Are We Moving Toward Curative Approaches in Chronic Lymphocytic Leukemia?

Martin Šimkovič[1,*], Eva Vejražková[1], Dominika Écsiová[1], Pavel Vodárek[1]

ABSTRACT

Over the past decade, chronic lymphocytic leukemia (CLL) management has undergone a fundamental transformation driven by the introduction of oral targeted inhibitors. Continuous Bruton tyrosine kinase (BTK) inhibition and time-limited BCL-2–based therapy has replaced chemoimmunotherapy as the standard of care, improving survival and quality of life. Ibrutinib and its next-generation analogues, acalabrutinib and zanubrutinib, provide durable disease control with improved safety. At the same time, venetoclax combined with anti-CD20 antibodies enables deep and measurable residual disease (MRD)-negative remissions within fixed-duration regimens. Recent trials have demonstrated the feasibility of MRD-guided treatment cessation and the potential benefit of combining BTK and BCL-2 inhibition to achieve durable, chemotherapy-free responses. Ongoing research focuses on optimizing treatment sequencing, overcoming acquired resistance through non-covalent BTK inhibitors, and integrating immunotherapeutic modalities such as bispecific antibodies and CAR-T cells.

The current paradigm emphasizes individualized, biomarker- and comorbidity-driven therapy based primarily on *TP53* and IGHV status, with treatment selection tailored to patient fitness, tolerance, and long-term safety. This review summarizes contemporary evidence, clinical practice recommendations, and future directions in the targeted management of CLL.

KEYWORDS

chronic lymphocytic leukemia; BTK inhibitors; BCL2 inhibitors; venetoclax; acalabrutinib; targeted therapy; comorbidities; personalized medicine

AUTHOR AFFILIATIONS

[1] 4th Department of Internal Medicine, University Hospital Hradec Králové, Faculty of Medicine in Hradec Králové, Charles University, Hradec Králové, Czech Republic

* Corresponding author: 4th Department of Internal Medicine, University Hospital Hradec Králové, Sokolská 581, 500 05 Hradec Králové, Czech Republic; simkovicm@lfhk.cuni.cz

Release: 7 January 2026
Published online: 24 March 2026

Acta Medica (Hradec Králové) 2025; 68(4): 113–122
https://doi.org/10.14712/18059694.2026.1

INTRODUCTION

Over the past decade, the therapeutic landscape of chronic lymphocytic leukemia (CLL) has evolved more profoundly than at any other time in its history. Once regarded as an incurable malignancy treated with largely palliative intent, CLL has become a prototype of precision oncology. The emergence of oral inhibitors targeting key signaling and apoptotic pathways has redefined therapeutic goals and outcomes, thereby establishing them as cornerstones of targeted treatment approaches in CLL (see Fig. 1). These advances have led to unprecedented improvements in survival and have shifted the therapeutic paradigm from chemoimmunotherapy to targeted oral medications (1, 2).

The biological understanding of CLL has expanded considerably. Recurrent cytogenetic and molecular abnormalities, including deletions of 13q14.3, 11q22–23, and 17p13, together with mutations in TP53, NOTCH1, SF3B1, and BIRC3, have been identified as critical determinants of prognosis and treatment response (3). The mutational status of the immunoglobulin heavy-chain variable region (IGHV) remains among the most potent predictors of clinical course, distinguishing an indolent, antigen-experienced form of the disease from its aggressive, unmutated counterpart (showing <2% difference from the germline sequence) (4). Furthermore, insights into B-cell receptor (BCR) signalling, the influence of the tumour microenvironment, and dysregulation of apoptosis have provided the biological rationale for inhibiting the BCR pathway and the antiapoptotic protein B-cell lymphoma 2 (BCL-2) (5).

Introducing the Bruton tyrosine kinase (BTK) inhibitor ibrutinib, the phosphoinositide-3-kinase δ inhibitor idelalisib, and the BCL-2 inhibitor venetoclax has revolutionized the management of CLL. Ibrutinib demonstrated sustained efficacy in treatment-naïve and relapsed settings, including patients with high-risk genomic features (6, 7). However, its off-target activity has been associated with cardiovascular adverse events and resistance mutations, prompting the development of next-generation, more selective BTK inhibitors such as acalabrutinib and zanubrutinib (8–10). In contrast, venetoclax induces deep remissions with frequent achievement of undetectable minimal residual disease (uMRD), thus enabling time-limited, chemotherapy-free treatment when combined with anti-CD20 monoclonal antibodies. These therapeutic advances have transformed CLL into a chronic, functionally curable condition in selected cases (11–13).

Despite remarkable progress, several clinically relevant questions remain unresolved. Optimal sequencing and duration of targeted therapies continue to be explored, as do the criteria for selecting patients suitable for fixed-duration versus continuous treatment. Moreover, the long-term immunologic consequences of these agents, the persistent risk of secondary malignancies, and the management of Richter transformation remain active research areas. Integrating genomic risk stratifi-

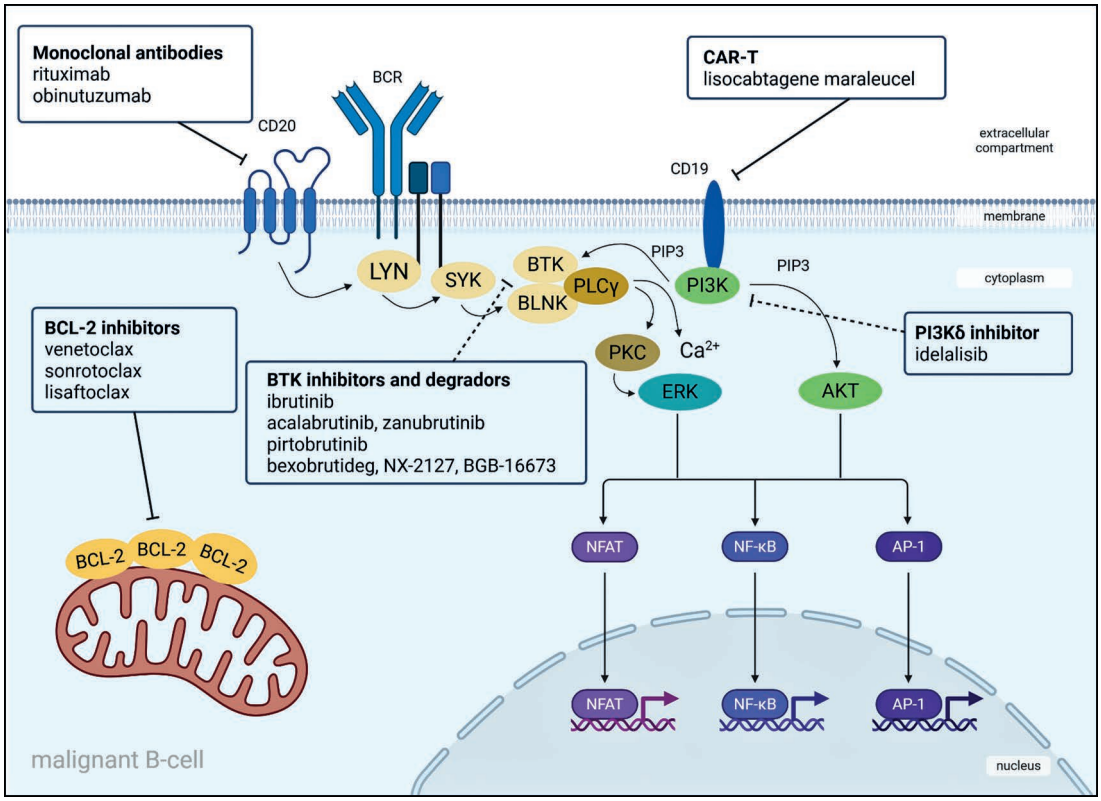

Fig. 1 Schematic representation of the sites of action of major therapeutic agents for CLL in the era of targeted oral inhibitors.
AKT, Ak Strain Transforming; BCR, B-cell receptor; Bcl-2, B-cell lymphoma 2; BLNK, B-cell linker protein; CAR-T, chimeric antigen receptor T cells; CD, cluster of differentiation; LYN, Lck/Yes novel tyrosine kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NFAT, nuclear factor of activated T cells; PI3K, phosphatidylinositol-3-kinase; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PLCγ, phospholipase C gamma; SYK, spleen tyrosine kinase. Created with BioRender.com.

cation and MRD monitoring into clinical algorithms may further refine individualized treatment approaches in the near future.

This review summarizes the current state of evidence and practical management of CLL in the era of targeted inhibitors, emphasizing treatment selection, sequencing strategies, immune implications, and challenges that will define the next decade of therapeutic development.

DIAGNOSIS AND PROGNOSTIC FACTORS

The diagnosis of chronic lymphocytic leukemia is based on the identification of a persistent clonal population of small, mature B lymphocytes in the peripheral blood exceeding 5×10^9/L, typically coexpressing CD5, CD19, CD23, and surface immunoglobulin of low density (14, 15). Flow cytometry remains the cornerstone of diagnosis, distinguishing CLL from other mature B-cell neoplasms, particularly mantle cell lymphoma, which is characterized by cyclin D1 overexpression and t(11;14)(q13;q32). Bone marrow examination is not routinely required for diagnosis, but may be helpful to clarify cytopenias or to confirm remission status after therapy. Lymph node biopsy should be reserved for cases with atypical immunophenotype or suspected Richter transformation.

The last decade has witnessed a significant shift toward molecularly informed risk stratification. Conventional clinical staging systems (Rai and Binet – see Table 1) remain relevant for initial assessment, yet their prognostic capacity is limited in the context of targeted therapies (16, 17). Modern prognostication relies on integrating cytogenetic, molecular, and immunogenetic parameters. Fluorescence in situ hybridization (FISH) is mandatory before initiating treatment and should include detection of del(17p), del(11q), trisomy 12, and del(13q). Among these, deletion 17p, usually accompanied by *TP53* mutation, confers the most adverse prognosis, predicting resistance to chemoimmunotherapy and inferior outcomes even with novel agents (15, 18, 19). Consequently, testing for *TP53* mutations and IGHV mutational status is now considered obligatory before selecting treatment.

The mutational status of IGHV divides CLL into two biologically distinct entities. Patients with mutated IGHV display an indolent clinical course and may achieve long-lasting remissions with time-limited therapy, whereas those with unmutated IGHV show increased dependence on B-cell receptor (BCR) signalling and derive greater benefit from continuous BTK inhibition. Specific stereotyped subsets, such as subset #2 utilizing *IGHV3-21*/*IGLV3-21* R110, are associated with aggressive disease irrespective of IGHV mutation status, underlining the complexity of CLL immunogenetics (4, 20, 21).

High-throughput sequencing studies have identified additional recurrently mutated genes affecting diverse cellular pathways – *NOTCH1*, *SF3B1*, *BIRC3*, *RPS15*, *MYD88*, *ATM*, and others – each conferring distinct biological and prognostic implications (3, 22, 23). While the cumulative number of driver mutations correlates with inferior outcome, only *TP53* and IGHV status currently influence therapeutic decision-making in routine practice. Nonetheless, broader genomic profiling provides valuable insight into clonal evolution, therapy resistance, and risk of Richter transformation.

Assessment of measurable residual disease (MRD) has emerged as an independent predictor of progression-free and overall survival, irrespective of treatment modality. Advances in flow cytometry and next-generation sequencing have enabled MRD detection below 10^{-5}, and uMRD has become a key endpoint in time-limited regimens combining venetoclax with anti-CD20 antibodies (24). Although MRD-guided therapy is not yet universally adopted outside clinical trials, its incorporation into future treatment algorithms is anticipated.

Finally, a comprehensive evaluation of comorbidities, performance status, and renal function remains essential for individualized management (25). Integrating biological and clinical variables – summarized in composite tools such as the CLL-International Prognostic Index (CLL-IPI, see Table 2) – allows refined risk stratification and optimization of therapy selection in the era of targeted inhibitors (26). Importantly, treatment initiation for CLL is indicated only after the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria for active or symptomatic disease have been met (Table 3) (18).

FIRST-LINE TREATMENT IN THE ERA OF TARGETED INHIBITORS

GENERAL OVERVIEW

The introduction of oral targeted inhibitors has profoundly reshaped the therapeutic algorithm for treatment-naïve patients with CLL. Chemoimmunotherapy (CIT) regimens such as fludarabine-cyclophosphamide-rituximab (FCR) or bendamustine-rituximab (BR), once the standard of care, have been mostly replaced by chemotherapy-free strategies (27, 28). These novel regimens combine inhibit-

Tab. 1 Rai and Binet Staging Systems in CLL.

Rai stage	Risk category	Findings (Rai)	Binet stage	Findings (Binet)
0	Low	Lymphocytosis[1]	A	No cytopenia and ≤2 lymphoid areas involved
I	Intermediate	Lymphadenopathy[2]	B	No cytopenia and >3 lymphoid areas involved
II	Intermediate	Hepatosplenomegaly[2]	C	Presence of anemia or thrombocytopenia
III	High	Anemia[3]		
IV	High	Thrombocytopenia[4]		

[1] Lymphocyte count > 5×10^9/L; [2] On physical examination; [3] Hemoglobin level < 110 g/l; [4] Platelet count < 100×10^9/L

Tab. 2 International Prognostic Index for Chronic Lymphocytic Leukemia (CLL-IPI).

Domain	Factor or CLL-IPI score	Points	Risk category / 5-year TFS
Prognostic factors contributing to the CLLIPI score			
Prognostic factor	Del17p on FISH or TP53 mutation	4	
	Unmutated IGHV genes	2	
	Serum β2 microglobulin >3.5 mg/L	2	
	Binet B, C or Rai stage I–IV	1	
	Age >65 years	1	
Risk stratification based on cumulative CLLIPI score			
Risk group	Cumulative CLLIPI score 0–1		Low risk – 78% 5-year TFS
	Cumulative CLLIPI score 2–3		Intermediate risk – 54% 5-year TFS
	Cumulative CLLIPI score 4–6		High risk – 32% 5-year TFS
	Cumulative CLLIPI score 7–10		Very high risk – 0% 5-year TFS

Tab. 3 iwCLL Criteria for the Definition of Symptomatic or Active Disease.

Criterion	Definition
Progressive bone marrow failure	Development or worsening of anemia and/or thrombocytopenia. Cut-off levels of Hb < 10 g/dL or platelet counts < 100 × 10^9/L are generally regarded as indications for treatment.
Splenomegaly	Massive splenomegaly (i.e., ≥ 6 cm below the left costal margin) or progressive or symptomatic splenomegaly.
Lymphadenopathy	Massive lymph nodes (i.e., ≥ 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
Progressive lymphocytosis	Increase of ≥ 50% over 2 months, or lymphocyte doubling time < 6 months, determined by linear regression of absolute lymphocyte counts measured at 2-weekly intervals.
Autoimmune cytopenias	Autoimmune anemia or thrombocytopenia poorly responsive to corticosteroids.
Extranodal involvement	Symptomatic or functional extranodal disease (e.g., skin, kidney, lung, spine).
Disease-related (B) symptoms	Any of the following: • Unintentional weight loss ≥ 10% within 6 months • Significant fatigue (ECOG PS ≥ 2; unable to work or perform usual activities) • Fevers ≥ 38.0 °C (≥ 100.5 °F) for ≥ 2 weeks without evidence of infection • Night sweats for ≥ 1 month without evidence of infection

ing key intracellular signalling pathways or apoptosis regulators with anti-CD20 monoclonal antibodies, achieving durable remissions and improved tolerability across diverse patient populations.

Bruton tyrosine kinase (BTK) inhibitors have become a cornerstone of first-line therapy. In several pivotal trials, Ibrutinib, the first-in-class covalent BTK inhibitor, demonstrated clear superiority over CIT (6, 24, 29). In the ECOG-1912 study, continuous ibrutinib plus rituximab significantly reduced the risk of progression and death compared with FCR in younger, fit patients (30). Similarly, in the RESONATE-2 and iLLUMINATE trials, ibrutinib-based regimens showed substantial improvements in progression-free survival (PFS) and overall survival (OS) versus chlorambucil-based chemoimmunotherapy in elderly or comorbid patients (6, 31). These results firmly established BTK inhibition as the evidence-based first-line approach irrespective of fitness status.

Nevertheless, the clinical use of ibrutinib is influenced by its off-target toxicity, including atrial fibrillation, hypertension, and bleeding, as well as by resistance mutations in *BTK* (*C481S, T474I, L528W, A428D*) or *PLCγ2* (8, 32). Developing second-generation covalent BTK inhibitors such as acalabrutinib and zanubrutinib, characterized by greater selectivity and improved safety, has represented a significant step forward (33). In the ELEVATE-TN trial, acalabrutinib – with or without obinutuzumab – significantly prolonged PFS compared with obinutuzumab-chlorambucil, demonstrating a more favorable cardiovascular safety profile (34). Likewise, the SEQUOIA study confirmed the efficacy of zanubrutinib in treatment-naïve patients, including those with deletion 17p, with an 18-month PFS rate approaching 90%. These data firmly support next-generation BTK inhibitors as the current standard of care for patients eligible for continuous therapy (35).

FIXED-DURATION VENETOCLAX-BASED THERAPY

In contrast to continuous BTK inhibition, venetoclax – an oral, selective BCL-2 inhibitor – enables time-limited therapy through deep remissions and frequent achievement of uMRD (Table 4). The phase 3 CLL14 study established venetoclax plus obinutuzumab (Ven-Obi) as the preferred first-line regimen for older or comorbid patients. After six years of follow-up, median PFS reached 76 months, markedly exceeding that of obinutuzumab-chlorambucil (36 months), with sustained benefit beyond treatment completion. MRD negativity at the end of therapy predicted both prolonged remission and improved survival (11). However, patients with *TP53* aberrations or deletion 17p

Tab. 4 Long-Term Outcomes of Fixed-Duration Chemo-Free Regimens in CLL.

Study	Phase	Line	Treatment	PFS / Median PFS
CAPTIVATE (FD cohort)	2	1st line	I + V	5.5year PFS ≈ 65%
GLOW	3	1st line	I + V	5.5year PFS 51.7%
FLAIR	3	1st line	I + V	4year PFS 93.5%
CLL13	3	1st line	VenG	4year PFS 81.8%
CLL14	3	1st line	VenG	Median PFS 76.2 months
MURANO	3	RR CLL	V + R	Median PFS 54.7 months

FD – fixed duration, I – ibrutinib, V – venetoclax, R – rituximab, VenG – venetoclax + obinutuzumab, PFS – progression-free survival, RR – relapsed/refractory.

derived less durable benefit, highlighting the need for alternative strategies in this subgroup.

Venetoclax-based regimens are generally well tolerated, though careful monitoring for tumor lysis syndrome remains mandatory during dose ramp-up. The main limitation of fixed-duration therapy is the uncertainty of long-term disease control in high-risk patients. Ongoing studies aim to determine whether MRD-guided re-treatment or extended therapy can further optimize outcomes.

COMBINATORIAL STRATEGIES

Given the complementary mechanisms of BTK and BCL-2 inhibition, combined regimens have been explored to achieve deep remissions while avoiding indefinite therapy. In the phase 2 CAPTIVATE trial, sequential ibrutinib-venetoclax therapy produced uMRD in over 70% of treatment-naïve patients, leading to sustained PFS after discontinuation (Wierda et al. 2024). The randomized phase 3 GLOW study confirmed the superiority of this fixed-duration combination over obinutuzumab-chlorambucil in elderly patients (Niemann et al. 2023). Similar efficacy was observed in the CLL13 trial, where venetoclax-obinutuzumab-ibrutinib achieved the highest MRD-negative rates and 3-year PFS exceeding 90%, surpassing both chemoimmunotherapy and venetoclax-obinutuzumab doublet therapy (18). These data support the feasibility of intensive, time-limited triplet approaches for selected patients.

The next frontier involves integrating MRD-driven treatment cessation into clinical practice. The FLAIR and CAPTIVATE-MRD cohorts demonstrate that tailoring therapy duration based on uMRD achievement can maintain durable responses while reducing cumulative toxicity, cost, and treatment fatigue (36).

PRACTICAL CONSIDERATIONS AND PATIENT SELECTION

Current guidelines recommend BTK inhibitors or venetoclax-based therapy as standard options for first-line treatment (2, 15). The choice between continuous versus time-limited therapy should be individualized according to patient preference, comorbidities, genomic risk, and tolerance profile.

Fixed-duration regimens achieve excellent outcomes, particularly in patients with mutated IGHV and without *TP53* aberrations, where venetoclax–obinutuzumab, venetoclax-ibrutinib or venetoklax-acalabrutinib is often selected for its limited duration and potential to induce deep remissions. In patients with del(17p) or *TP53* mutations, continuous BTK inhibitor therapy may be preferred due to its more favorable disease control.

For younger fit patients, chemoimmunotherapy (FCR regimen) may be considered only in rare cases with mutated IGHV without del(11q) and p53 abnormality, in situations where targeted therapy is unavailable due to reimbursement restrictions, as targeted inhibitors generally provide comparable or superior outcomes with lower toxicity.

The rapid evolution of CLL therapy underscores the need for dynamic, biomarker-driven treatment algorithms. Integrating MRD monitoring and genomic profiling into routine clinical decision-making will refine individualized treatment and may eventually allow a functional cure in a subset of patients.

MANAGEMENT OF RELAPSED OR REFRACTORY CLL

GENERAL PRINCIPLES

Targeted therapies have transformed the management of relapsed or refractory chronic lymphocytic leukemia (R/R CLL). The traditional distinction between "relapsed" and "refractory" disease – formerly defined by the duration of response to chemoimmunotherapy – has become less relevant in the era of continuous BTK and time-limited BCL-2 inhibition. The current therapeutic approach is guided primarily by the mechanism of prior therapy, the response duration, and the presence of specific resistance mutations.

For patients previously treated with chemoimmunotherapy, the introduction of BTK inhibitors or venetoclax-based regimens has led to significant improvements in survival (13, 37, 38, 39). For those relapsing after targeted therapy, optimal sequencing remains a matter of active investigation. Molecular profiling is increasingly applied to help guide treatment decisions, including assessment for *BTK* and *PLCγ2* mutations and *BCL2* resistance variants (40–42).

COVALENT BTK INHIBITORS

Ibrutinib has demonstrated durable disease control in relapsed CLL, with median progression-free survival (PFS)

exceeding five years in the RESONATE study's long-term follow-up (38, 39). However, continuous exposure frequently results in cumulative toxicity or the development of resistance, typically mediated by mutations in BTK or PLCγ2. Second-generation BTK inhibitors, such as acalabrutinib and zanubrutinib, retain efficacy in patients who discontinue ibrutinib for intolerance rather than progression, with substantially lower rates of atrial fibrillation and bleeding.

Direct head-to-head comparisons, such as ELEVATE-RR, confirmed equivalent efficacy between acalabrutinib and ibrutinib in R/R CLL, but with fewer cardiovascular adverse events in the acalabrutinib arm (9). Similarly, zanubrutinib demonstrated prolonged PFS and reduced toxicity in the ALPINE trial, establishing it as a preferred covalent BTK inhibitor in relapsed settings (43). Nevertheless, resistance due to *BTK* mutations remains a universal challenge for all covalent agents (32).

NON-COVALENT BTK INHIBITORS

The emergence of non-covalent (reversible) BTK inhibitors has provided an effective strategy for patients resistant to covalent BTK inhibitors. Pirtobrutinib, a highly selective, reversible BTK inhibitor, has shown high response rates across multiple studies, including heavily pretreated cohorts and those harboring *BTK C481* mutations. The BRUIN trial's overall response rate exceeded 70%, with a median PFS of 19 months and favorable tolerability (44).

BCL-2 INHIBITION AND SEQUENCING STRATEGIES

Venetoclax remains a potent option in relapsed CLL, particularly for patients who have not been previously exposed to BCL-2 inhibition. In the pivotal MURANO trial, time-limited venetoclax plus rituximab achieved a median PFS of 54 months, markedly superior to bendamustine-rituximab (13). Retreatment with VenR resulted in uMRD in 32% of patients, with a median PFS of 23 months, confirming the feasibility of VenR re-administration as an effective strategy for appropriately selected patients with relapsed/refractory CLL (13).

THE SEQUENCING OF THERAPY

In the current era of targeted CLL therapy, key questions remain regarding the optimal sequencing of treatment regimens and whether the efficacy of BTK and BCL2 inhibitors depends on their order of administration or on the reasons for discontinuing prior therapy. Time-limited therapy offers clear advantages, including lesser financial burden, long-term toxicity and a reduced risk of resistance development. It is therefore currently preferred in clinical practice, particularly for patients without p53 aberrations. Venetoclax-based regimens remain effective in patients previously exposed to BTK inhibitors (45, 46), and conversely, BTK inhibitors are effective in patients previously treated with venetoclax (47). However, these findings are based on small analyses, and a comprehensive overview of efficacy in treatment sequencing is lacking. Similarly, no randomized trial has yet directly compared continuous therapy and time-limited therapy using oral inhibitors. Initial data will be presented at the 2025 ASH Annual Meeting, where the first detailed results from the CLL17 study (NCT04608318) will become available.

CELLULAR AND IMMUNOTHERAPY APPROACHES

While targeted agents have improved outcomes for most patients, a subset with double-refractory disease – resistant to BTK and BCL-2 inhibitors – continues to represent an unmet need (48). Chimeric antigen receptor (CAR)-T cell therapy has emerged as a promising option for such patients, achieving durable remissions in approximately 40–50% of cases (49). Early results with bispecific antibodies targeting CD20 and CD3, such as epcoritamab and mosunetuzumab, show substantial activity in heavily pretreated CLL and Richter transformation (50, 51).

RICHTER TRANSFORMATION

Richter transformation (RT) remains one of the most challenging scenarios in CLL management. Historically treated with anthracycline-based chemoimmunotherapy (e.g., R-CHOP), outcomes have remained poor, with median overall survival rarely exceeding one year. Recent insights into the clonal and molecular heterogeneity of RT have led to the evaluation of targeted approaches. Venetoclax-based combinations (e.g., Ven-R-EPOCH) have yielded encouraging response rates and a median PFS of around 10 months. Early-phase studies combining venetoclax with immune checkpoint inhibitors (atezolizumab) or BTK inhibitors (zanubrutinib) have demonstrated promising activity and manageable toxicity. Cellular immunotherapy with CAR-T cells or allogeneic stem-cell transplantation remains the only potentially curative approach for eligible patients.

FUTURE DIRECTIONS

The treatment of relapsed or refractory CLL has evolved from empiric chemotherapy to a mechanism-based, genomically informed discipline. Covalent and non-covalent BTK inhibitors, BCL-2 inhibition, and emerging immunotherapeutic strategies offer durable control for most patients. The rational sequencing of these agents, guided by molecular resistance profiles and MRD dynamics, represents the cornerstone of modern CLL management. In the near future, integrating novel immune and targeted modalities may extend survival and achieve disease eradication in selected patients.

IMMUNE DYSREGULATION IN CLL

CLL is inherently associated with profound immune dysfunction (52–54). Impairments affect the innate and adaptive arms of the immune system, contributing to the characteristic susceptibility to infections, autoimmune phenomena, and secondary malignancies. Defects arise from quantitative hypogammaglobulinemia and qualita-

tive dysfunction of T and NK cells, monocytes, and dendritic populations.

Hypogammaglobulinemia occurs in up to 70% of patients during the disease course and correlates with both disease stage and cumulative therapy exposure (52–55). However, impaired T-cell synapse formation, T-cell exhaustion, and expansion of regulatory T cells further weaken antitumor immunity (56–59). Monocytes in CLL often acquire a nurse-like phenotype, supporting leukemic survival within the microenvironment (60–62). Together, these mechanisms result in an immunosuppressive milieu that occurs even in early disease stages such as monoclonal B-cell lymphocytosis (MBL) (63).

IMPACT OF TARGETED THERAPY ON IMMUNE FUNCTION

Unlike conventional cytotoxic chemotherapy, BTK and BCL-2 inhibitors exert variable but generally favorable effects on immune reconstitution. BTK inhibitors, particularly ibrutinib, increase total T-cell counts and reduce exhaustion markers (PD-1, CTLA-4), suggesting partial restoration of T-cell competence. They also diminish the proportion of regulatory T cells. However, their off-target inhibition of interleukin-2-inducible kinase (ITK) may transiently impair T-cell proliferation and antibody-dependent cellular cytotoxicity (ADCC) mediated by NK cells (6, 64, 65).

Second-generation BTK inhibitors, such as acalabrutinib and zanubrutinib, exhibit greater selectivity for BTK and minimize these off-target immune effects. Venetoclax, by contrast, has been associated with gradual immune recovery, including normalization of immunoglobulin levels, T-cell subsets, and NK-cell function (66, 67). Combined BTK and BCL-2 inhibition, as evaluated in the CAPTIVATE trial, has shown comparable immune restoration to monotherapy, suggesting that the observed immune improvement may primarily result from adequate CLL cytoreduction rather than direct immunomodulation (68).

INFECTIOUS COMPLICATIONS

Despite immune reconstitution during targeted therapy, infectious complications remain a significant cause of morbidity and mortality in CLL. The incidence of serious infections has been estimated at approximately 4–5 per 100 patient-years, increasing with age, prior therapy, and hypogammaglobulinemia (52, 53, 69, 70). Bacterial respiratory infections predominate, whereas opportunistic infections are less common than during chemoimmunotherapy but can occur with prolonged BTK or PI3K inhibitor use.

BTK inhibitors, especially ibrutinib, have been linked to invasive fungal infections such as *Aspergillus* and *Cryptococcus*, possibly due to off-target inhibition of macrophage signalling pathways. PI3K inhibitors carry additional risk for *Pneumocystis jirovecii* pneumonia and cytomegalovirus reactivation, warranting prophylaxis and close monitoring (71, 72). Conversely, venetoclax-based regimens appear to have a lower risk of opportunistic infections, provided neutropenia is appropriately managed.

The COVID-19 pandemic highlighted the vulnerability of CLL patients to viral infections -seroconversion after SARS-CoV-2 vaccination is frequently impaired, particularly during active BTK or BCL-2 inhibitor therapy. Booster doses, prophylactic monoclonal antibodies, and antiviral agents remain essential components of infection prevention strategies in this population (73–76).

SECONDARY MALIGNANCIES

Patients with CLL exhibit an increased risk of secondary neoplasms, reflecting a combination of disease-related immune suppression, genotoxic therapy exposure, and host susceptibility. Population-based studies report an incidence of secondary cancers nearly fourfold higher than in the general population, most commonly non-melanoma skin cancers, solid epithelial tumors, and therapy-related myeloid neoplasms (77, 78). The introduction of targeted therapy has not eliminated this risk. Monitoring and preventive strategies remain crucial. Regular dermatologic screening, avoidance of unnecessary immunosuppression, and adherence to vaccination programs are key components of survivorship care in CLL.

CLINICAL IMPLICATIONS

Recognition and management of immune dysfunction are integral to optimizing outcomes in CLL. Baseline evaluation of immunoglobulin levels, vaccination status, and infection history should guide preventive measures, including immunoglobulin replacement in selected patients. The overall immunologic impact of targeted therapy appears favorable compared with chemotherapy. However, long-term follow-up is required to determine its influence on infection risk, secondary malignancies, and immune senescence. The evolving integration of immune-monitoring biomarkers may ultimately refine patient stratification and enhance the safety of novel combination regimens.

FUTURE DIRECTIONS AND CHALLENGES

The rapid evolution of targeted therapy has fundamentally altered the natural history of CLL. However, the research trajectory suggests that the most transformative decade may remain. The overarching goals of modern CLL management are to achieve durable, chemotherapy-free remissions, individualize therapy based on biological risk, and ultimately attain a functional cure through time-limited, combination-based, or immune-mediated strategies.

TOWARDS MRD-GUIDED, TIME-LIMITED THERAPY

The concept of measurable residual disease (MRD) has evolved from a research endpoint into a potential clinical decision tool. As demonstrated in trials such as CLL14, CAPTIVATE, and GLOW, achieving uMRD strongly correlates with prolonged remission and survival (11, 79, 80). Future treatment paradigms will likely integrate MRD-guided therapy cessation and re-initiation strate-

gies, enabling dynamic adjustment of therapy duration according to disease kinetics rather than fixed schedules.

Several ongoing studies, including FLAIR, CLL18, and MAJIC, explore whether MRD-driven discontinuation of BTK and BCL-2 inhibitors can maintain durable control while reducing cumulative toxicity, cost, and patient burden (81, 82).

NEXT-GENERATION TARGETED INHIBITORS

BTK degraders (e.g., NX-2127, NX-5948, BGB-16673, ABBV-101, AC676) represent the emerging fourth generation of BTK-targeted therapy (83, 84). Unlike traditional inhibitors that block kinase activity, these agents induce ubiquitination and proteasomal degradation of the entire BTK protein, thereby eliminating its enzymatic and scaffolding functions. This strategy may overcome resistance mechanisms that persist despite kinase inhibition. Parallel progress has been achieved with next-generation BCL-2 inhibitors, including lisaftoclax and sonrotoclax, which aim to enhance potency and address acquired venetoclax resistance (85, 86). In preclinical models, sonrotoclax demonstrated superior cytotoxicity and retained activity against BCL-2 variants such as *G101V*, highlighting a convergent effort to refine targeted therapy through more complete and durable pathway suppression.

EMERGING IMMUNOTHERAPIES

Chimeric antigen receptor (CAR) T-cell therapy – particularly constructs optimized for the CLL microenvironment (e.g., 4-1BB–based or dual-target CARs) – continues to show promise for durable remission. However, careful patient selection and toxicity management remain critical (87). In 2024, the first CAR-T product for relapsed or refractory CLL, lisocabtagene maraleucel (liso-cel), an anti-CD19 construct incorporating a 4-1BB costimulatory domain, received regulatory approval in the United States. In the phase 1/2 TRANSCEND CLL 004 study, liso-cel achieved an overall response rate of 44% and complete remission in 20% of patients previously treated with BTK or BCL-2 inhibitors. Although the median duration of response for the overall cohort was approximately 12 months, patients who achieved complete remission experienced markedly prolonged disease control and durable survival outcomes.

In parallel, the convergence of targeted therapy and immunotherapy is reshaping clinical practice: CD3×CD20 bispecific antibodies, such as epcoritamab, have yielded encouraging responses in heavily pretreated CLL, including cases refractory to both BTK and BCL-2 inhibitors (50).

CONCLUDING REMARKS

Chronic lymphocytic leukemia has evolved from an indolent yet incurable malignancy into a largely controllable chronic condition, and for selected patients, a disease potentially curable through rationally designed, time-limited therapy. Integrating molecular diagnostics, MRD-directed strategies, and next-generation targeted and immune therapies defines the current research frontier. Continued collaboration between academic investigators, industry partners, and cooperative groups will be essential to transform these advances into a new standard of durable, individualized, and ultimately curative treatment for CLL.

ACKNOWLEDGEMENTS

Supported by programme COOPERATIO (research area ONCO) and DRO MH CZ (UHHK, 00179906).

REFERENCES

1. Walewska R, Eyre TA, Bloor A, et al. 2025 British Society for Haematology Guideline for the Treatment of Chronic Lymphocytic Leukaemia. Br J Haematol. 2025 Oct 9.
2. Eichhorst B, Ghia P, Niemann CU, et al. ESMO Clinical Practice Guideline interim update on new targeted therapies in the first line and at relapse of chronic lymphocytic leukaemia. Ann Oncol. 2024; 35(9): 762–8.
3. Landau DA, Tausch E, Taylor-Weiner AN, et al. Mutations Driving CLL and Their Evolution in Progression and Relapse. Nature. 2015; 526(7574): 525–30.
4. Damle RN, Wasil T, Fais F, et al. Ig V Gene Mutation Status and CD38 Expression as Novel Prognostic Indicators in Chronic Lymphocytic Leukemia. Blood. 1999; 94(6): 1840–7.
5. Cimmino A, Calin GA, Fabbri M, et al. miR-15 and miR-16 Induce Apoptosis by Targeting BCL2. Proc Natl Acad Sci USA. 2005; 102(39): 13944–9.
6. Burger JA, Barr PM, Robak T, et al. Final Analysis of the RESONATE-2 Study: Up to 10 Years of Follow-up of First-Line Ibrutinib Treatment for CLL/SLL. Blood. 2025 Jul 30.
7. Niemann CU, Munir T, Moreno C, et al. Fixed-Duration Ibrutinib-Venetoclax versus Chlorambucil-Obinutuzumab in Previously Untreated Chronic Lymphocytic Leukaemia (GLOW): 4-Year Follow-up from a Multicentre, Open-Label, Randomised, Phase 3 Trial. Lancet Oncol. 2023; 24(12): 1423–33.
8. Gambril JA, Ghazi SM, Sansoterra S, et al. Atrial fibrillation burden and clinical outcomes following BTK inhibitor initiation. Leukemia. 2024; 38(10): 2141–9.
9. Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial. J Clin Oncol. 2021 Jul 26.
10. Brown JR, Byrd JC, Ghia P, et al. Cardiovascular Adverse Events in Patients with Chronic Lymphocytic Leukemia Receiving Acalabrutinib Monotherapy: Pooled Analysis of 762 Patients. Haematologica. 2020.
11. Al-Sawaf O, Robrecht S, Zhang C, et al. Venetoclax-Obinutuzumab for Previously Untreated Chronic Lymphocytic Leukemia: 6-Year Results of the Randomized Phase 3 CLL14 Study. Blood. 2024 Jul 14.
12. Fürstenau M, Kater AP, Robrecht S, et al. First-Line Venetoclax Combinations versus Chemoimmunotherapy in Fit Patients with Chronic Lymphocytic Leukaemia (GAIA/CLL13): 4-Year Follow-up from a Multicentre, Open-Label, Randomised, Phase 3 Trial. Lancet Oncol. 2024; 25(6): 744–59.
13. Kater AP, Harrup RA, Kipps TJ, et al. The MURANO Study: Final Analysis and Retreatment/Crossover Substudy Results of VenR for Patients with Relapsed/Refractory CLL. Blood. 2025 Feb 26.
14. Hallek M. Chronic Lymphocytic Leukemia: 2025 Update on the Epidemiology, Pathogenesis, Diagnosis, and Therapy. Am J Hematol. 2025; 100(3): 450–80.
15. Špaček M, Šimkovič M, Pospíšilová Š, et al. Recommendations for Chronic Lymphocytic Leukaemia Diagnosis and Therapy. Transfuze Hematol Dnes. 2025; 31(3).
16. Döhner H, Stilgenbauer S, Benner A, et al. Genomic Aberrations and Survival in Chronic Lymphocytic Leukemia. N Engl J Med. 2000; 343(26): 1910–6.
17. Rossi D, Rasi S, Fabbri G, et al. Mutations of NOTCH1 Are an Independent Predictor of Survival in Chronic Lymphocytic Leukemia. Blood. 2012; 119(2): 521–9.
18. Puente XS, Pinyol M, Quesada V, et al. Whole-Genome Sequencing Identifies Recurrent Mutations in Chronic Lymphocytic Leukaemia. Nature. 2011; 475(7354): 101–5.
19. Wang L, Lawrence MS, Wan Y, et al. SF3B1 and Other Novel Cancer Genes in Chronic Lymphocytic Leukemia. N Engl J Med. 2011; 365(26): 2497–506.

20. Oscier DG, Rose-Zerilli MJ, Winkelmann N, et al. The Clinical Significance of NOTCH1 and SF3B1 Mutations in the UK LRF CLL4 Trial. Blood. 2013; 121(3): 468–75.
21. Baliakas P, Hadzidimitriou A, Sutton LA, et al. Recurrent Mutations Refine Prognosis in Chronic Lymphocytic Leukemia. Leukemia. 2015; 29(2): 329–36.
22. Stilgenbauer S, Schnaiter A, Paschka P, et al. Gene Mutations and Treatment Outcome in Chronic Lymphocytic Leukemia: Results from the CLL8 Trial. Blood. 2014; 123(21): 3247–54.
23. Rossi D, Khiabanian H, Spina V, et al. Clinical Impact of Small TP53 Mutated Subclones in Chronic Lymphocytic Leukemia. Blood. 2014; 123(14): 2139–47.
24. Landau DA, Carter SL, Stojanov P, et al. Evolution and Impact of Subclonal Mutations in Chronic Lymphocytic Leukemia. Cell. 2013; 152(4): 714–26.
25. Nadeu F, Delgado J, Royo C, et al. Clinical Impact of the Subclonal Architecture and Mutational Complexity in Chronic Lymphocytic Leukemia. Leukemia. 2018; 32(3): 645–53.
26. Langerbeins P, Giza A, Robrecht S, et al. Reassessing the Chronic Lymphocytic Leukemia International Prognostic Index in the Era of Targeted Therapies. Blood. 2024; 143(25): 2588–98.
27. Fischer K, Bahlo J, Fink AM, et al. Long-Term Remissions after FCR Chemoimmunotherapy in Previously Untreated Patients with CLL: Updated Results of the CLL8 Trial. Blood. 2016; 127(2): 208–15.
28. Eichhorst B, Fink AM, Bahlo J, et al. First-Line Chemoimmunotherapy with Bendamustine and Rituximab versus Fludarabine, Cyclophosphamide, and Rituximab in Patients with Advanced Chronic Lymphocytic Leukaemia (CLL10): An International, Open-Label, Randomised, Phase 3, Non-Inferiority Trial. Lancet Oncol. 2016; 17(7): 928–42.
29. Shanafelt TD, Wang XV, Hanson CA, et al. Tolerability and Long-Term Disease Control by IGHV Mutation Status among Patients with CLL on Ibrutinib Arm of E1912. Blood Adv. 2025; 9(1): 224–8.
30. Shanafelt TD, Wang XV, Hanson CA, et al. Long-Term Outcomes for Ibrutinib-Rituximab and Chemoimmunotherapy in CLL: Updated Results of the E1912 Trial. Blood. 2022; 140(2): 112–20.
31. Moreno C, Greil R, Demirkan F, et al. First-Line Treatment of Chronic Lymphocytic Leukemia with Ibrutinib plus Obinutuzumab versus Chlorambucil plus Obinutuzumab: Final Analysis of the Randomized, Phase III iLLUMINATE Trial. Haematologica. 2022; 107(9): 2108–20.
32. Blombery P, Chatzikonstantinou T, Gerousi M, et al. Resistance to Targeted Therapies in Chronic Lymphocytic Leukemia: Current Status and Perspectives for Clinical and Diagnostic Practice. Leukemia. 2025; 39(9): 2049–60.
33. Tam CS, Thompson PA. BTK Inhibitors in CLL: Second Generation Drugs and Beyond. Blood Adv. 2024; 8(5): 1021–32.
34. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without Obinutuzumab versus Chlorambucil and Obinutuzumab for Treatment-Naive Chronic Lymphocytic Leukaemia (ELEVATE-TN): A Randomised, Controlled, Phase 3 Trial. Lancet. 2020; 395(10232): 1278–91.
35. Shadman M, Munir T, Robak T, et al. Zanubrutinib Versus Bendamustine and Rituximab in Patients With Treatment-Naïve Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma: Median 5-Year Follow-Up of SEQUOIA. J Clin Oncol. 2025; 43(7): 780–7.
36. Wierda WG, Allan JN, Siddiqi T, et al. (a) Ibrutinib Plus Venetoclax for First-Line Treatment of Chronic Lymphocytic Leukemia: Primary Analysis Results From the Minimal Residual Disease Cohort of the Randomized Phase II CAPTIVATE Study. J Clin Oncol. 2021; 39(34): 3853–65.
37. Ghia P, Pluta A, Wach M, et al. Acalabrutinib Versus Investigator's Choice in Relapsed/Refractory Chronic Lymphocytic Leukemia: Final ASCEND Trial Results. HemaSphere. 2022; 6(12): e801.
38. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia. N Engl J Med. 2014; 371(3): 213–23.
39. Munir T, Brown JR, O'Brien S, et al. Final Analysis from RESONATE: Up to Six Years of Follow-up on Ibrutinib in Patients with Previously Treated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma. Am J Hematol. 2019; 94(12): 1353–63.
40. Woyach JA, Jones D, Jurczak W, et al. Mutational Profile of Previously Treated Chronic Lymphocytic Leukemia Patients Progressing on Acalabrutinib or Ibrutinib. Blood. 2024; 144(10): 1061–8.
41. Mashima K, Kuang Y, Fernandes SM, et al. Mutations and Translocations Associated with Venetoclax Resistance in Chronic Lymphocytic Leukemia. Leukemia. 2025; 39(8): 2026–9.
42. Brown JR, Li J, Eichhorst B, et al. Acquired Mutations in Patients with Relapsed/Refractory CLL Who Progressed in the ALPINE Study. Blood Adv. 2025; 9(8): 1918–26.
43. Brown JR, Eichhorst B, Lamanna N, et al. Sustained Benefit of Zanubrutinib vs Ibrutinib in Patients with R/R CLL/SLL: Final Comparative Analysis of ALPINE. Blood. 2024; 144(26): 2706–17.
44. Mato AR, Woyach JA, Brown JR, et al. Pirtobrutinib after a Covalent BTK Inhibitor in Chronic Lymphocytic Leukemia. N Engl J Med. 2023; 389(1): 33–44.
45. Jones JA, Mato AR, Wierda WG, et al. Venetoclax for Chronic Lymphocytic Leukaemia Progressing after Ibrutinib: An Interim Analysis of a Multicentre, Open-Label, Phase 2 Trial. Lancet Oncol. 2018; 19(1): 65–75.
46. Lew TE, Bennett R, Lin VS, et al. Venetoclax-Rituximab Is Active in Patients with BTKi-Exposed CLL, but Durable Treatment-Free Remissions Are Uncommon. Blood Adv. 2024; 8(6): 1439–43.
47. Mato AR, Roeker LE, Jacobs R, et al. Assessment of the Efficacy of Therapies Following Venetoclax Discontinuation in CLL Reveals BTK Inhibition as an Effective Strategy. Clin Cancer Res. 2020; 26(14): 3589–96.
48. Yoon JT, Zhou Y, Mikhaleva M, et al. Characteristics and Outcomes of Patients with Double Refractory and Double Exposed Chronic Lymphocytic Leukemia. Blood Adv. 2025; 9(11): 2808–17.
49. Siddiqi T, Maloney DG, Kenderian SS, et al. Lisocabtagene Maraleucel (Liso-Cel) in R/R CLL/SLL: 24-Month Median Follow-Up of TRANSCEND CLL 004. Blood. 2023; 142(Suppl 1): 330.
50. Danilov A, Fakhri B, Awan FT, et al. Epcoritamab Monotherapy in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia: Results from CLL Expansion and Optimization Cohorts of EPCORE CLL-1. Blood. 2024; 144(Abstract 144): 883.
51. Kater AP, Ye JC, Sandoval-Sus J, et al. Subcutaneous Epcoritamab in Patients with Richter's Syndrome: Early Results from Phase 1b/2 Trial (EPCORE CLL-1). Blood. 2022; 140(Suppl 1): 850–1.
52. Andersen MA, Niemann CU. Immune Failure, Infection and Survival in Chronic Lymphocytic Leukemia in Denmark. Haematologica. 2018; 103(7): e330.
53. Andersen MA, Vojdeman FJ, Klarskov Andersen M, et al. Hypogammaglobulinemia in Newly Diagnosed Chronic Lymphocytic Leukemia Is a Predictor of Early Death. Leuk Lymphoma. 2016; 57(7): 1592–9.
54. Wadhwa PD, Morrison VA. Infectious Complications of Chronic Lymphocytic Leukemia. Semin Oncol. 2006; 33(2): 240–9.
55. Ishdorj G, Streu E, Lambert P, et al. IgA Levels at Diagnosis Predict for Infections, Time to Treatment, and Survival in Chronic Lymphocytic Leukemia. Blood Adv. 2019; 3(14): 2188–98.
56. Riches JC, Davies JK, McClanahan F, et al. T Cells from CLL Patients Exhibit Features of T-Cell Exhaustion but Retain Capacity for Cytokine Production. Blood. 2013; 121(9): 1612–21.
57. Nunes C, Wong R, Mason M, et al. Expansion of a CD8(+)PD-1(+) Replicative Senescence Phenotype in Early Stage CLL Patients Is Associated with Inverted CD4:CD8 Ratios and Disease Progression. Clin Cancer Res. 2012; 18(3): 678–87.
58. Nunes C. Correction: Expansion of a CD8+PD-1+ Replicative Senescence Phenotype in Early Stage CLL Patients Is Associated with Inverted CD4:CD8 Ratios and Disease Progression. Clin Cancer Res. 2012; 18(13): 3714.
59. Roessner PM, Seiffert M. T-Cells in Chronic Lymphocytic Leukemia: Guardians or Drivers of Disease? Leukemia. 2020; 34(8): 2012–24.
60. Tsukada N, Burger JA, Zvaifler NJ, et al. Distinctive Features of 'Nurselike' Cells That Differentiate in the Context of Chronic Lymphocytic Leukemia. Blood. 2002; 99(3): 1030–7.
61. Moreira J, Rabe KG, Cerhan JR, et al. Infectious Complications among Individuals with Clinical Monoclonal B-Cell Lymphocytosis (MBL): A Cohort Study of Newly Diagnosed Cases Compared to Controls. Leukemia. 2013; 27(1): 136–41.
62. Sun C, Tian X, Lee YS, et al. Partial Reconstitution of Humoral Immunity and Fewer Infections in Patients with Chronic Lymphocytic Leukemia Treated with Ibrutinib. Blood. 2015; 126(19): 2213–19.
63. Long M, Beckwith K, Do P, et al. Ibrutinib Treatment Improves T Cell Number and Function in CLL Patients. J Clin Invest. 2017; 127(8): 3052–64.
64. Burger JA, Ghia P, Rosenwald A, et al. The Microenvironment in Mature B-Cell Malignancies: A Target for New Treatment Strategies. Blood. 2009; 114(16): 3367–75.
65. Sharpe C, Davis J, Mason KD, et al. More Than a BTK Inhibitor; Ibrutinib Profoundly Impacts the Function of Cell Mediated Immunity. Blood. 2018; 132(Suppl 1): 4417.
66. de Weerdt I, Hofland T, de Boer R, et al. Distinct Immune Composition in Lymph Node and Peripheral Blood of CLL Patients Is Reshaped during Venetoclax Treatment. Blood Adv. 2019; 3(17): 2642–52.
67. Kater AP, Eichhorst B, Owen C, et al. Long-Term Host Immune Changes Following Treatment with Venetoclax Plus Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia. Blood. 2022; 140(Suppl 1): 7010–12.

68. Moreno C, Solman IG, Tam CS, et al. Immune Restoration with Ibrutinib plus Venetoclax in First-Line Chronic Lymphocytic Leukemia: The Phase 2 CAPTIVATE Study. Blood Adv. 2023; 7(18): 5294–5303.
69. Francis S, Karanth M, Pratt G, et al. The Effect of Immunoglobulin VH Gene Mutation Status and Other Prognostic Factors on the Incidence of Major Infections in Patients with Chronic Lymphocytic Leukemia. Cancer. 2006; 107(5): 1023–33.
70. Andersen MA, Rostgaard K, Niemann CU, et al. Antimicrobial Use before Chronic Lymphocytic Leukemia: A Retrospective Cohort Study. Leukemia. 2021; 35(3): 747–51.
71. Varughese T, Taur Y, Cohen N, et al. Serious Infections in Patients Receiving Ibrutinib for Treatment of Lymphoid Cancer. Clin Infect Dis. 2018; 67(5): 687–92.
72. Coutré SE, Barrientos JC, Brown JR, et al. Management of Adverse Events Associated with Idelalisib Treatment: Expert Panel Opinion. Leuk Lymphoma. 2015; 56(10): 2779–86.
73. Herishanu Y, Avivi I, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 Vaccine in Patients with Chronic Lymphocytic Leukemia. Blood. 2021; 137(23): 3165–73.
74. Scarfò L, Chatzikonstantinou T, Rigolin GM, et al. COVID-19 Severity and Mortality in Patients with Chronic Lymphocytic Leukemia: A Joint Study by ERIC, the European Research Initiative on CLL, and CLL Campus. Leukemia. 2020; 34(9): 2354–63.
75. Šimkovič M, Turcsányi P, Špaček M, et al. COVID-19 in Patients with Chronic Lymphocytic Leukemia: A Multicenter Analysis by the Czech CLL Study Group. Ann Hematol. 2023; 102(4): 811–17.
76. Campanella A, Capasso A, Heltai S, et al. Additional Booster Doses in Patients with Chronic Lymphocytic Leukemia Induce Humoral and Cellular Immune Responses to SARS-CoV-2 Similar to Natural Infection Regardless Ongoing Treatments. Am J Hematol. 2024; 99(4): 745–50.
77. Chatzikonstantinou T, Scarfò L, Karakatsoulis G, et al. Other Malignancies in the History of CLL: An International Multicenter Study Conducted by ERIC, the European Research Initiative on CLL, in HARMONY. eClinicalMedicine. 2023; 65: 102307.
78. Tsimberidou AM, Wen S, McLaughlin P, et al. Other Malignancies in Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma. J Clin Oncol. 2009; 27(6): 904–10.
79. Wierda WG, Allan JN, Siddiqi T, et al. (b) Ibrutinib Plus Venetoclax for First-Line Treatment of Chronic Lymphocytic Leukemia: Primary Analysis Results from the Minimal Residual Disease Cohort of the Randomized Phase II CAPTIVATE Study. J Clin Oncol. 2021; 39(34): 3853–65.
80. Kater AP, Owen C, Moreno C, et al. Fixed-Duration Ibrutinib-Venetoclax in Patients with Chronic Lymphocytic Leukemia and Comorbidities. NEJM Evid. 2022; 1(7): EVIDoa2200006.
81. Munir T, Girvan S, Cairns DA, et al. Measurable Residual Disease-Guided Therapy for Chronic Lymphocytic Leukemia. N Engl J Med. 2025 Jun 15.
82. Ryan CE, Davids MS, Hermann R, et al. MAJIC: A Phase III Trial of Acalabrutinib + Venetoclax versus Venetoclax + Obinutuzumab in Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma. Future Oncol. 2022; 18(33): 3689–99.
83. Casan JML, Seymour JF. Degraders Upgraded: The Rise of PROTACs in Hematological Malignancies. Blood. 2024; 143(13): 1218–30.
84. Zhong G, Kong R, Feng S, et al. Targeted Protein Degradation in Hematologic Malignancies: Latest Updates from the 2023 ASH Annual Meeting. J Hematol Oncol. 2024; 17(1): 14.
85. Liu J, Li S, Wang Q, et al. Sonrotoclax Overcomes BCL2 G101V Mutation-Induced Venetoclax Resistance in Preclinical Models of Hematologic Malignancy. Blood. 2024; 144(3): 1825–36.
86. Zhou K, Sun M, Wei X, et al. Updated Efficacy and Safety Results of Lisaftoclax (APG-2575) in Patients with Heavily Pretreated Chronic Lymphocytic Leukemia (CLL): Pooled Analyses of Two Clinical Trials. Blood. 2023; 142(Suppl 1): 1900.
87. Siddiqi T, Maloney DG, Kenderian SS, et al. Lisocabtagene Maraleucel in Chronic Lymphocytic Leukaemia and Small Lymphocytic Lymphoma (TRANSCEND CLL 004): A Multicentre, Open-Label, Single-Arm, Phase 1–2 Study. Lancet. 2023; 402(10402): 641–54.