the approval

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of CAR-T cells and the development of proteolysis-targeting chimeras (PROTACs) to target and degrade BTK. All these agents represent a fundamental shift in the management of CLL patients who meet the 2018 iwCLL criteria for initiating treatment.

However, none of these drugs have been approved for early-stage, asymptomatic CLL, despite their greater effectiveness. This is partly because they have not yet demonstrated a benefit for specific high-risk genetic or molecular CLL patients, who are more suitable candidates for early-stage clinical research.

Only a few early intervention clinical trials with BTKi (ibrutinib or acalabrutinib), venetoclax, lenalidomide, and anti-CD20 monoclonal antibodies in asymptomatic, treatment-naïve early-stage CLL patients at increased risk of progression have been initiated and conducted in the last years (Table 1).

One randomized phase 3 trial has been published; two randomized phase 2 and 3 trials are recruiting; one trial is active, not recruiting; two randomized phase 2 trials assessing vaccination and BTKi are active, not recruiting; one phase 3 trial assessing patients with high risk for infections is recruiting. One observational trial assessing the economic analysis of early vs. delayed therapy in early high-risk CLL is recruiting.

A phase 2 study with curcumin and cholecalciferol in untreated Rai stage 0–II CLLL/SLL enrolled 35 patients and was completed with publication of results at clinical trials.gov (NCT02100423).

In this present review, we outline the development of prognostic models and discuss their impact on achieving successful outcomes in trials involving asymptomatic CLL patients through careful stratification and selection. We highlight past studies conducted in early-stage, asymptomatic CLL, and consolidate recent findings from clinical trials involving new therapeutic agents.

Risk stratification models for patients with newly diagnosed CLL

Risk stratification models in CLL have evolved from the Binet and Rai staging systems [4,5] to contemporary models integrating clinical, biological, and genomic parameters. An increasing number of prognostic biomarkers have been identified, supported by evidence deriving from both clinical trials and real-world studies [6–19].

Refining prognostic models to more accurately classify early-stage CLL patients into high or very high-risk groups for disease progression allows for the enrollment of these patients in early intervention clinical trials, rather than leaving them under observation alone.

Risk models for CLL progression, time to first treatment, and overall survival in the early-stage CLL

Remarkable efforts have been made to develop prognostic models, but most datasets are not representative of the general CLL population, and translation into clinical practice is limited [20]. In the alkylating agent era, most prognostic models were designed to predict overall survival (OS) as the primary endpoint. Thereafter, for effectively identifying high-risk patients who may benefit from early intervention, progression-free survival (PFS) and time to first treatment (TTFT) served as a more precise primary endpoint. Six such models reporting different biomarkers to predict time to treatment requirement exist:

1. The MDACC model with 930 patients and a median follow-up of 26 months. The five prognostic factors are unmutated IGHV status, diameter in centimeters of largest palpated cervical lymph node, FISH deletion 17p or 11q, more than three involved lymph nodes sides, and LDH. A nomogram with point scores ranging from 0 to 87.4 points predicts the four-year and two-year TTFT [21].
   This model integrates clinical, genetic and serological biomarkers, allowing for global application. The MDACC prognostic index has been validated in an independent Italian cohort and compared with the CLL-IPI. Both the *C*-statistic and Akaike information criterion (AIC) were lower than for the MDACC prognostic index than for the CLL-IPI.

2. The GCLLSG model with 1948 patients in the GCLLSG cohort and 676 patients in the external Mayo validation cohort and a median follow-up of 63.4 months. The seven prognostic factors are FISH deletion 17p, FISH deletion 11q, thymidine kinase level >10 U/L, serum β_2-microglobulin levels >3.5 mg/l or >1.7 and ≤3.5 mg/l, unmutated IGHV, ECOG PS >0, male sex, age >60 years. Patients are categorized into four groups predicting five-year treatment free survival [22].
   The GCCLSG model integrates thymidine kinase, which is a parameter that is challenging to obtain, as it is available only in specialized laboratories.

3. The CLL-IPI is based on a meta-analysis of 3472 treatment-naïve CLL patients in the main cohort, 838 in the Mayo validation cohort, and

Table 1. Early intervention clinical studies in the era of novel agent therapies.

Study	Official title	*N*	Status	Study design	Study population	Primary endpoint	Intervention
CLL12 GCLLSG NCT02863718	A placebo-controlled, double-blind, randomized, multicenter, three arm phase III trial to compare the efficacy and safety of ibrutinib vs. placebo in previously untreated Binet stage A chronic lymphocytic leukemia patients with risk of early disease progression	515	Completed	Randomized, double blind phase 3	Untreated Binet stage A CLL without need for treatment	EFS	All subjects with intermediate, (very) high risk according to the GCLLSG risk model randomized to the experimental treatment arm with ibrutinib 420 mg daily will be treated up to active progressive disease with treatment indication according to iwCLL-Guidelines and no later than 60 months after randomization; low-risk patients observed.
EVOLVE CLL/SLL study NCI NCT04269902	Randomized, phase III study of early intervention with venetoclax and obinutuzumab versus delayed therapy with venetoclax and obinutuzumab in newly diagnosed asymptomatic high-risk patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): EVOLVE CLL/SLL study	247	Recruiting	Randomized phase 3	High-risk CLL-IPI ≥4 or complex cytogenetics, newly diagnosed asymptomatic CLL/small lymphocytic lymphoma (SLL) patients	OS at 6 years	*Early V-O:* Treatment begins as soon as eligibility criteria are met. Patients receive obinutuzumab IV over 4 h on days 1, 2, 8, and 15 of cycle 1 and on day 1 of cycles 2–6. Patients also receive venetoclax PO QD on days 22–28 of cycle 1 and on days 1–28 of cycles 2–12. Treatment repeats every 28 days for 12 cycles in the absence of disease. *Delayed V-O:* Treatment begins once 2018 IWCLL indications are met. Patients receive obinutuzumab IV over 4 h on days 1, 2, 8, and 15 of cycle 1 and on day 1 of cycles 2–6. Patients also receive venetoclax PO QD on days 22–28 of cycle 1 and on days 1–28 of cycles 2–12. Treatment repeats every 28 days for 12 cycles in the absence of disease progression or unacceptable toxicity.
Acalabrutinib with or without obinutuzumab in early stage CLL/SLL Mayo Clinic NCT03516617	Randomized phase 2 study comparing acalabrutinib to acalabrutinib and obinutuzumab in the treatment of patients with early-stage chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) who are at high risk of disease progression	120	Recruiting	Randomized phase 2	Untreated CLL/SLL and high- or very high-risk CLL-IPI score randomized into 2 treatment arms. Low-intermediate CLL-IPI to be observed	Rate of minimal residual disease (MRD)-negative complete response (arm A and arm B) Time to first therapy in patients (arm C)	*Arm A (acalabrutinib)* Patients receive acalabrutinib PO BID on days 1–28. Treatment repeats every 28 days for six cycles in the absence of disease progression or unacceptable toxicity. Patients then receive acalabrutinib PO BID on days 1–84. Treatment repeats every 84 days for six cycles in the absence of disease progression or unacceptable toxicity. Patients may continue treatment with acalabrutinib If MRD negative CR/CRi is not achieved after 12 cycles. *Arm B (acalabrutinib, obinutuzumab)* Patients receive acalabrutinib PO BID on days 1–28 and obinutuzumab IV on days 1, 2, 8, and 15 of cycle 1 and days 1 of subsequent cycles. Treatment repeats every 28 days for six cycles in the absence of disease progression or unacceptable toxicity. Patients then receive acalabrutinib PO BID on days 1–84. Treatment repeats every 84 days for six cycles in the absence of disease progression or unacceptable toxicity. Patients may continue treatment with acalabrutinib if MRD negative CR/CRi is not achieved after 12 cycles. *Arm C (observation)* Patients will be observed every 6 months for up to 2 years.

(*Continued*)

Table 1. Continued.

Study	Official title	*N*	Status	Study design	Study population	Primary endpoint	Intervention
Ibrutinib as early therapy in CLL MDACC NCT03207555	Ibrutinib monotherapy in early stage chronic lymphocytic leukemia (CLL) without IWCLL/NCI-WG 2008 treatment indications but with high-risk features for disease progression	29	Active, not recruiting	Phase 2	Untreated CLL and estimated TTFT of 3 years or less according to the MCACC nomogram	CR; CRi	Ibrutinib 420 mg daily for up to 2 years (24 cycles).
Ohio State University Comprehensive Cancer Center NCT02518555	Early intervention trial of ibrutinib for patients with asymptomatic, high-risk chronic lymphocytic leukemia/small lymphocytic lymphoma	42	Active, not recruiting	Randomized phase 2	Untreated, asymptomatic CLL/SLL and ≥1 high-risk genomic features: Del17p13.1 (tumor protein p53 [TP53]) as detected by fluorescence *in situ* hybridization (FISH) Del11q22.3 ataxia telangiectasia mutated (ATM) as detected by FISH Complex karyotype (≥3 cytogenetic abnormalities on stimulated karyotype) Unmutated immunoglobulin variable region heavy chain (IgVH) (≥98% sequence homology compared with germline sequence) Zeta-chain (TCR) associated protein kinase 70 kDa (ZAP-70) gene promoter hypomethylation <20%	PFS at 2 years	*Concurrent vaccines and ibrutinib:* Patients receive ibrutinib PO QD on days 1–28. Patients also receive pneumococcal 13-valent conjugate vaccine IM on day 1 of courses 3 and 5 and trivalent influenza vaccine IM and DTaP vaccine IM on day 1 of course 4. Treatment repeats every 28 days for up to 24 courses in the absence of disease progression or unacceptable toxicity. *Sequential vaccines and ibrutinib:* Patients receive pneumococcal 13-valent conjugate vaccine IM on day 1 of courses 1 and 3 and trivalent influenza IM and DTaP vaccine IM on day 1 of course 2. Beginning in course 4, patients receive ibrutinib PO QD on days 1–28. Treatment repeats every 28 days for up to 27 courses in the absence of disease progression or unacceptable toxicity.
Lenalidomide and vaccine therapy NCI NCT01351896	Phase II study of lenalidomide to repair immune synapse response and humoral immunity in early-stage, asymptomatic chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) with high-risk genomic features	48	Active, not recruiting	Randomized phase 2	Untreated, asymptomatic CLL/SLL and ≥1 high-risk genomic features: CLL/SLL cells must demonstrate one or more of the following high-risk genomic features: Deletion (Del) (17p13.1) as detected by fluorescence *in situ* hybridization (FISH) in >20% of cells Del(11q22.3) as detected by FISH in >20% of cells Complex karyotype (≥3 cytogenetic abnormalities on stimulated karyotype) Unmutated immunoglobulin variable heavy chain (IgVH) (≥98% sequence homology compared with germline sequence)	Response to vaccination	*Concurrent PCV13 and lenalidomide* Patients receive low-dose lenalidomide PO once daily on days 1–28. Treatment repeats every 28 days for at least 24 cycles in the absence of disease progression or unacceptable toxicity. Patients also receive PCV13 IM on day 1 of courses 3 and 5. *Sequential PCV13 and lenalidomide* Patients receive PCV13 IM on days 1 and 78 (cycles 1 and 3). Patients also receive low-dose lenalidomide as in arm 1 beginning on day 1 of course 4. Treatment repeats every 28 days for at least 24 cycles in the absence of disease progression or unacceptable toxicity.

(*Continued*)

Study	Official title	*N*	Status	Study design	Study population	Primary endpoint	Intervention
Acalabrutinib and venetoclax treatment of newly diagnosed patients with CLL at high risk of infection or early treatment (PreVent-ACaLL) Rigshospitalet, Denmark NCT03868722	Short-term combined acalabrutinib and venetoclax treatment of newly diagnosed patients with CLL at high risk of infection and/or early treatment, who do not fulfil IWCLL treatment criteria.	212	Recruiting	Phase 3	High risk of infection and/or progressive treatment within 2 years according to CLL-TIM	Patients with untreated CLL at high (65%) risk for infection and/or in need of CLL treatment within 2 years if diagnosis	*Treatment:* Treatment with acalabrutinib and venetoclax is initiated within 14 days after randomization. *No intervention*.
Economic analysis of early versus delayed Therapy in early high-risk CLL Canadian Cancer Trials Group NCT05371808	An economic analysis of early vs delayed therapy in newly diagnosed asymptomatic high-risk patients with chronic lymphocytic leukemia/small lymphocytic lymphoma: a companion analysis to CCTG CLC.3/SWOG 1925 randomized phase III clinical trial	247	Recruiting	Observational	Patient must be eligible for the core CLC3/S1925 protocol.	To determine incremental cost-utility ratio of an early novel therapy approach compared to a deferred approach in Canadian patients with high-risk CLL (enrolled in the randomized component of the SWOG S1925/CLC3 study).	EQ-5D-5L instrument Work Productivity and Daily Activity Impairment (WPAI) survey Resource Utilization Form (SMRC)

416 in the SCAN validation cohort. Median follow-up was 79.9 months.

Nowadays, the CLL-IPI is widely used. The five parameters to predict clinical outcomes in CLL patients are *TP53* status (*TP53* gene abnormalities (deletion 17p and/or *TP53* mutations), unmutated IGHV, serum β_2-microglobulin levels >3.5 mg/l, Rai clinical stage I–IV, and age >65 years. The CLL-IPI categorizes patients into four different risk groups based on these factors, with significantly different outcomes for PFS, TTFT, and OS.

The CLL-IPI was not specifically developed for early-stage CLL and includes also patients who required treatment soon after diagnosis but represents 32% of patients with early-stage CLL, most of them had an indication for treatment [23].

4. The CLL1-PM model with 539 early-stage patients and a median follow-up of 8.5 years. The six parameters are deletion 17p, unmutated IGHV, deletion 11q, serum β_2-microglobulin levels >3.5 mg/l, lymphocyte doubling time <12 months, and age >60 years. The CLL1-PM model categorizes patients into four risk groups with significantly different outcome for PFS, TTFT, and OS [2].

   The CLL1-PM model was specifically developed for early stage CLL. It has shown higher performance metrics compared to the CLL-IPI, like higher *C*-statistic and better AIC scores, both for OS and TTFT. Since LDT is not available at the time of diagnosis, its prognostic role for the prediction of TTFT has been frequently debated.

5. The IPS-E model with individual early-stage patient data from 11 international cohorts of patients with early-stage CLL with 4933 patients. The three parameters are unmutated IGHV, absolute lymphocyte count higher than 15×10^9/L, and presence of palpable lymph nodes. The IPS-E separated patients into three risk groups with significantly different outcome for TTFT [24].

   Both the IPS-E and CLL1-PM model were specifically developed for early stage CLL, in addition, the IPS-E was grounded in clinical trials and real-world data which provided a broad and representative basis for its predictions. The IPS-E integrates easily obtainable parameters at the first diagnosis, making it practical for initial assessments and ongoing monitoring.

6. The Chinese Score with 334 newly diagnosed, untreated Chinese CLL patients without treatment indication upon diagnosis. The parameters associated with TTT are Binet stage, blood lymphocyte level, TP53 abnormality, unmutated IGHV, prior HBV, and EBV infections. The score separated patients into three risk groups with significantly different outcomes for TTFT [25].

   The Chinese score integrates prior hepatitis B virus (HBV) and Epstein-Barr virus (EBV) infections which can influence CLL prognosis by impacting immune function and the progression of the disease. Both parameters are not routinely assessed at the time of diagnosis outside of China.

Risk models for CLL progression, time to first treatment, and overall survival in the era of targeted drugs

The CLL1 trial highlighted that early-stage very low-risk patients have a life expectancy superimposable to the general population without treatment. To note, the rapid adoption of targeted therapies in the management of CLL has also transformed this leukemia in a disease that currently has a life expectancy almost superimposable to the general population. Therefore, the continuous identification of biomarkers selecting high-risk early-stage patients who benefit the most from early risk-adapted treatment is essential. Additionally, earlier and faster readouts than OS are needed, such as MRD at specific timepoints following time-limited treatment. The impact of continuous therapies, which can lead to long-term toxicities, has been frequent topic of debate in early-stage CLL management.

The first newly developed prognostic model in the era of targeted drugs was the four-factor prognostic model predictive of PFS and OS that was validated in 804 CLL patients in phase 2 and 3 trials treated uniformly with ibrutinib 420 mg per day. Univariable analysis of 18 pretreatment parameters was performed using PFS and OS endpoints. Multivariable analysis and machine-learning algorithms identified four factors for a prognostic model that was validated in internal and external cohorts. Factors independently associated with inferior PFS and OS were as follows: *TP53* aberration, prior treatment, β_2-microglobulin ≥5 mg/L, and lactate dehydrogenase >250 U/L. Each of these four factors contributed one point to a prognostic model that stratified patients into three risk groups: three to four points, high risk; two points, intermediate risk; zero to one point, low risk. The 3-year PFS rates

for all 804 patients combined were 47%, 74%, and 87% for the high-, the intermediate-, and the low-risk group, respectively ($p < .0001$). The 3-year OS rates were 63%, 83%, and 93%, respectively ($p < .0001$). The model identified patients at an increased risk of ibrutinib failure at treatment initiation who should be considered for clinical trials [26]. It is important to note, that the analysis also included relapsed patients and was not exclusively focused on early intervention.

The prognostic value of the CLL-IPI was recently reassessed using a pooled data set of CLL patients from 10 clinical trial of the German CLL Study Group (GCLLSG) treated first-line with targeted drugs ($N = 991$) or chemoimmunotherapy ($N = 1256$) [27].

With a median observation time of 40.5 months, the 3-year PFS rates for targeted drug-treated patients varied by CLL-IPI risk group: 96.5% (low), 87.6% (intermediate), 82.4% (high), and 78.7% (very high). Differences between consecutive CLL-IPI risk groups were observed for intermediate vs. low ($p = .002$), for high vs. intermediate ($p = .048$), but not for very high vs. high. CLL-IPI factors β_2-microglobulin, IGHV mutational status, and *TP53* status each retained prognostic value for PFS. The 3-year OS rates by CLL-IPI risk group were 100%, 96%, 93.9%, and 89.4%, respectively, with no differences between consecutive risk groups. Age, Binet stage, β_2-microglobulin, and *TP53* status each retained prognostic value for OS. In chemoimmunotherapy patients (median observation time 66.9 months), 3-year PFS rates for CLL-IPI risk groups were 78.1%, 51.4%, 40.1%, and 16.5%, respectively. Corresponding 3-year OS-rates were 97.4%, 93.1%, 81.8%, and 57.3%, respectively. In a matched-pair analysis, PFS-differences in targeted therapies ($N = 812$) vs. chemoimmunotherapy ($N = 812$) across all risk groups, and OS-differences in all but low-risk patients were demonstrated. The CLL-IPI maintains its prognostic value in predicting PFS outcomes with targeted drugs, but its predictive power for survival appeared diminished. TTFT was not reported (Figure 1).

Consecutive design and development of early interventional trials

There are two different strategies how to design the early intervention study: a randomized placebo-controlled trial or a randomized trial comparing immediate treatment at diagnosis vs. deferred treatment upon disease progression. In any case, the readout for early-stage studies takes years and consumes high resources considered that OS is the ultimate measure of patient benefit. Since the FDA accepted surrogate endpoints like PFS or response rates to accelerate the approval of drugs to treat hematological neoplasms, additional primary and secondary endpoints like EFS, MRD, quality of life, and infections or secondary malignancies may be of interest in patients with untreated CLL. Currently, there are no data to support the proposal that early intervention with any MRD level or any duration of PFS will ultimately result in an improved overall outcome.

Studies of early intervention in patients with asymptomatic CLL in the chemoimmunotherapy era

Several early intervention studies have been conducted. In a small phase 3 study of interferon alfa ($n = 21$) vs. observation ($n = 23$), the use of interferon alfa did not improve PFS and OS in patients with Binet stage A CLL [28].

In two randomized phase 3 studies that enrolled a total of 1535 patients, the French Cooperative Group in Chronic Lymphocytic Leukemia reported that continuous chlorambucil therapy (administered orally as a single agent at a daily dose of 0.1 mg/kg) or intermittent chlorambucil therapy (administered with prednisone: chlorambucil dosed at 0.3 mg/kg daily for five days each month, and prednisone dosed at 40 mg/m^2 daily for five days each month) for a total of 3 years improved disease control compared with no treatment [29]. Similar results were published by Shustik et al. in a Cancer and Leukemia Group B (CALGB) study comparing treatment with chlorambucil (administered at a dose of 0.5 mg/kg orally on day 1 of each month, with subsequent monthly dose increases of 0.1 mg/kg until clinical improvement or toxicity) in 48 patients who had early-stage CLL vs. no treatment [30].

Neither study showed an OS benefit when chlorambucil was compared with no treatment. A meta-analysis of chlorambucil-based treatments by the CLL Trialists' Collaborative Group also demonstrated no improvement in OS for immediate vs. deferred chlorambucil-based treatments [31]. Given the lack of an OS benefit with these approaches, chlorambucil-based treatments for early-stage asymptomatic CLL have not been incorporated into clinical practice. Of note, early intervention with chlorambucil was associated with a distinctly adverse outcome. The group observed that continuous chlorambucil therapy was associated with a higher rate of adverse events compared to other treatment regimens or intermittent use. Common adverse effects reported with continuous chlorambucil therapy include myelosuppression (e.g. anemia, leukopenia, and thrombocytopenia), gastrointestinal issues (e.g. nausea, vomiting, and diarrhea), and potentially long-term effects such as secondary malignancies.

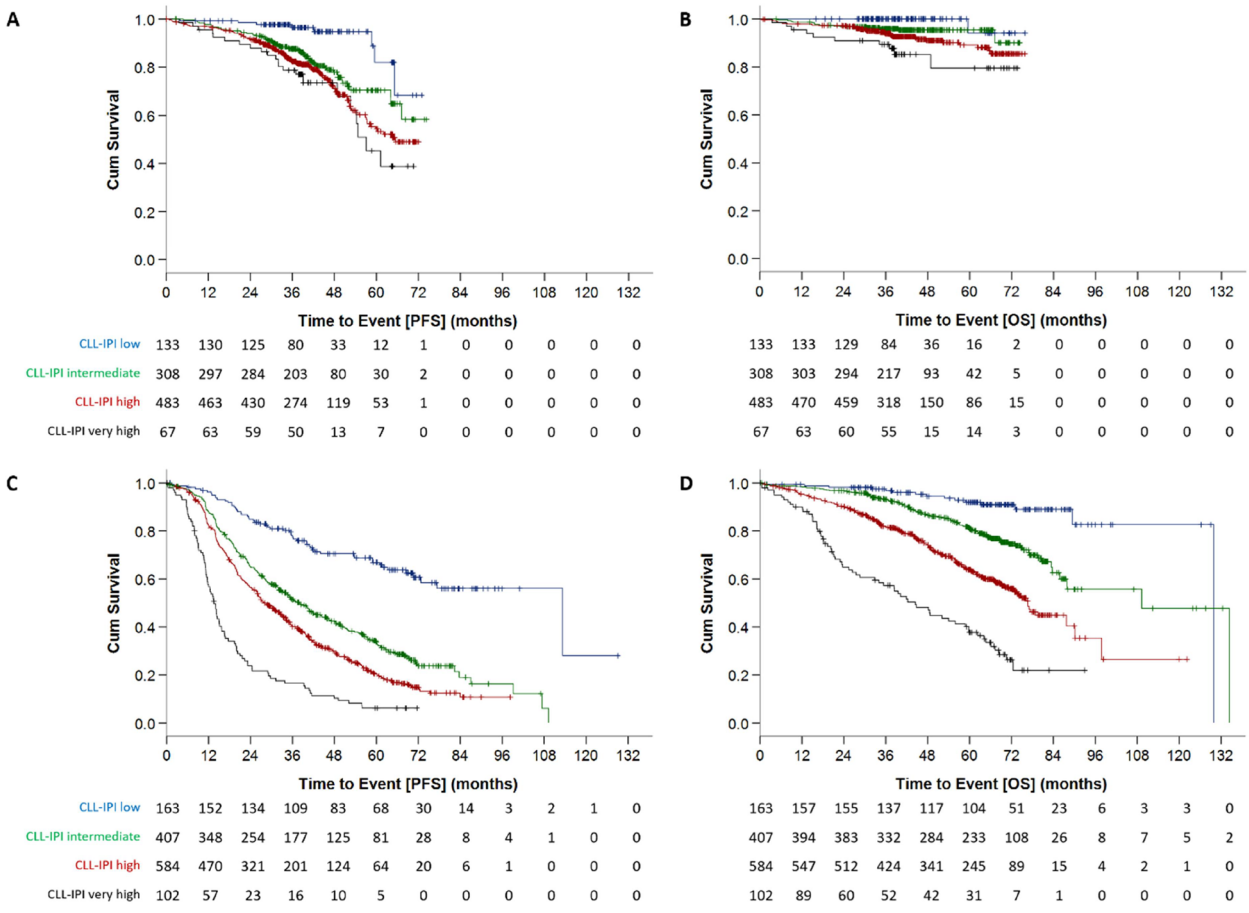

Figure 1. PFS and OS according to CLL-IPI risk groups. Progression-free (A) and overall (B) survival in patients treated with targeted drugs. Progression-free (C) and overall (D) survival in patients treated with chemo-immunotherapy [25].

The Medical Research Council (MRC) CLL Trials 1 and 2 significantly contributed to the understanding and treatment of CLL by evaluating different chlorambucil combinations and their efficacy. However, these trials also highlighted various adverse events associated with the treatments: risk of myelosuppression, gastrointestinal symptoms, and secondary malignancies [32].

Based on the hypothesis that qualitatively good complete remission leads to an extension of the progression-free interval and the OS, the CLL1 trial of the GCLLSG was designed in 1997 when fludarabine was considered as the most efficacious treatment for CLL, which compared fludarabine (25 mg/m^2 intravenously daily for five days, repeated every 28 days for a maximum of six cycles) with observation and treatment deferral until active CLL in patients who had early-stage CLL. To be eligible for trial participation, all patients were required to have two of the following four adverse characteristics: diffuse bone marrow infiltration, rapid lymphocyte doubling time <12 months, serum β_2-microglobulin level >3.5 mg/L, and serum thymidine kinase >7 U/L. Among the 189 patients enrolled in the study, fludarabine therapy led to a significant improvement in PFS (30 vs. 13 months; $p < .01$) and in treatment-free survival (74 vs. 41 months; $p = .04$). Nonetheless, improvement in OS did not occur (127 months vs. not reached; $p = .75$) [33]. The immunosuppressive effects of fludarabine increased the risk of infections, including bacterial, viral, and fungal infections. Pneumonia and other serious infections have been reported, particularly in patients with preexisting immune compromise. Long-term use of fludarabine has been associated with an increased risk of secondary malignancies, including secondary leukemias and other cancers.

The consecutive CLL7 study applied up to six cycles of standard FCR vs. observation and treatment deferral until active CLL in 201 patients with asymptomatic CLL. Patients in this study had at least two of the following four adverse characteristics: rapid LDT, serum thymidine kinase level above 10 IU/L, unmutated immunoglobulin heavy chain variable (IGHV) genes, and high-risk fluorescence *in situ* hybridization (FISH) results, including del(11q), del(17p), and trisomy 12. After approximately 5 years of follow-up, the median

event-free survival (EFS) was significantly better with FCR than with observation (median not reached vs. 18.5 months; $p < .001$); however, the 5-year OS rate did not differ between the two arms (82.9% vs. 79.9%, respectively; $p = .86$) [34]. Given the excessive toxicities associated with FCR (mainly hematologic toxicities and infections) and the lack of a difference in OS, fludarabine-based therapies are not recommended in patients with early-stage asymptomatic CLL.

Studies of early intervention in patients with asymptomatic CLL in the targeted drugs era

The main studies of early intervention in CLL that use targeted drugs are summarized in Table 1. The first study of novel agents in patients with asymptomatic CLL was CLL12. In this placebo-controlled, double-blind, randomized phase 3 study, asymptomatic patients with Binet stage A CLL were risk stratified according to the GCLLSG model [35]. Low-risk patients were observed, whereas patients with intermediate-, high-, or very high-risk disease were randomly assigned to ibrutinib at 420 mg daily or placebo. Treatment was continued until symptomatic disease progression (but no later than 60 months after randomization). The study recruited 515 patients. A total of 363 patients were randomized to the intervention with ibrutinib ($n = 182$) or placebo ($n = 181$). After a median follow-up of 31 months, the median EFS was not reached in the ibrutinib arm and was 47.8 months in the placebo arm. The final analysis of the complete data setting including OS is currently pending.

Several phase 2 studies that are exploring novel agents for early-stage CLL are looking at BTKis alone or in combination. A phase 2 study from The Ohio State University randomly assigned 44 patients with high-risk genomics (unmutated IGHV genes, high-risk results by FISH, or complex karyotype) to receive ibrutinib concurrently with or sequentially after vaccine administration against PCV13, trivalent influenza, and DTaP. Therapy with ibrutinib was reported to be safe, with no grade 4 toxicities and no grade 3/4 hematologic AEs. Grade 3 atrial fibrillation developed in two patients. Early treatment was associated with improvement in QoL measures of cancer-related stress: anxiety and loss of sleep. Three phase 2 studies of patients with high-risk asymptomatic early-stage CLL assessing the efficacy and safety of ibrutinib, acalabrutinib with or without obinutuzumab are ongoing, with no outcome results reported to date. EVOLVE is a phase 3 North American Intergroup Study for patients with previously untreated early-stage CLL who are at high or very high risk for disease progression according to the CLL-IPI. Patients will be randomly assigned to therapy with venetoclax and obinutuzumab at diagnosis or to delayed therapy with venetoclax and obinutuzumab when disease progression occurs and they meet 2018 iwCLL criteria for the initiation of therapy. The primary endpoint of this study is OS in the immediate-therapy vs. the delayed-therapy arm (NCT04269902). Another study, PreVent-ACaLL (NCT03868722) will randomly assign 212 patients at high risk for infection and/or needing therapy, according to the CLL-TIM algorithm to the combination therapy with acalabrutinib and venetoclax vs. placebo for a fixed duration of 12 weeks. The primary endpoint of this study is survival free of grade 3 or higher infection in the treatment arm vs. the observation arm after 24 weeks (12 weeks after the end of treatment).

Adverse events in early intervention trials with targeted drug

Currently, ibrutinib, acalabrutinib with or without obinutuzumab and venetoclax with obinutuzumab are study drugs in recruiting early interventional trials. Since BTKi are continuously administered agents, the long-term toxicity is critical for early intervention studies and close reporting of adverse events is necessary.

So far, only the CLL12 trial reported complete adverse events, emphasizing that special attention was paid to prespecified adverse events such as bleeding events, cardiac arrhythmias, hypertensive disorders, cardiac events other than arrhythmia, and diarrhea. Bleeding events of any CTC grade (grade 3 or higher) were reported in 33.5% (3.8%) of the patients who received ibrutinib and in 14.8% (1.9%) of those who received placebo. Cardiac arrhythmias occurred at any grade in 34 (21.5%, 21 [13.3%] grade 1–2) patients in the ibrutinib group and in 12 (7.7%, 10 [6.5%] grade 1–2) patients in the placebo group. Hypertensive disorders occurred at any grade in 18 (11.4%) patients receiving ibrutinib and seven (4.5%) patients receiving placebo. The incidence of grade 3 or higher hypertensive disorders was the same in both groups (three patients [1.9%] each). In the context of CLL management, especially in early-stage disease, it is important to discuss how certain adverse effects and challenges, such as cardiac arrhythmias, hypertension, bleeding, and early drug resistance, especially as informed by the CLL 12 trial, are weighed against the overall benefits of therapy. Advances in monitoring and managing adverse effects might improve patient safety and ongoing monitoring and

early intervention for potential adverse effects allow for prompt adjustments in therapy, which can help manage side effects and maintain overall treatment efficacy.

Conclusions

Despite the availability of targeted agents, robust clinical evidence demonstrating that early treatment improves OS in asymptomatic or early-stage patients is limited. Targeted therapies can have significant side effects, including infections, bleeding risks, or other complications. Initiating treatment early might expose patients to these risks before the disease causes any substantial issues; therefore, clinical guidelines generally recommend starting treatment based on specific criteria such as symptomatic disease or evidence of disease progression. The long-term safety profile of targeted agents is still being evaluated. Early treatment might lead to exposure to potential long-term toxicities without clear evidence of a corresponding benefit in survival or quality of life.

A thoroughly design of early intervention trials in asymptomatic, early-stage CLL patients with targeted therapies requires combined enhancements of better prognostic models to select the appropriate patient who might benefit from the early, risk-adapted treatment together with the development of anti-CLL therapies which are less toxic, time-limited with long-term safety. New technologies like machine-learning algorithms may help to include new prognostic parameters and collaborative efforts in developing adapted prognostic models for early-stage clinical trials will shape the next generation of early, risk-adapted CLL trials. Early and continuous reports of outcomes and adverse events from early intervention trial should be shared via common databases or open sources like clinicaltrials.gov. The enrollment of patients in rationally designed trials is highly recommended. Outside of clinical trials, we follow the 2018 iwCLL guidelines for initiating therapy in patients with newly diagnosed early-stage CLL.

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