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GUIDELINES - EVIDENCE-BASED

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EHA Guidelines on management of chronic lymphocytic leukemia and Richter transformation

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Abstract

Previous editions of the European guidelines for the management of chronic lymphocytic leukemia (CLL) were developed by experts in CLL under the auspices of the European Society for Medical Oncology (ESMO). These previous editions have served as a reference text for many physicians caring for patients with CLL. The current, 2026 edition, represents the new, updated guidelines that, for the first time (and in agreement with ESMO), were written on behalf of the European Hematology Association (EHA), which will be solely responsible for subsequent editions, published annually to keep pace of the fast-moving field of CLL research and clinical applications. The new guidelines support approaching the management of CLL in a more holistic fashion, from the initial diagnosis (including active surveillance) to treatment need, with particular emphasis on the interplay between disease- and patient-specific criteria for decision-making, to the latest stage of possible Richter transformation, which is now specifically mentioned in the title of the guidelines. These new recommendations are the result of a consensus reached among medical experts from several European countries and, for the first time, have involved patient advocacy representatives, which is in line with EHA standard operating procedures for clinical practice guideline development. Updates in terms of treatment options include the recently European Medicines Agency-approved, time-limited combination therapy acalabrutinib and venetoclax ± obinutuzumab as first-line treatment, and continuous pirtobrutinib for patients exposed to covalent Bruton's tyrosine kinase inhibitors in the relapsed/refractory setting.

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INTRODUCTION AND METHODOLOGY

The following clinical practice guidelines for diagnosis, treatment, and follow-up in patients with chronic lymphocytic leukemia (CLL) and Richter transformation (RT) were, for the first time, written solely under the auspices of the European Hematology Association (EHA), following the spirit and aims of previous versions coordinated by the European Society for Medical Oncology (ESMO).

Starting with this update, EHA has taken the responsibility, in agreement with ESMO, to gather representative hematologists from most European countries and with relevant expertise in the management and treatment of patients with CLL, but including now also experts in molecular diagnosis and prognostic stratification. More emphasis is now given to the overall management of patients, from the moment of the initial diagnosis through the active surveillance period, to the time when they need therapy, including the ensuing burden of subsequent relapses and lines of therapies up to rare, but possible, RT. To this aim, patient advocacy representatives are now also involved, bringing the unique perspective of the people who actually are carrying the burden and distress of the disease.

Updates are now planned annually, given the fast pace of the developments in the field, which is marked by a continuous flurry of novel diagnostic/prognostic procedures, as well as new drug approvals.

For this specific edition, the update follows the approval of the time-limited combination therapy acalabrutinib + venetoclax ± obinutuzumab as first-line treatment, and of continuous pirtobrutinib for patients exposed to covalent Bruton's tyrosine kinase (BTK) inhibitors in the relapsed/refractory (R/R) setting.

Recommendations are based on available scientific data and the authors' collective expert opinion through a consensus reached using the methodology as described by EHA standard operating procedures for clinical practice guideline development.[1] The relevant literature, including conference proceedings, where relevant, was selected by the expert authors. The European Medicines Agency (EMA) approval status at the time of completion of these guidelines was added, where relevant.

We use Level of Evidence and Grade of Recommendation as described in Tables 1A and 1B for evidence-based recommendations.[2] We are also providing for the first time the Magnitude of Clinical Benefit Scores for Hematologic Malignancies (MCBS:H), which indicates with a score of 4 or 5 a substantial benefit in the noncurative setting.[3,4]

TABLE 1A Level of evidence.

I	Evidence from at least one large randomized controlled trial (RCT) of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions

TABLE 1B Grade of recommendation.

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

INCIDENCE AND EPIDEMIOLOGY

CLL and small lymphocytic lymphoma (SLL) are considered a single entity by the World Health Organization (WHO) 2022 classification (Table 2).[5] The incidence rate of CLL in Europe is 4.7 per 100,000 according to WHO.[6] The median age at diagnosis is 70 years and men are affected nearly twice as much as women. In Western countries, the death rate has decreased from 2.0 per 100,000 decades ago to 1.0 per 100,000 as reported for the 2018–2022 time period.[7]

DIAGNOSIS, PATHOLOGY, AND MOLECULAR BIOLOGY

Diagnosis

A diagnosis of CLL is established by immunophenotyping using flow cytometry to document the presence of $\geq 5 \times 10^9$/L clonal B lymphocytes that are positive for CD19, CD5, and CD23.[5,8,9] CLL cells typically express low levels of CD20, CD79B, and surface immunoglobulin, with either κ or λ immunoglobulin light-chain restriction or (apparent) absence at flow analysis.[5,8] Additional phenotyping (CD43, CD200, ROR1) may assist in differential diagnosis from other clonal B-lymphoproliferations.[10] SLL, which accounts for about 5% of cases, lacks significant leukemic manifestation ($< 5 \times 10^9$/L clonal B cells) and presents with involvement of secondary lymphoid tissues (Table 2).

Monoclonal B-cell lymphocytosis (MBL) is characterized by the presence of circulating monoclonal B cells with a CLL phenotype, yet at a concentration lower than required for the clinical diagnosis of CLL, without cytopenias, pathological enlargement of secondary lymphoid tissues, or B symptoms. MBL, found in otherwise healthy individuals, is classified into two subtypes based on the number of circulating, CLL-like B cells[5,8]: CLL/SLL-type MBL ($< 5 \times 10^9$/L and $\geq 0.5 \times 10^9$/L) and low-count CLL-type MBL ($< 0.5 \times 10^9$/L) (Table 2). CLL/SLL-type MBL may evolve into CLL requiring therapy at a rate of 1% per year,[11] whereas low count MBL is not practically associated with overt CLL, albeit persists with time.[12,13]

Biomarker-guided stratification in patients with CLL

The clinical course of CLL can be very heterogeneous, reflecting its underlying biological heterogeneity.[14–17] This highlights the need for biomarkers capable of predicting outcomes, particularly the response to a given treatment. Many biomarkers have been identified and found to carry an independent prognostic value. However, patient stratification in clinical practice is in particular based on the somatic hypermutation (SHM) status of clonotypic-rearranged immunoglobulin heavy variable (IGHV) genes and *TP53* aberrations.

IGHV gene SHM status

The SHM status of the IGHV genes dichotomizes CLL into two major categories with different biology and natural history.[14,15] Patients bearing IGHV genes with minimal or no SHM (those differing from

TABLE 2 Definition of CLL, SLL, and MBL.

Disease entity	Subtype	Clonal B lymphocytes in peripheral blood	Lymph nodes or splenomegaly or hepatomegaly
Chronic lymphocytic leukemia (CLL)	–	$\geq 5 \times 10^9$/L	No/Yes (possible for Binet Stage A)
Small lymphocytic lymphoma (SLL)	–	$< 5 \times 10^9$/L	Yes
Monoclonal B-cell lymphocytosis (MBL)	CLL/SLL-type MBL (previously high-count MBL)	$\geq 0.5 \times 10^9$/L, but $< 5 \times 10^9$/L	No
	Low-count MBL/clonal B-cell expansion	$< 0.5 \times 10^9$/L	No

the germline by 2% maximum or with ≥98% identity) are classified as IGHV-unmutated (U-CLL); these patients often carry adverse prognostic genetic features and typically experience more rapidly progressive disease. In contrast, patients bearing IGHV genes with a significant SHM burden (<98% identity to the germline) are classified as IGHV-mutated CLL (M-CLL) and generally experience indolent disease.[14,15] The SHM status of the IGHV genes robustly predicts time to first treatment and, more importantly, discriminates patients with different durations of response to different treatments.[18,19] Moreover, SHM status remains stable over time, in contrast to other biomarkers (i.e., genomic aberrations by FISH or cytogenetics or *TP53* mutations), which may change with disease evolution.[20]

However, not all U-CLL or M-CLL cases are equivalent,[21] as exemplified by stereotyped subsets (i.e., subgroups of cases expressing [quasi]identical B-cell receptor immunoglobulin).[18] The most clinically relevant subsets are #2[22,23] and #8[24,25] both of which are associated with aggressive disease. However, most evidence regarding the clinical and predictive significance of subsets derives from retrospective studies and is still inconclusive, particularly concerning response to targeted therapy.[26]

Determination of the SHM status of IGHV genes is performed by DNA/cDNA sequencing using either Sanger or next-generation sequencing (NGS)[19]; by default, sequencing also provides information regarding subset membership if performed according to European Research Initiative on CLL (ERIC) recommendations (i.e., sequencing covers the entire variable heavy complementarity-determining region 3 [VH CDR3] region). NGS offers unprecedented depth of analysis, but comes with challenges, including, among others, the relevance of the 98% germline identity cut-off value, the importance of intraclonal diversification, and the significance, if any, of minor clonotypes coexisting with the major one (especially when their SHM status differs).

Recommendation	Determine SHM status of IGHV genes following ERIC recommendations[19] in all patients with CLL before first-line treatment
Relevant for:	All patients in need of first-line therapy
Timepoint:	Before first-line treatment
Level of Evidence	II
Grade of Recommendation	B

TP53 gene aberrations

A *TP53* aberration is defined as either the deletion of the *TP53* gene locus on 17p13 [del(17p)] or the presence of a mutation (i.e., a somatic change in the sequence of the *TP53* gene [*TP53*mut]).

The independent negative impact of *TP53* aberrations on overall survival (OS) and chemoimmunotherapy (CIT) response has been well documented, and assessing both types of aberrations has become a part of the diagnostic/prognostic assessment.[27] The frequency of *TP53* aberrations is low at diagnosis (5%–10% of patients), higher in patients entering first-line treatment (10%–20%), and increases further at later disease stages, predominantly in patients treated with CIT, and RT (up to 50%).[28–31] The deletion of the 17p13 locus typically co-occurs with mutations of the second *TP53* allele. They may also be present independently, with a sole del(17p) being less frequent than a sole *TP53* mutation, which might be also associated with inactivation of the second allele via copy-neutral loss of heterozygosity. *TP53* aberrations are often subclonal, and the concurrent presence of several distinct *TP53*-aberrant subclones is not exceptional.[32]

The presence of *TP53* aberrations associates with a shorter time to first treatment, at least in patients with U-CLL.[21,33] In CIT-treated patients, *TP53* aberrations shorten OS regardless of number of affected alleles and clone size.[27,34,35] Further information on the impact of *TP53* aberrations for targeted treatment of CLL is included in Section 6 of this publication.

Based on the current evidence, both del(17p) and *TP53* gene mutations should be assessed before each line of treatment. Fluorescent in-situ hybridization (FISH) is recommended for detecting del(17p), while NGS is the preferred method for detecting *TP53* mutations. In contrast to Sanger sequencing, NGS is capable of detecting *TP53* mutations present in small subpopulations that possess a selective advantage under pressure of DNA-damaging therapy, and that could undergo a clonal expansion.[36] The variant allele frequency (VAF) threshold for determining clinical significance in patients undergoing targeted therapy remains undefined, and reliance on previously established, arbitrary Sanger-like cut-offs is no longer scientifically justifiable.[37] Moreover, low-VAF mutations may represent a major clone in a sample with low cancer-cell fraction. Because targeted agents act independently of the p53 pathway, they are assumed not to directly accelerate the expansion of *TP53*-deficient clones.[29,38] Issues therefore remain, such as the impact of allele constitution, oligoclonality, and the clone size in different targeted treatment regimens.

Recommendation	Determine *TP53* aberrations [del(17p) and *TP53* gene mutations] by FISH and NGS following ERIC recommendations[37] in all patients with CLL before each treatment line
Relevant for:	All patients in need of therapy at any line
Timepoint:	Before treatment at any line
Level of Evidence	II
Grade of Recommendation	B

Other genomic aberrations

Aberrations in genes other than *TP53* (e.g., *SF3B1*, *NOTCH1*, *POT1*, *XPO1*, *NFKBIE*, etc.) have been associated with clinical outcomes in patients with CLL,[39–41] with a possible differential impact in M-CLL versus U-CLL.[21] However, existing evidence derives from either unplanned post-hoc analyses of clinical trial cases or from retrospective series, thus precluding firm conclusions from being drawn. On these grounds, testing for such aberrations is not recommended in routine clinical practice, and should be reserved for research purposes only.

In recent years, there has been a revival of interest in cytogenetics in CLL, particularly regarding complex karyotype (CK).[42,43] In CLL, CK is defined as the presence of ≥3 clonal, structural, or numerical abnormalities, with mounting evidence from (mostly) retrospective studies suggesting that ≥5 aberrations ("high-CK") confers the worst prognosis.[43] CK is associated with advanced-stage disease, U-CLL, and, particularly, *TP53* aberrations. High-CK has emerged as an independent prognostic factor for inferior progression-free survival (PFS) in patients with wild-type *TP53* treated with venetoclax-based combinations.[44] However, the available evidence is still not robust enough to allow for recommendation.[45] The use of CK outside of the research setting is further precluded by technical limitations and limited reproducibility between testing for CK by single-nucleotide polymorphism array-based methods and stimulated cytogenetics.

Because CLL is familial, but not hereditary, genomic testing for family members is not indicated.

Recommendation	Due to limited reproducibility, assessment of CK is not recommended before treatment initiation outside clinical trials
Relevant for:	All patients in need of therapy at any line
Timepoint:	Before treatment at any line
Level of Evidence	III
Grade of Recommendation	B

STAGING AND PROGNOSTIC SCORES

There are two clinical staging systems for CLL, both carrying prognostic value when applied at the time of diagnosis. These were the first prognostic scores to be described in CLL.

- The modified Rai classification defines five different stages and three prognostic subgroups[46,47]
- The Binet staging system, more frequently used in Europe, distinguishes three subgroups[48]

Both staging systems use physical examination and full blood count for risk-group classification, and neither requires nor considers radiological imaging (Table 3).[49]

Patients with asymptomatic early-stage disease (Binet A or Binet B) do not need any further risk assessment, such as biological profiling of CLL. Several clinical trials were not able to show any benefit in terms of OS following treatment, even with targeted drugs, in asymptomatic early-stage patients in the presence of high-risk disease characteristics.[50–53]

Classification as high-risk disease (i.e., neither by International Prognostic nor Index for Chronic Lymphocytic Leukemia[54] or International Prognostic Score for Asymptomatic Early-Stage CLL[55]) is not an indication to start treatment for CLL in asymptomatic patients without active disease, as defined by International Workshop on CLL (iwCLL) guidelines.

Although SLL is staged using the Lugano classification system, as other types of lymphoma,[49] risk assessment and treatment indication for SLL correspond to those for CLL.

NEED FOR TREATMENT

Active disease requiring therapy is defined by the IWCLL guidelines.[9]

In patients with symptomatic or "active" and advanced CLL (with cytopenias—Binet C or Rai III/IV—or large lymphadenopathies), additional tests are recommended before treatment to assess patient's conditions and disease characteristics that may influence choice of therapy.

Pretreatment evaluation includes history and physical examination, laboratory tests, and imaging (Table 4). Additional to the iwCLL 2018 guidelines, radiographic imaging with computed tomography (CT) or magnetic resonance imaging (MRI) scan of neck, chest, abdomen, and pelvis is recommended to assess the tumor load and risk of tumor lysis syndrome whenever treatment with the BCL-2 (B-cell lymphoma-2) inhibitor venetoclax is considered.

According to iwCLL 2018 at least 1 of the following criteria should be met:

1. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia. Cut-off levels of hemoglobin <100 g/L or platelet counts <100 G/L are generally regarded as indication for treatment. However, in some patients, platelet counts <100 G/L may remain stable over a long period; this situation does not automatically require therapeutic intervention.

TABLE 3 Binet and Rai classification system.

Binet stage	Rai stage	Risk category	Lymphocytosis	Lymphadenopathy[a]	Splenomegaly Hepatomegaly[a]	Hemoglobin (g/L)[b]	Platelets (G/L)[b]
Binet A	Rai 0	Low risk	Present	None to <3 absent (Rai)	None to <3 Absent (Rai)	≥110/100 for Rai/Binet	≥100
Binet B	Rai I	Intermediate risk	Present	≥3 Present (Rai)	≥3 Absent (Rai)	≥110/100 for Rai/Binet	≥100
	Rai II		Present	≥3 Irrelevant (Rai)	≥3 Mandatory (Rai)	≥110/100 for Rai/Binet	≥100
Binet C	Rai III	High risk	Present	Irrelevant	Irrelevant	<110/100 for Rai/Binet	≥100
	Rai IV		Present	Irrelevant	Irrelevant	Irrelevant	<100

Note: SLL is staged using the Lugano classification system.

[a]Enlarged lymph nodes ≥1 cm in diameter or organomegaly by palpation.

[b]Due to bone marrow infiltration (after i.e., excluding autoimmune cytopenia).

TABLE 4 Pretherapy testing.

History:	1. Focus on symptomatic CLL: B symptoms (weight loss, fevers, night sweats, and fatigue), infections 2. History of infections (frequency, severity) and vaccinations 3. Focus on relevant comorbidities: cardiovascular, hepatic, or renal disease 4. Co-medications with impact on CLL treatment: anticoagulation, antiplatelet therapy, and potential interactions
Physical examinations:	1. ECOG performance status 2. Size of lymph nodes, splenomegaly, hepatomegaly 3. Complete examination of heart, lungs, abdomen, and skin
Laboratory tests:	1. Complete blood count and differential 2. Direct antiglobulin test 3. Serum chemistry: renal function, hepatic function, lactate dehydrogenase, uric acid, beta-2-microglobulin, immunoglobulin IgA, IgG, IgM 4. Serology for hepatitis B virus, hepatitis C virus, HIV 5. Consider bone marrow biopsy in case of severe/unclear cytopenia for evaluation of percentage of CLL infiltration vs. autoimmune cytopenia
Genetic testing: (of peripheral blood lymphocytes)	1. FISH (or array comparative genomic hybridization for del(17p) 2. *TP53* gene mutations (by sequencing, NGS preferred), reported according to ERIC recommendation 3. Molecular analysis for IGHV gene mutation status reported according to ERIC recommendations[a]
Cardiac testing:	1. Electrocardiogram, cardiac history, and cardiovascular risk assessment in all patients whenever treatment with a BTK inhibitor is considered 2. If previous cardiac history or ongoing uncontrolled cardiac comorbidities refer to a cardiologist
Radiological imaging:	1. Only required in specific clinical circumstances, for example, CT scans of neck, chest, abdomen and pelvis for evaluation of risk for tumor lysis syndrome only in patients for whom the BCL-2 inhibitor venetoclax is considered.

[a]IGHV gene mutation status remains stable during the disease course, hence needs to be determined only once, usually before first-line therapy. Genetic testing for deletion of chromosome 17 by FISH and sequencing for detection of *TP53* mutations as well as all other tests are required before first and any subsequent lines of treatment.

2. Massive lymph nodes (i.e., >10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
3. Massive (i.e., >6 cm below the left costal margin) or progressive or symptomatic splenomegaly.
4. Progressive lymphocytosis with an increase of >50% over a 2-month period, or lymphocyte doubling time (LDT) < 6 months. LDT can be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months; patients with initial blood lymphocyte counts >30 G/L may require a longer observation period to determine the LDT. Factors contributing to lymphocytosis other than CLL (e.g., infections, steroid administration) should be excluded.
5. Autoimmune complications including anemia or thrombocytopenia poorly responsive to corticosteroids.
6. Symptomatic or functional extranodal involvement (e.g., skin, kidney, lung, spine).
7. Disease-related symptoms as defined by any of the following:
   a. Unintentional weight loss of >10% within the previous 6 months.
   b. Significant fatigue (i.e., Eastern Cooperative Oncology Group [ECOG] performance status of 2 or worse; cannot work or unable to perform usual activities).
   c. Fevers >100.5°F or 38.0°C for 2 or more weeks without evidence of infection.
   d. Night sweats for >1 month without evidence of infection.

Recommendation	Treatment should only be initiated when iwCLL criteria are met
Relevant for:	All patients with progression
Level of Evidence	I[a]
Grade of Recommendation	A

[a]This has only been properly tested in the treatment-naive setting; implemented in the R/R CLL setting with very limited evidence.

COMPREHENSIVE MANAGEMENT DURING ACTIVE SURVEILLANCE: GENERAL APPROACH INCLUDING MANAGEMENT OF AUTOIMMUNE CYTOPENIAS (AIC)

Here, we provide a concise description of the minimal requirements for the management of patients following diagnosis of CLL during active surveillance.

Infection prophylaxis

Vaccinations

A hallmark of CLL is progressive immunodeficiency.[56] Vaccination against pneumococcus, varicella zoster, and hepatitis B viruses is advised, despite somewhat impaired response,[57–61] while less evidence is present for respiratory syncytial virus. Vaccination against seasonal viruses, such as influenza and SARS-CoV-2/COVID19, should be administered and repeated according to the national recommendations.

Specifically, the varicella zoster virus (VZV) recombinant vaccine against VZV glycoprotein E (Shingrix®) is safe, and has good immunogenicity and efficacy (even in heavily pre-treated patients).[62] If a patient has a history of shingles, (val)aciclovir could be considered as secondary prophylaxis in addition to the VZV vaccine.

At diagnosis, conjugate pneumococcal vaccine 20-valent (PCV20) is recommended, followed at least 2 months later by polysaccharide pneumococcal vaccine polyvalent (PPV23). Vaccination should be repeated every 5 years. Patients who have been previously vaccinated with PPV23 only should receive a "catch-up" dose of PCV20.

Live vaccines (measles/mumps/rubella, live polio, yellow fever, and varicella vaccine [Zostavax®]) should not be given. Patients should avoid contact with children who have received the live nasal influenza vaccine or the polio oral vaccine for seven days.

Recommendation	Vaccination against pneumococcus, varicella zoster, and hepatitis B viruses
Relevant for:	All patients under surveillance, even with expected impaired response to vaccination
Level of Evidence	III
Grade of Recommendation	B

Recommendation	Seasonal repetitive vaccination against influenza and SARS-CoV-2/COVID19
Relevant for:	All patients under surveillance, even with expected impaired response to vaccination
Level of Evidence	III
Grade of Recommendation	B

Recommendation	No live vaccines should be given
Relevant for:	All patients
Level of Evidence	III
Grade of Recommendation	B

Antimicrobial prophylaxis

Recommendation	Antimicrobial prophylaxis is not generally recommended
Relevant for:	All patients
Level of Evidence	IV
Grade of Recommendation	D

Immunoglobulin replacement therapy

The incidence of recurrent infections combined with hypogammaglobulinemia increases with duration of CLL. Immunoglobulin (Ig) replacement therapy is advised for patients who suffer recurrent or acute infections and have a total IgG <4 g/L.[63] Subcutaneous Ig preparations are associated with higher IgG trough levels, fewer adverse events, and improved patient quality of life compared to intravenous formulations.[64–66]

Recommendation	Ig replacement is only advised with recurrent symptomatic or active infections needing hospitalization, in addition to laboratory-confirmed hypogammaglobulinemia
Relevant for:	All patients with recurrent symptomatic or active infections in addition to laboratory confirmed hypogammaglobulinemia
Level of Evidence	II
Grade of Recommendation	B

Prevention of secondary cancers and lifestyle

Patients with CLL have an increased risk for other cancers, even prior to receiving treatment.[67] Family counselling should only be considered in patients with a strong family history of CLL, other cancers, autoimmune disease or immunodeficiency, or a confirmed diagnosis of constitutional cancer syndromes (e.g., Li Fraumeni syndrome). Polygenic single-nucleotide polymorphisms conferring a higher risk for familial CLL remain an area of active research and should not be screened for.[68] All patients should be informed of the availability of cancer prevention screenings for the general population and should be motivated particularly to join them. They should also be informed of the importance of non-smoking due to the increased risk of lung cancer and the use of ultraviolet protection due to the skin cancer risk. Need for regular skin assessment by a dermatologist or general practitioner should be considered with all patients, in particular in those considered at risk of skin cancer (e.g., light skin combined with sun exposure).

Recommendation	All patients should be informed of the availability of cancer prevention screenings and should be motivated particularly to join them
Relevant for:	All patients
Level of Evidence	III
Grade of Recommendation	B

Management of AIC

AIC has been reported in 5%–10% of patients during their CLL course, and precedes a diagnosis of CLL in 9% of cases.[69] A bone marrow biopsy may be needed to differentiate between CLL involvement leading to cytopenia and AIC. Many patients present no concomitant indication to treat the underlying CLL, and can be managed with immunosuppression together with supportive measures (as in idiopathic AIC).[70]

Autoimmune hemolytic anemia

Up to 33% of patients with CLL have a positive direct antiglobulin test at some stage, but overt warm autoimmune hemolytic anemia (wAIHA) occurs less often.[71] For patients with wAIHA and concurrent CLL not meeting iwCLL criteria for treatment, immunosuppression is recommended before considering CLL-directed therapy.

Most interventional studies have focused on studying wAIHA irrespective of the underlying cause. Two small, randomized studies demonstrate superiority of steroids + rituximab versus steroids alone in patients with active wAIHA with regards to response rates and duration.[72] If CLL-directed therapy is indicated in line with iwCLL criteria, BTK or BCL-2 inhibitors in combination with an anti-CD20 antibody may be an option to control wAIHA as well as the underlying CLL.[73]

Cold agglutinin disease

Cold agglutinin disease should be treated by keeping patients and transfusions warm. Patients needing medical intervention should receive rituximab monotherapy in the first line as steroids cause more adverse events and are less effective.[74]

Immune thrombocytopenia (ITP)

Approximately 2%–5% patients with CLL develop ITP, mainly when not receiving CLL-directed treatment[75,76]; about 30% of cases also have a history of AIHA (Evans syndrome). Response to first-line treatment with steroids or intravenous Ig is 50%–60%.[71] Weekly rituximab for 4 weeks is an effective treatment.[77] The thrombopoietin-receptor agonist eltrombopag has shown responses in CLL-associated ITP in a phase 2 study.[78] Splenectomy is an exceptional procedure in selected refractory cases. However, before considering second- or third-line therapy of ITP, treatment of CLL is recommended.

Other autoimmune manifestations

Pure red cell aplasia and autoimmune neutropenia are rare complications with an incidence of <1%. The treatment approach is the same as for AIHA.[79]

Recommendation	**Patients with an established diagnosis of AIC and requirement of treatment for CLL should receive CLL treatment as recommended for all other CLL**
	Patients without need of treatment for CLL should receive corticosteroid treatment ± Ig(s) In case of unsatisfactory response, the anti-CD20 antibody rituximab may be used, or CLL treatment should be started
Relevant for:	All patients with CLL and AIC
Level of Evidence	IV
Grade of Recommendation	A

Psychological implications, support, and lifestyle

CLL is a chronically relapsing and remitting leukemia. It is being diagnosed at a younger patient age than in the past due to easier access to blood testing. It is therefore particularly important that patients can establish a long-term relationship of trust with their physician and other healthcare professionals.

A diagnosis of CLL often comes as a total surprise, and can be overwhelming for patients and their families, who may find it difficult to understand, before the complexities of treatments, the concept of active monitoring without an intervention, resulting in "watch, wait, worry," right at the time of the initial diagnosis when the word "leukemia" bears dramatic scenarios in the public domain.[80] Patients will expect and are entitled to be honestly informed about their disease, and in particular of the peculiarities in comparison to other hematological malignancies where interventions are immediately required.

Physicians should be encouraged to differentiate the timing of the follow-up according to the dynamic and clinical behavior of the disease throughout time. Analysis of other molecular prognostic factors should be limited and encouraged to patients in need of treatment. Patients should be empowered to implement lifestyle measures like good hand hygiene to reduce risk of infections, while informing about the importance of continued social interactions to reduce risk of isolation, emphasizing that contact infection can be largely prevented by hand sanitizers, and that risk of infection in the outdoor setting is very limited. A healthy diet without processed ingredients, aerobic exercise, and managing fatigue by adjustment of daily activities are strongly advised, along with medical interventions such as vaccination and cancer screenings. The role of vitamin D and other supplements in prevention of disease progression remains uncertain.[81,82]

Recommendation	**Vitamin D and other supplements do not have to be prescribed routinely for CLL, because their benefit with respect to prevention of progressing disease is uncertain**
Relevant for:	All patients
Level of Evidence	III
Grade of Recommendation	C

Support to people living with CLL

Regardless of the disease phase, patients with CLL have diverse needs. A patient-centered approach should take into account different aspects, such as the spectrum of symptoms and clinical manifestations of the disease, the patient's age and overall physical condition (including comorbidities), the treatment aim, the medication plan and its impact on the quality of life, life expectancy, lifestyle and exposures (including concurrent medication), patient preferences, and health literacy, among others.[10] Some of these aspects are dynamic by nature, adding further difficulties in adequately addressing the individual patient's needs.

Communication with the healthcare team and the attending physician is very important throughout the disease trajectory, especially when decisions are to be made or transitions are taking place, for example when a new therapy option is discussed or when the goal of care changes.[83]

Patient associations are another important vehicle for enhancing CLL-related literacy. Attending peer-group meetings and interacting with peers may help patients feel part of a wider community and, thus, develop a sense of belonging. Seeing others who had been diagnosed with CLL years previously and listening to their stories can reduce patients' fears and give hope, making them feel more certain and more in control of their future, as well as more empowered to communicate better with their healthcare team. This reinforces the potential for applying patient-centered and integrated care,[84] leading to higher compliance during follow-up and lower levels of stress in daily life.

National patient support organizations are a valuable resource for people affected by a diagnosis of CLL (not only patients but also care partners and families). More generally, international non-profit organizations worldwide can provide access to reliable information, support, and peer connection to aid empowerment. Examples of resources available for use by all relevant stakeholders (including people living with CLL and their care providers, patient advocacy groups, and healthcare professionals) are those offered by:

- CLL Advocates Network (CLLAN) directory of organizations and resources: https://www.clladvocates.net/.
- PEOPLE WITH CLL-ERIC: https://ericll.org/for-patients/people-with-cll/.

FIRST-LINE TREATMENT FOR CLL

Given the availability of multiple, similarly effective agents for treatment-naive CLL, treatment selection should be guided by a range of factors beyond drug efficacy alone. Key considerations include *TP53* aberrations and IGHV mutational status, patient preference,

ECOG performance status, and the presence of comorbid conditions (in particular cardiovascular conditions including hypertension), as well as duration of treatment and method of administration, the treatment toxicity profile, and potential drug–drug interactions (Figure 2). Dose modifications may be required in patients with renal impairment, hepatic dysfunction, or polypharmacy. Drug–drug interactions must be carefully assessed, particularly with venetoclax, which is metabolized via cytochrome P450, family 3, subfamily A (CYP3A), and may interact with azoles, macrolides, or other commonly used medications. Participation within a clinical trial should also be encouraged whenever possible. For greater clarity, the various treatment options have been categorized into time-limited, continuous, and those for patients with *TP53* aberrations.

Response assessment should be done according to the iwCLL criteria, which differentiate between clinical practice and clinical trials. In clinical practice specific examinations as CT scans or bone marrow biopsy are not routinely required unless clinically indicated.

Time-limited treatment

Time-limited treatment, typically based on combinations including the BCL-2 antagonist venetoclax, either in combination with a covalent BTK inhibitor or/and the CD20 antibody obinutuzumab, induces deep responses, limits the emergence of resistant clones, and reduces long-term toxicity. Two phase III RCTs have outlined the superiority of venetoclax + obinutuzumab to CT regimens (chlorambucil + obinutuzumab, bendamustine + rituximab [BR], and fludarabine + cyclophosphamide + rituximab [FCR]) in terms of PFS and treatment-free interval (clinical trials CLL14 and CLL13). Long-term follow-up data for CLL14 (venetoclax + obinutuzumab vs. chlorambucil, obinutuzumab) in 432 patients with treatment-naive disease with coexisting comorbidity burden revealed a median PFS of 76.2 months (hazard ratio [HR]: 0.40; P < 0.0001).[85] For venetoclax + obinutuzumab-treated patients, a shorter PFS was noted in the unmutated IGHV group, and a median PFS not reached for patients with mutated IGHV (HR: 2.66; 95% confidence interval [CI]: 1.63, 4.34). Similar results were obtained within the CLL13 study for patients with low comorbidity burden comparing FCR or BR with venetoclax + rituximab, venetoclax + obinutuzumab, and venetoclax + obinutuzumab + ibrutinib. Five-year PFS was higher with venetoclax + obinutuzumab + ibrutinib (85.5%) and venetoclax + obinutuzumab (81.8%) versus venetoclax, rituximab (70.1%) and CIT (62.0%).[86] However, infection rates were higher with the triple combination (Grade 3 and 4 infections: 21%). Venetoclax + obinutuzumab was superior to the rituximab combination.

Combining venetoclax with covalent BTK inhibitors is another option for time-limited treatment. With ibrutinib, high efficacy has been observed in three phase 3 RCTs (GLOW, FLAIR, and CLL17) and in the phase 2 CAPTIVATE study.[87–90] Venetoclax + ibrutinib, given as time-limited treatment for a total of 15 months within the GLOW study in older (age ≥65 years) or unfit patients, yielded PFS rates of 59.9% after a median of 64 months.[89] The CAPTIVATE study enrolled younger patients (age ≤70 years) to receive venetoclax + ibrutinib, and reported PFS and OS at 5.5 years of 66% and 97%, respectively.[90] Estimated 5.5 PFS year rates were 55% (95% CI: 45, 64) for patients with unmutated IGHV and 79% (95% CI: 68, 87) for patients with mutated IGHV.[90] A non-fixed duration, but measurable residual disease (MRD)-driven approach of venetoclax + ibrutinib was assessed in the FLAIR trial.[87] With a median follow-up of 62.2 months, 5-year PFS was 93.9% with venetoclax + ibrutinib, 79.0% with ibrutinib alone, and 58.1% with FCR.[87] In a subgroup analysis for the unmutated IGHV group, an OS advantage was seen in the venetoclax + ibrutinib arm over both ibrutinib and FCR. This study, as well as two other phase 2 trials with MRD-driven design (arm D of SEQUOIA[91] and HO158/NextSTEP trial[92]) for the combinations venetoclax + zanubrutinib and venetoclax + ibrutinib, highlight excellent outcomes using MRD-driven guidance for personalized venetoclax + BTK inhibitor duration, but this combination is currently unlicensed. Besides the second-generation BTK inhibitor zanubrutinib, acalabrutinib has also been evaluated in combination with venetoclax, and was approved in 2025 based on the phase 3 AMPLIFY study comparing acalabrutinib + venetoclax ± obinutuzumab for a total of 14 cycles versus FCR or BR.[93] The estimated 36-month PFS rates were 76.5% for the doublet, 83.1% for the triplet, and 66.5% for CIT (P = 0.004) with a major difference in particular in CLL with unmutated IGHV status and an OS advantage seen in the venetoclax + acalabrutinib arm, but not for the triplet arm (HR: 0.33, P < 0.0001).[93]

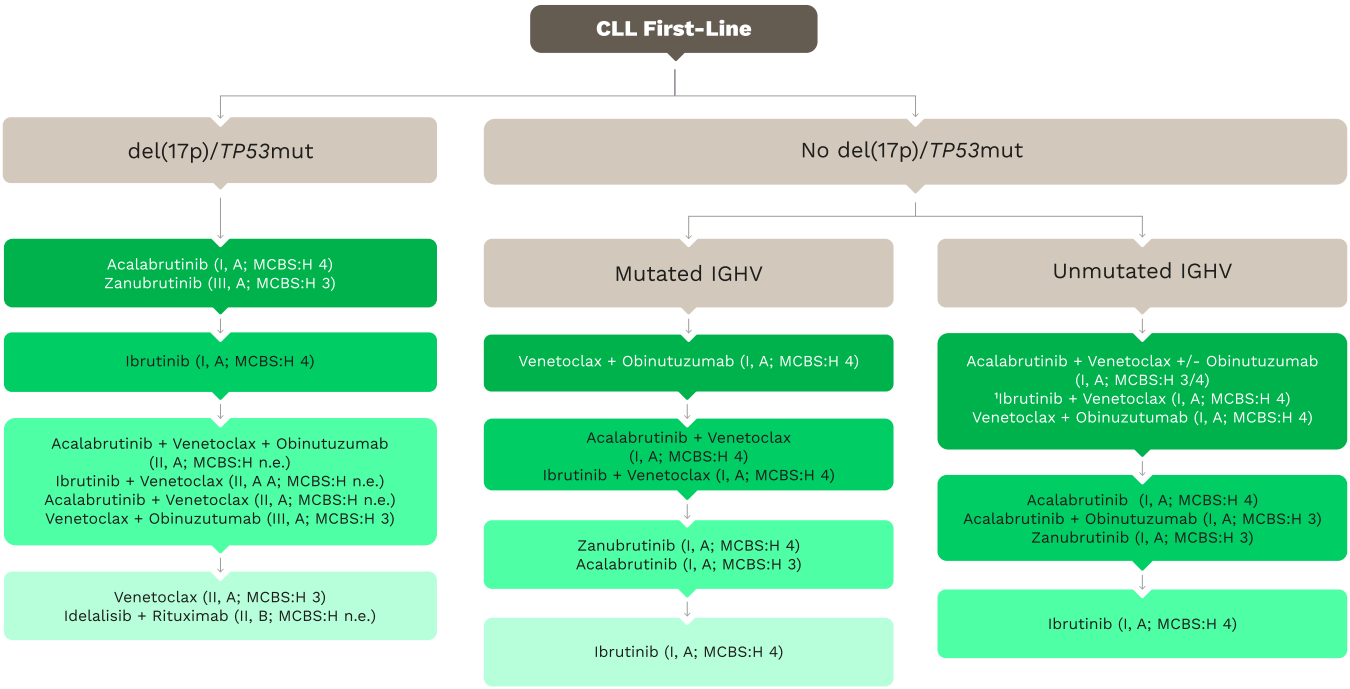
The direct comparison between ibrutinib and venetoclax + obinutuzumab and venetoclax + ibrutinib showed no difference in PFS after 3 years of observation in the CLL17 trial.[88] In contrast to the subgroup of patients with *TP53* aberrations, in whom there was a trend towards inferior PFS, no major differences were observed between continuous and time-limited treatment at this time point for patients with mutated and unmutated IGHV status, which may change over time. However—when possible, considering renal function and ramp-up process—time-limited treatment should be given preference in the latter subgroups of patients.

Based on the RCT data outlined above, time-limited treatment CIT (FCR, BR, chlorambucil + obinutuzumab) is no longer recommended when targeted treatment options are available.

Recommendation	**CITs are no longer recommended, because they are either inferior (BR, chlorambucil + obinutuzumab) to targeted agents or associated with a higher risk for adverse events including secondary neoplasia such as myeloid malignancies (FCR)**
Relevant for:	All patients
Level of Evidence	I
Grade of Recommendation	A

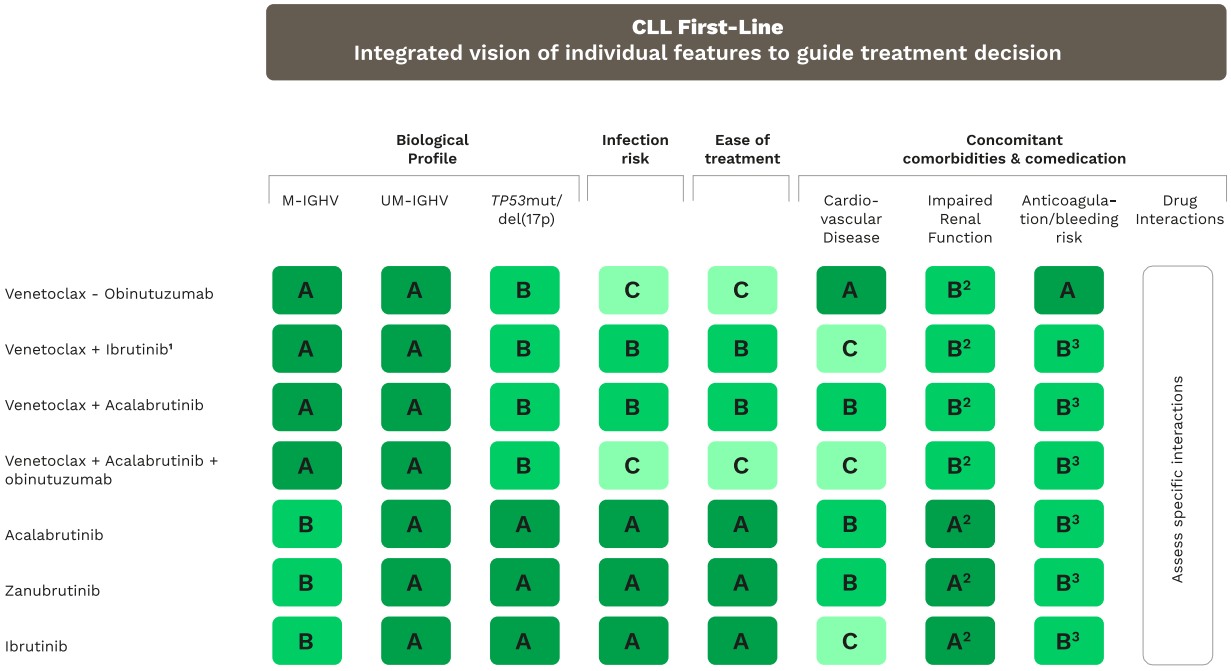
Recommendation	**Time-limited targeted therapies should be preferred over continuous therapy in patients with CLL without *TP53* aberrations (Figure 1)**
Relevant for:	All patients
Level of Evidence	I
Grade of Recommendation	A

Recommendation	**The selection of combination therapy should take into consideration the biological profile of the CLL and the adverse event profile of the agents, as well as the patient's comorbidities, co-medications, history of infections, and ease of treatment (Figure 2). In particular, in patients with CLL and mutated IGHV status, continuous therapy should be avoided**
Relevant for:	All patients
Level of Evidence	II
Grade of Recommendation	A



The order of each box listed reflects the ranking based on the recommendations, highlighted also by the different shades of green.
The order within each box is based on the MCBS:H score or otherwise preference, as the therapeutic choice should be guided not only by efficacy but also by comorbidities, drug interactions, logistics, and patient's preferences (see figure 2 "Heat map").
¹This combination has potentially more afficacy in an MRD-guided approach, but is not approved (see the text). N.e. = not evaluated.

FIGURE 1 **Decision algorithm for first-line therapy of patients with CLL.** CLL, chronic lymphocytic leukemia; IGHV, immunoglobulin heavy variable.



A= Strongly recommended; **B**= Recommended; **C**= consider alternatives.
¹: This combination appears particularly effective in UM-IGHV when used within an MRD-guided strategy, but is not currently approved.
²: caution with CrCl < 50 mL/min for venetoclax and < 30 mL/min for BTKi. For venetoclax recommended TLS preventions should be followed in patients with CrCl 50 -79 mL/min.
³: contraindicated with anti-Vitamin K.

FIGURE 2 **First-line therapy of patients with CLL: Integrated vision of individual features to guide treatment decision.** CLL, chronic lymphocytic leukemia; IGHV, immunoglobulin heavy variable.

Continuous treatment

Overall, covalent BTK inibition (as either a single agent or in combination with CD20 antibodies) has excellent efficacy in both mutated and unmutated IGHV subgroups, and has demonstrated advantage over CIT in large, randomized trials.

Long-term data from the RESONATE-2 study comparing ibrutinib with chlorambucil, with up to 10 years of follow-up, demonstrate that patients treated with ibrutinib experience a sustained PFS benefit versus with chlorambucil (median PFS: 8.9 years).[94]

Second-generation covalent BTK inhibitors, such as acalabrutinib and zanubrutinib, are more selective than ibrutinib, and have demonstrated less off-target inhibition with fewer toxicities—most notably, fewer cardiac toxicities.[95,96]

In the phase 3, ELEVATE-TN study, 535 patients with previously-untreated CLL were randomized to acalabrutinib + obinutuzumab, acalabrutinib monotherapy, or chlorambucil + obinutuzumab.[97] The estimated 72-month PFS rates were highest for the combination of acalabrutinib + obinutuzumab (78% vs. 62% for acalabrutinib monotherapy and 17% for CIT), but was associated with more toxicity, in particular cytopenias and infections.[97] Because of the cost-benefit balance the addition of CD20 antibody should be considered with caution (Figure 1). Continuous treatment with zanubrutinib resulted in a 76% PFS rate after 5 years (median observation time) in the phase 3 SEQUOIA trial of continuous therapy with zanubrutinib versus BR in elderly fit patients.[98]

The improved safety profiles of second-generation BTK inhibitors vs ibrutinib, most notably reduced cardiac toxicity, while directly assessed only in the R/R setting in the ELEVATE R/R[99] and ALPINE[96] clinical trials, has led to a general recommendation of either acalabrutinib or zanubrutinib over ibrutinib in both the first-line and R/R setting. However, treatment with ibrutinib can be continued if already initiated and well tolerated. Data is emerging to support continuous therapy with second-generation BTK inhibitors in elderly or frail (e.g., less resilient) patients who may not be candidates for time-limited treatment.[100] Acalabrutinib + obinutuzumab is more effective than acalabrutinib alone but with additional toxicity, and should not be preferred over acalabrutinib alone (Figure 1).[97]

The noncovalent BTK inhibitor (ncBTKi) pirtobrutinib was successfully evaluated in phase III frontline triaals against BR and ibrutinib though it is not yet approved, in this setting.[101,102] In addition, the lack of data on subsequent successful use of cBTKi following ncBTKi is currently preventing recommendations to use this compound in frontline.

It is recommended to perform a thorough cardiovascular work-up before initiating BTK inhibitor therapy in order to identify conditions amenable to pre-emptive intervention, including optimization of antihypertensive therapy. BTK inhibitor therapy should generally be avoided in those with a history of ventricular arrhythmias or uncontrolled heart failure. If there is coexisting cardiovascular disease or the need for anticoagulant treatment, the use of BCL-2 inhibitors is favored over BTK inhibitors (Figure 2).

Recommendation	**Acalabrutinib and zanubrutinib should be preferred over ibrutinib for continuous treatment of all new patients on the basis of their favorable toxicity profiles**
Patients who are well controlled on ibrutinib without notable adverse events should not be switched to second-generation BTK inhibitors	

Recommendation	**Acalabrutinib and zanubrutinib should be preferred over ibrutinib for continuous treatment of all new patients on the basis of their favorable toxicity profiles**
Relevant for:	All patients
Level of Evidence	I
Grade of Recommendation	A

TP53 disruption

Targeted therapies have improved outcomes for patients with *TP53* disruption. BTK inhibitors show activity in patients with *TP53* disruption. A phase 2 trial, PCYC-1102, showed a median PFS of 53 months with ibrutinib as a single agent in 34 patients with treatment-naïve CLL and *TP53* alterations.[103] Second-generation BTK inhibitors are also effective in this patient cohort, reflected in high PFS rates in both the ELEVATE-TN[97] and SEQUOIA arm C studies,[104] and should be preferred over ibrutinib for safety reasons, as depicted above. The approved venetoclax + ibrutinib combination was evaluated in the phase 2 CAPTIVATE study, which showed 5.5-year PFS of 30% overall and 47% in those who achieved undetectable MRD.[90] Zanubrutinib + venetoclax, given for 24 cycles (with extension in the majority patients due to persistence of detectable MRD) showed a promising PFS rate of 88% after 3 years in 66 patients with *TP53* aberrant disease in the arm D SEQUOIA study,[91] but this combination is not yet licensed. Venetoclax + obinutuzumab showed a shorter PFS in the subgroup analysis of CLL17 (HR for venetoclax + obinutuzumab vs ibrutinib: 1.20, 95% CI: 0.40, 3.59; HR for venetoclax + ibrutinib vs. ibrutinib: 0.70, 95% CI: 0.22, 2.16).[88] Triple combinations with acalabrutinib + venetoclax + obinutuzumab or ibrutinib + venetoclax + obinutuzumab show remarkable results in phase 2 trials for these very high-risk patients (70% at 4 years and 80% PFS at 3 years, respectively),[105,106] but data from randomized trials comparing doublet versus triplet therapy are still pending. These data indicate that triple combinations may be considered for patients with *TP53* disruption, provided they are able to tolerate the higher toxicity burden (in particular, infections).

Until longer-term data from ongoing trials are available, continuous treatment with BTK inhibitors may be the preferred option in patients with *TP53* disruption, with careful consideration of underlying cardiac comorbidities. The phosphoinositide 3-kinase (PI3K) inhibitor idelalisib in combination with rituximab, or continuous treatment with venetoclax monotherapy, remain approved options in patients with *TP53* disruption, if BTK inhibitors are unsuitable or unavailable.

Recommendation	**Continuous treatment is suggested over time-limited treatment, unless time-limited treatment is preferred by shared decision-making**
Relevant for:	All patients with *TP53* disruption
Level of Evidence	I
Grade of Recommendation	A

Recommendation	Triplet therapies may add additional benefit with respect to longer treatment-free intervals in vs doublet combinations
Relevant for:	Patients with *TP53* disruption who may tolerate the higher risk of infections associated with triplet therapy
Level of Evidence	III
Grade of Recommendation	B

TREATMENT OF RELAPSED/REFRACTORY DISEASE

Despite the significant advances in targeted therapy, a substantial proportion of patients with CLL will relapse and require subsequent lines of therapy. Relapse is commonly recognized by increasing lymphocytosis, (re-)occurrence of cytopenias, or lymphadenopathy. However, treatment should only be initiated in patients with cytopenias, bulky lymphadenopathy, or symptomatic disease, fulfilling iwCLL criteria for treatment.

The choice of treatment in R/R CLL depends on the type of prior therapy (time-limited treatment vs. continuous), duration of response, reason for treatment discontinuation (progression vs. intolerance), presence of adverse biological features including *TP53* aberrations, and IGHV status. Additionally, patient age, comorbidities, patient preferences, drug access, and ease of administration may influence therapeutic decisions as described in Section 6 of this publication (*First-line treatment for CLL*).

For all patients with R/R disease, particularly those with poor risk features or after multiple prior therapies, participation in a clinical trial should be actively considered whenever available. Clinical trials provide access to innovative and potentially more effective treatments under closely monitored conditions without increasing risk (compared with standard care).

Relapse after CIT

Patients relapsing after CIT should not be re-treated with chemotherapy if targeted therapies are available and accessible. Randomized trials and real-world data have shown superior efficacy of targeted agents over repeated CIT. Venetoclax + rituximab[107] or a second-generation covalent BTK inhibitor (cBTKi) such as acalabrutinib[95] or zanubrutinib[96] is preferred (Figure 3A).

Relapse after covalent BTK inhibitor therapy

Patients with disease progression following treatment with cBTKi should not be exposed to another cBTKi but switched to a venetoclax-based regimen (Figure 3B)[108,109] or to the ncBTKi pirtobrutinib (approved in this setting).

Patients stopping cBTKi due to adverse events and then relapsing after a period of observation may be treated again with the same or another cBTKi or ncBTKi[110–112]

Studies have reported overall response rates (ORRs) of 70%–80% for venetoclax after cBTKi failure, with improved outcomes versus idelalisib or CIT.[113] Venetoclax + rituximab offers the advantage of time-limited treatment, and is often preferred for patients with comorbidities or intolerance to cBTKi[114] Pirtobrutinib has shown a 69% response rate and a median PFS of 14 months in patients pretreated with cBTKi (50% of those patients were double-exposed, i.e., pretreated also with venetoclax).[110,115] Efficacy is higher in patients with earlier relapse, and cardiac adverse events appear to be lower versus ibrutinib in a head-to-head comparison.[102]

Relapse after time-limited treatment venetoclax

Re-treatment with a venetoclax-based regimen, especially venetoclax + rituximab, is feasible in selected patients who have had a durable prior response.[90,107,113,114] Re-treatment is more effective when the prior treatment-free interval exceeds 2 years, whereas early relapse warrants switching drug class (Figure 3C).[107,116] In both clinical trials and in real-world settings, ORRs of 72%–80% have been reported, with median PFS of approximately 23–25 months.[107,113] Venetoclax + obinutuzumab is not approved in relapsed disease, but obinutuzumab has shown superiority over rituximab when used in combination with venetoclax as a first-line treatment.[86] Venetoclax + ibrutinib or other combinations of BCL-2 inhibitors + BTK inhibitors in the R/R setting are also not approved, but initial data appear promising.[92]

Alternatively, cBTKi therapy is appropriate in the relapse setting after time-limited treatment venetoclax if not previously used otherwise ncBTKi becomes the preferred option.[88,117]

Double-exposed and double-refractory disease

"Double-exposed" refers to patients who have received both BTK and BCL-2 inhibitors, but have discontinued either as planned or for adverse events. In this subgroup of patients, discontinuation is not due to progression, and patients can be re-exposed to either class of drugs as a combination of the two drug classes is off-label in this setting.[118,119]

"Double-refractory" refers to patients who have disease progression following treatment with both classes (after continuous cBTKi and after continuous venetoclax or early after time-limited treatment venetoclax-based therapy), and represents a high-risk group for which the ncBTKi pirtobrutinib is the preferred treatment option[120]; in cases where access is not possible, idelalisib + rituximab can also be used.[121,122]

"Double-exposed with single refractoriness" refers to patients who have received both BTK and BCL-2 inhibitors, but having disease progression following treatment only to one the classes. These patients can be re-exposed to the class they are not refractory to or may switch to ncBTKi pirtobrutinib.

Allogeneic stem cell transplantation (alloSCT) should be considered for patients who are double-refractory, using pirtobrutinib or idelalisib + rituximab as a bridge to transplant in eligible patients with controlled disease with aim of achieving maximal response before transplantation. AlloSCT can provide long-term remission in about 50% of eligible patients with disease control prior to transplant, though data in the double-refractory setting are scant.[123–125]

Consideration for inclusion in clinical trials of novel agents (such has BTK degraders,[126] bispecific antibodies,[127] chimeric antigen receptor [CAR] T-cell therapy[128]) is strongly recommended in patients who are double-refractory. Autologous T-cell therapies including CAR T cells (e.g., lisocabtagene maraleucel [liso-cel]) are not approved in EU, but are available in other countries. In the TRANSCEND CLL 004 study, complete response (CR) rates with CAR T-cell therapy were ~18% lower in CLL than in other B-cell malignancies. BTK degraders show promising results in phase 1 clinical trials, with ORRs in the range of 70% and with satisfactory safety profiles. Bispecific antibodies have yielded CR rates near 40%, although data are early and mostly in monotherapy.

FIGURE 3 **(A) Treatment of patients with relapsed/refractory CLL (after continuous CIT). (B)** Treatment of patients with relapsed/refractory CLL (on/after continuous Tx). **(C)** Treatment of patients with relapsed/refractory CLL (after venetoclax-based treatment). CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia.

Recommendation	Time-limited treatment with venetoclax + CD20 antibody or continuous treatment with a second-generation covalent BTK inhibitor are preferred treatments for most patients with R/R CLL [I, A]
Relevant for:	All patients with relapse/progressive disease after CIT
Level of Evidence	I
Grade of Recommendation	A

Recommendation	Patients with prior intolerance to ibrutinib should be offered acalabrutinib, zanubrutinib, or a venetoclax-based regimen. Patients with intolerance to acalabrutinib or zanubrutinib may switch to another second-generation covalent BTK inhibitor
Relevant for:	All patients with intolerance to covalent BTK inhibitors
Level of Evidence	II
Grade of Recommendation	B

Recommendation	Patients with disease progression on covalent BTK inhibitor therapy should switch to venetoclax-based regimens or be treated with a non-covalent BTK inhibitor
Relevant for:	All patients with disease progression on covalent BTK inhibitor therapy
Level of Evidence	II
Grade of Recommendation	B

Recommendation	After time-limited treatment with venetoclax (either in combination with a BTK inhibitor or a CD20 antibody), a covalent BTK inhibitor or re-treatment with venetoclax may be considered, depending on prior response and time since discontinuation
Relevant for:	All patients with relapse after prior time-limited treatment with venetoclax-based therapy
Level of Evidence	IV
Grade of Recommendation	B

Recommendation	Patients with double-refractory CLL should receive the non-covalent BTK inhibitor pirtobrutinib, or, if not available, idelalisib + rituximab; these agents should also be considered as a bridge to alloSCT in eligible patients

(Continues)

Recommendation	Patients with double-refractory CLL should receive the non-covalent BTK inhibitor pirtobrutinib, or, if not available, idelalisib + rituximab; these agents should also be considered as a bridge to alloSCT in eligible patients

	Participation in clinical trials, if accessible, is highly recommended
Relevant for:	Double-refractory disease (i.e., venetoclax-resistant disease with progression on covalent BTK inhibitor therapy)
Level of Evidence	II/III
Grade of Recommendation	A

Recommendation	Patients with double-refractory CLL should avoid discontinuation of ongoing therapy until the next line of treatment is available to prevent disease flare
Relevant for:	Patients with disease progression on targeted treatment
Level of Evidence	III
Grade of Recommendation	B

MANAGEMENT OF RT

RT refers to an aggressive lymphoma occurring in 2%–10% of patients with CLL. The decision algorithm is detailed in Figure 4.

Pathological examination, ideally through excisional biopsy, is required to establish the diagnosis and exclude other entities such as accelerated CLL.[5,8,129,130] The most common histologic subtype is diffuse large B-cell lymphoma (RT-DLBCL), which requires the presence of sheets of large cells. Less frequently, RT presents as classical Hodgkin lymphoma (RT-cHL). Pseudo-RT should be recognized in patients discontinuing BTK inhibitors and should be promptly differentiated.[8] An elevated 18-FDG-PET/CT uptake correlates with RT, and can guide biopsy, although the optimal threshold is debated in the targeted therapies era.[131]

The evaluation of the clonal relationship between RT and the underlying CLL by IGHV-IGHD-IGHJ gene sequencing is recommended for optimal management of patients. Clonally-related RT (~80% of cases) exhibit poorer outcomes compared to clonally-unrelated RT,[132] though there is no data from a large multivariate analysis confirming the inferior prognosis. Assessment for del(17p)/*TP53* aberrations (present in 50%–60% of cases and associated with poor prognosis) is advised.[132]

Patients with clonally-unrelated RT-DLBCL should be treated as de novo DLBCL. No standard therapy has been defined for clonally related disease, and clinical trials should be the preferred option. RT-cHL should be treated per cHL guidelines.

Accelerated CLL, which is described as CLL with an increased proliferation rate and without transformation, should be treated as CLL.

When the clonal relation is not established, CIT regimens generally used for de novo DLBCL are the default options in RT-DLBCL, but these have demonstrated limited efficacy, with CR rates ranging from 5% to 38%, with median OS rarely exceeding one year. No data

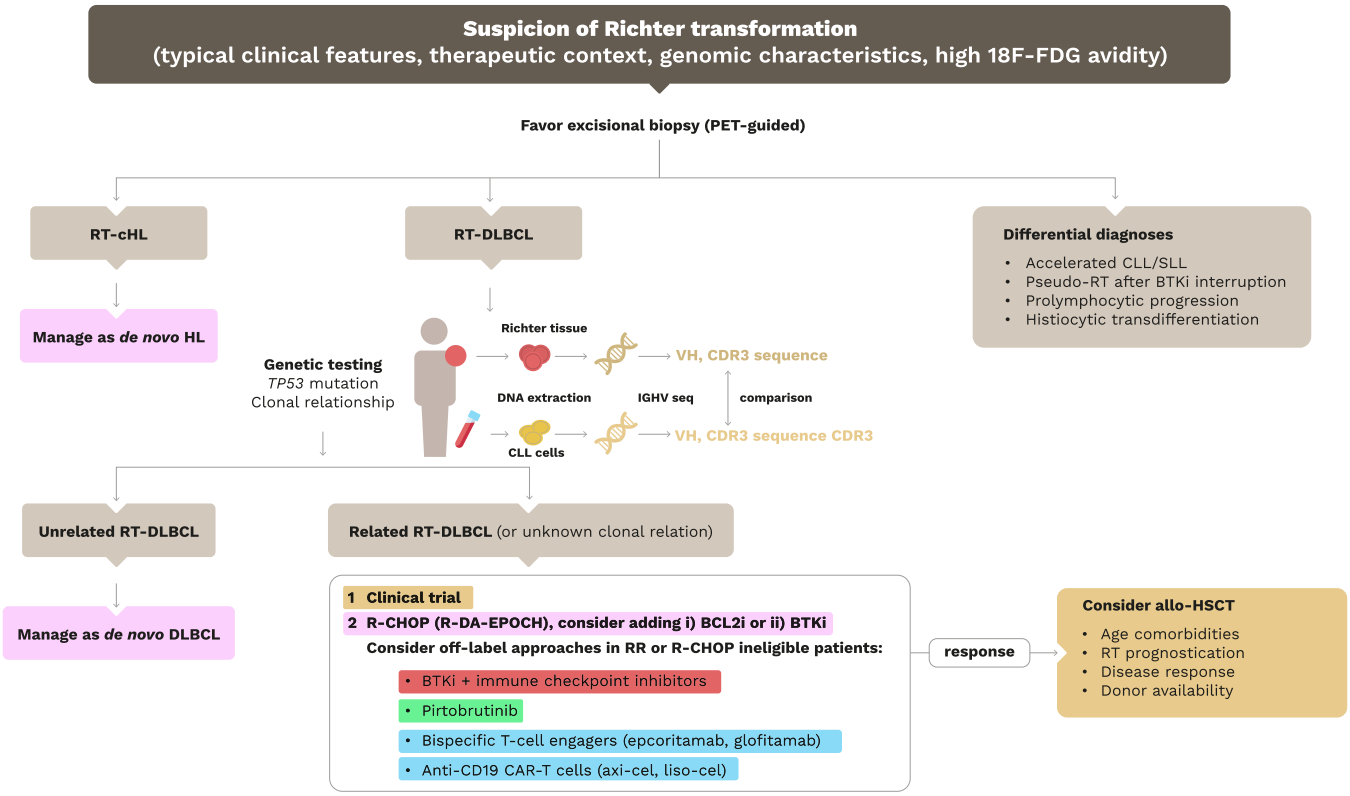


FIGURE 4 **Decision algorithm for patients with Richter transformation**. 18F-FDG, 2-deoxy-2-(^{18}F)fluoro-D-glucose; allo-HSCT, allogeneic hematopoietic stem cell transplantation; axi-cel, axicabtagene ciloleucel; BCL-2i, inhibitor of the B-cell lymphoma 2 protein; BTKi, Bruton tyrosine kinase inhibitor; CAR, chimeric antigen receptor; cHL, classical Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; PET, positron emission tomography; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DA-EPOCH, dose-adjusted rituximab, etoposide prednisolone, vincristine, cyclophosphamide and doxorubicin; RR, relapsed/refractory; RT, Richter transformation; liso-cel, lisocabtagene maraleucel.

from randomized studies is available. Enrolling patients in clinical trials is therefore the preferred option.

Phase 2 studies have evaluated targeted therapies and immunotherapies developed for use in lymphoid malignancies. BCL-2 or BTK inhibitors have shown limited efficacy as monotherapies. Acalabrutinib has demonstrated an ORR of 40%.[133] The subgroup analysis of the phase 1/2 BRUIN study showed that 50% of their patients with RT achieved an overall response with the ncBTK inhibitor pirtobrutinib.[134] Acalabrutinib and pirtobrutinib could be potentially used as bridging therapy prior a more intensive approach.

Given the short duration of response, hematopoietic stem-cell transplantation should be considered in eligible patients with clonally related RT-DLBCL and satisfactory response.[135,136]

The combination of venetoclax and R-da-EPOCH achieved a CR rate of 50%.[137] Immune checkpoint inhibitor combinations have yielded an ORR of 58% in the RT1 trial (zanubrutinib and tislelizumab)[138] and 68% in the MOLTO trial (obinutuzumab, atezolizumab, and venetoclax).[139]

Bispecific T-cell engagers (TCE) and CAR T-cell therapies represent other promising approaches. The BLINART trial showed that the anti-CD3/anti-CD19 TCE blinatumomab induced CR in 20% of patients with no CR after two cycles of R-CHOP.[140] In a recent evaluation, the anti-CD3/anti-CD20 TCE epcortimamab demonstrated an ORR of 48%.[141] In two retrospective analysis of 69 and 54 patients, respectively, receiving CD19-directed CAR T-cell therapy, the CR rate was 46% in both, with a median PFS of 4.7 and 8 months, respectively.[142,143]

Recommendation	**DLBCL in patients with CLL should undergo evaluation of clonal relationship, because *de novo* DLBCL should be treated according to DLBCL guidelines**
Relevant for:	Patients with histological proven DLBCL and concurrent/previous CLL
Level of Evidence	III
Grade of Recommendation	B

Recommendation	**Patients with RT-DLBCL should be offered participation in clinical trials whenever possible**
Relevant for:	All patients with RT-DLBCL
Level of Evidence	II
Grade of Recommendation	A

Recommendation	**Outside of clinical trials, CIT is the standard regimen for RT-DLBCL**
Relevant for:	All patients with RT-DLBCL

Recommendation	Outside of clinical trials, CIT is the standard regimen for RT-DLBCL
Level of Evidence	III
Grade of Recommendation	C

Recommendation	Patients with clonal RT-DLBCL in remission, and being fit enough, should be offered alloSCT for consolidation (when a suitable donor is available)
Relevant for:	Fit patients with RT-DLBCL
Level of Evidence	III
Grade of Recommendation	B

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Barbara Eichhorst and **Paolo Ghia**: Conceptualization; writing—original draft; writing—review and editing; supervision. **Francesc Bosch**: Writing—original draft; writing—review and editing. **Ruth Clifford**: Writing—original draft; writing—review and editing. **Michael Gregor**: Writing—original draft; writing—review and editing. **Romain Guieze**: Writing—original draft; writing—review and editing. **Arnon P. Kater**: Writing—original draft; writing—review and editing. **Carsten U. Niemann**: Writing—original draft; writing—review and editing. **Sarka Pospisilova**: Writing—original draft; writing—review and editing. **Tadeusz Robak**: Writing—original draft; writing—review and editing. **Anna Schuh**: Writing—original draft; writing—review and editing. **Kostas Stamatopoulos**: Writing—original draft; writing—review and editing. **Tamar Tadmor**: writing—original draft; writing—review and editing. **Nick York**: Writing—original draft; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

BE: Received research grants from Abbvie, AstraZenca, BeOne, Janssen and Roche; in addition she served as consulted or speaker for Abbvie, AstraZenca, BeOne, Galapagos, Lilly, MSD and Roche. PG: Advisory board/consultant: AbbVie, AstraZeneca, BeOne, BMS, Johnson & Johnson, Lilly, MSD, Nurix, Roche. Research funding: AbbVie, AstraZeneca, BeOne, BMS, Johnson & Johnson, Lilly, MSD FB: Received research grants, speaker honoraria/consulting: Abbvie, Allogene, Amgen, Autolus, AstraZeneca, BeOne, BMS, Gilead (Kite), Johnson&Johnson, Lilly, MSD, Novartis, Roche, Takeda, TG threapeutics RC: No conflict of interest. MG: Advisory board participation/consulting: AbbVie, Amgen, AstraZeneca, BeOne, BMS, Daichi/Sankyo, GSK, Johnson & Johnson, Lilly, Sanofi, Servier (all fees paid to the institution). Travel grant: AbbVie, BeOne, Johnson & Johnson, Pfizer, Servier. RG: Speaker Honoraria: Johnson and Johnson, Abbvie, BeOne Medicines, Astrazeneca, Lilly; Advisory Board Participation: Johnson and Johnson, Abbvie, BeOne Medicines, Astrazeneca, Lilly, Ascentage Pharma; Consultancy Roles: Johnson and Johnson, Abbvie, BeOne Medicines, Astrazeneca, Lilly; Research Funding: Johnson and Johnson, Abbvie, BeOne Medicines, Astrazeneca, Lilly. APK: has received research grants from Johnson & Johnson, AbbVie, Roche/Genentech, Bristol Myers Squibb, AstraZeneca, and Genmab, and honoraria (paid to the institution) from BeiGene, Johnson & Johnson, AstraZeneca, AbbVie, and Genmab. CUN: has received research funding and/or consultancy fees from Abbvie, AstraZeneca, Janssen, Beigene, Genmab, Octapharma, Takeda, MSD, Lilly, CSL Behring, Galapagos, Synamics, Novo Nordisk Foundation. SP: No conflict of interest. TR: Speaker Honoraria: AstraZeneca, BeOne Medicines; Advisory Board Participation: AstraZeneca, BeOne Medicines, Lilly and Johnson & Johnson; Consultancy Roles: AstraZeneca, Eli Lilly; Research Funding: AbbVie, Acerta Pharma, AstraZeneca, BeOne Medicines, Gilead Sciences, GSK, Johnson & Johnson, Eli Lilly, Merck; Institutional Support: None; Travel grants: AstraZeneca, BeOne Medicines; Johnson & Johnson, AS: Received research grants from AstraZeneca and Johnson & Johnson. Served as consultant or speaker for Abbvie, AstraZeneca, BeOne, and Lilly. KS: Honoraria: AbbVie, AstraZeneca, BeOne Medicines, Johnson&Johnson, Lilly. Advisory Board participation: AbbVie, AstraZeneca, BeOne Medicines, Johnson&Johnson. Research funding: AbbVie, AstraZeneca, BeOne Medicines, Johnson&Johnson. TT: Advisory Board Participation: Johnson and Johnson, Abbvie, BeOne Medicines, Astrazeneca, Lilly, Roche. Research Funding: Johnson and Johnson, Abbvie, BeOne Medicines, Roche. NY: Advisory board participation, consultation & honoraria: AstraZeneca, Johnson and Johnson, Takeda.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. European Hematology Association. EHA guidelines methodology for diagnosis and therapy of blood disorders. https://ehaweb.org/app/uploads/2025/05/EHA-Guidelines-Methodology-3.pdf
2. Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis*. 2001;33(2):139-144. doi:10.1086/321805
3. Cherny NI, Oosting SF, Dafni U, et al. ESMO-Magnitude of Clinical Benefit Scale version 2.0 (ESMO-MCBS v2.0). *Ann Oncol*. 2025;36(8):866-908. doi:10.1016/j.annonc.2025.04.006
4. Kiesewetter B, Dafni U, de Vries EGE, et al. ESMO-Magnitude of Clinical Benefit Scale for haematological malignancies (ESMO-MCBS:H) version 1.0. *Ann Oncol*. 2023;34(9):734-771. doi:10.1016/j.annonc.2023.06.002
5. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of haematolymphoid tumours: lymphoid neoplasms. *Leukemia*. 2022;36(7):1720-1748. doi:10.1038/s41375-022-01620-2
6. Bray FCM, Aitken JF, Bardot A, et al. *Cancer Incidence in Five Continents* XII: IARC Scientific Publication, 2024.
7. SEER. Cancer stat facts: leukemia — chronic lymphocytic leukemia (CLL). https://seer.cancer.gov/statfacts/html/clyl.html

8. Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of mature lymphoid neoplasms: a report from the Clinical Advisory Committee. *Blood*. 2022;140(11):1229-1253. doi:10.1182/blood.2022015851
9. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018;131(25):2745-2760. doi:10.1182/blood-2017-09-806398
10. Stamatopoulos K, Pavlova S, Al-Sawaf O, et al. Realizing precision medicine in chronic lymphocytic leukemia: remaining challenges and potential opportunities. *HemaSphere*. 2024;8(7):e113. doi:10.1002/hem3.113
11. Rawstron AC, Bennett FL, O'Connor S.J.M., et al. Monoclonal B-cell lymphocytosis and chronic lymphocytic leukemia. *N Engl J Med*. 2008;359(6):575-583. (In eng)
12. Slager SL, Parikh SA, Achenbach SJ, et al. Progression and survival of MBL: a screening study of 10 139 individuals. *Blood*. 2022;140(15):1702-1709. doi:10.1182/blood.2022016279
13. Fazi C, Scarfò L, Pecciarini L, et al. General population low-count CLL-like MBL persists over time without clinical progression, although carrying the same cytogenetic abnormalities of CLL. *Blood*. 2011;118(25):6618-6625. doi:10.1182/blood-2011-05-357251
14. 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):1840-1847.
15. Hamblin TJ, Davis Z, Gardiner A, Oscier DG, Stevenson FK. Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. *Blood*. 1999;94(6):1848-1854
16. Döhner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. *N Engl J Med*. 2000;343(26):1910-1916. (In eng) doi:10.1056/nejm200012283432602
17. Stevenson FK, Forconi F, Kipps TJ. Exploring the pathways to chronic lymphocytic leukemia. *Blood*. 2021;138(10):827-835. doi:10.1182/blood.2020010029
18. Agathangelidis A, Chatzikonstantinou T, Stamatopoulos K. B-cell receptor immunoglobulin stereotypy in chronic lymphocytic leukemia: key to understanding disease biology and stratifying patients. *Semin Hematol*. 2024;61(2):91-99. doi:10.1053/j.seminhematol.2023.12.005
19. Agathangelidis A, Chatzidimitriou A, Chatzikonstantinou T, et al. Immunoglobulin gene sequence analysis in chronic lymphocytic leukemia: the 2022 update of the recommendations by ERIC, the European Research Initiative on CLL. *Leukemia*. 2022;36(8):1961-1968. doi:10.1038/s41375-022-01604-2
20. Baliakas P, Hadzidimitriou A, Sutton LA, et al. Recurrent mutations refine prognosis in chronic lymphocytic leukemia. *Leukemia*. 2014;29:329-336. doi:10.1038/leu.2014.196
21. Mansouri L, Thorvaldsdottir B, Sutton LA, et al. Different prognostic impact of recurrent gene mutations in chronic lymphocytic leukemia depending on IGHV gene somatic hypermutation status: a study by ERIC in HARMONY. *Leukemia*. 2023;37(2):339-347. doi:10.1038/s41375-022-01802-y
22. Tobin G, Thunberg U, Johnson A, et al. Chronic lymphocytic leukemias utilizing the VH3-21 gene display highly restricted Vλ2-14 gene use and homologous CDR3s: implicating recognition of a common antigen epitope. *Blood*. 2003;101(12):4952-4957. doi:10.1182/blood-2002-11-3485
23. Jaramillo S, Agathangelidis A, Schneider C, et al. Prognostic impact of prevalent chronic lymphocytic leukemia stereotyped subsets: analysis within prospective clinical trials of the German CLL Study Group (GCLLSG). *Haematologica*. 2020;105(11):2598-2607. doi:10.3324/haematol.2019.231027
24. Rossi D, Spina V, Cerri M, et al. Stereotyped B-cell receptor is an independent risk factor of chronic lymphocytic leukemia transformation to Richter syndrome. *Clin Cancer Res*. 2009;15(13):4415-4422. doi:10.1158/1078-0432.CCR-08-3266
25. Gounari M, Ntoufa S, Apollonio B, et al. Excessive antigen reactivity may underlie the clinical aggressiveness of chronic lymphocytic leukemia stereotyped subset #8. *Blood*. 2015;125(23):3580-3587. doi:10.1182/blood-2014-09-603217
26. Bussot L, Poulain S, Nudel Ortmans M, et al. Targeted therapies overcome the poor prognosis of stereotyped Subset#2 chronic lymphocytic leukemia: a real-world multicentric study. *Leukemia*. 2025;39(5):1247-1251. doi:10.1038/s41375-025-02555-0
27. 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):3247-3254. (In Eng)
28. Griffin R, Wiedmeier-Nutor JE, Parikh SA, et al. Differential prognosis of single and multiple TP53 abnormalities in high-count MBL and untreated CLL. *Blood Adv*. 2023;7(13):3169-3179. doi:10.1182/bloodadvances.2022009040
29. Malcikova J, Pavlova S, Kunt Vonkova B, et al. Low-burden TP53 mutations in CLL: clinical impact and clonal evolution within the context of different treatment options. *Blood*. 2021;138(25):2670-2685. doi:10.1182/blood.2020009530
30. Parry EM, Leshchiner I, Guièze R, et al. Evolutionary history of transformation from chronic lymphocytic leukemia to Richter syndrome. *Nat Med*. 2023;29(1):158-169. doi:10.1038/s41591-022-02113-6
31. Klintman J, Appleby N, Stamatopoulos B, et al. Genomic and transcriptomic correlates of Richter transformation in chronic lymphocytic leukemia. *Blood*. 2021;137(20):2800-2816. doi:10.1182/blood.2020005650
32. Malcikova J, Stano-Kozubik K, Tichy B, et al. Detailed analysis of therapy-driven clonal evolution of TP53 mutations in chronic lymphocytic leukemia. *Leukemia*. 2015;29(4):877-885. doi:10.1038/leu.2014.297
33. Brieghel C, Kinalis S, Yde CW, et al. Deep targeted sequencing of TP53 in chronic lymphocytic leukemia: clinical impact at diagnosis and at time of treatment. *Haematologica*. 2019;104(4):789-796. doi:10.3324/haematol.2018.195818
34. Gonzalez D, Martinez P, Wade R, et al. Mutational status of the TP53 gene as a predictor of response and survival in patients with chronic lymphocytic leukemia: results from the LRF CLL4 trial. *J Clin Oncol*. 2011;29(16):2223-2229. doi:10.1200/JCO.2010.32.0838
35. Zenz T, Eichhorst B, Busch R, et al. TP53 mutation and survival in chronic lymphocytic leukemia. *J Clin Oncol*. 2010;28(29):4473-4479. (In eng)
36. Pavlova S, Malcikova J, Radova L, et al. Detection of clinically relevant variants in the TP53 gene below 10% allelic frequency: a multicenter study by ERIC, the European Research Initiative on CLL. *HemaSphere*. 2025;9(1):e70065. doi:10.1002/hem3.70065
37. Malcikova J, Pavlova S, Baliakas P, et al. ERIC recommendations for TP53 mutation analysis in chronic lymphocytic leukemia—2024 update. *Leukemia*. 2024;38(7):1455-1468. doi:10.1038/s41375-024-02267-x
38. Cafforio L, Raponi S, Cappelli LV, et al. Treatment with ibrutinib does not induce a TP53 clonal evolution in chronic lymphocytic leukemia. *Haematologica*. 2022;107(1):334-337. doi:10.3324/haematol.2020.263715
39. Nadeu F, Diaz-Navarro A, Delgado J, Puente XS, Campo E. Genomic and epigenomic alterations in chronic lymphocytic leukemia. *Ann Rev Pathol Mech Dis*. 2020;15:149-177. doi:10.1146/annurev-pathmechdis-012419-032810
40. Knisbacher BA, Lin Z, Hahn CK, et al. Molecular map of chronic lymphocytic leukemia and its impact on outcome. *Nat Genet*. 2022;54(11):1664-1674. doi:10.1038/s41588-022-01140-w
41. Robbe P, Ridout KE, Vavoulis DV, et al. Whole-genome sequencing of chronic lymphocytic leukemia identifies subgroups with distinct biological and clinical features. *Nat Genet*. 2022;54(11):1675-1689. doi:10.1038/s41588-022-01211-y

42. Baliakas P, Iskas M, Gardiner A, et al. Chromosomal translocations and karyotype complexity in chronic lymphocytic leukemia: a systematic reappraisal of classic cytogenetic data. *Am J Hematol*. 2014;89(3):249-255. doi:10.1002/ajh.23618
43. Baliakas P, Jeromin S, Iskas M, et al. Cytogenetic complexity in chronic lymphocytic leukemia: definitions, associations and clinical impact. *Blood*. 2019;133:1205-1216. doi:10.1182/blood-2018-09-873083
44. Fürstenau M, Thus YJ, Robrecht S, et al. High karyotypic complexity is an independent prognostic factor in patients with CLL treated with venetoclax combinations. *Blood*. 2023;142(5):446-459. doi:10.1182/blood.2023019634
45. Baliakas P, Espinet B, Mellink C, et al. Cytogenetics in chronic lymphocytic leukemia: eric perspectives and recommendations. *Hemasphere*. 2022;6(4):e707 (In eng) doi:10.1097/hs9.0000000000000707
46. Rai KR. A critical analysis of staging in CLL. In: Gale RP, Rai KR, eds. *Chronic Lymphocytic Leukemia: Recent Progress and Future Directions*. Alan R.Liss; 1987:253-264.
47. Rai K., Sawitsky A, Cronkite E., Chanana A., Levy R., Pasternack B. Clinical staging of chronic lymphocytic leukemia. *Blood*. 1975;46(2):219-234.
48. Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. *Cancer*. 1981;48(1):198-206. (In eng) doi:10.1002/1097-0142(19810701)48:1<198::aid-cncr2820480131>3.0.co;2-v
49. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. *J Clin Oncol*. 2014;32:3059-3067. doi:10.1200/JCO.2013.54.8800
50. Dighiero G, Maloum K, Desablens B, et al. Chlorambucil in indolent chronic lymphocytic leukemia. *N Engl J Med*. 1998;338(21):1506-1514.
51. Hoechstetter MA, Busch R, Eichhorst B, et al. Early, risk-adapted treatment with fludarabine in Binet stage A chronic lymphocytic leukemia patients: results of the CLL1 trial of the German CLL study group. *Leukemia*. 2017;31(12):2833-2837. (In eng) doi:10.1038/leu.2017.246
52. Herling CD, Cymbalista F, Groß-Ophoff-Müller C, et al. Early treatment with FCR versus watch and wait in patients with stage Binet A high-risk chronic lymphocytic leukemia (CLL): a randomized phase 3 trial. *Leukemia*. 2020;34(8):2038-2050. (In eng) doi:10.1038/s41375-020-0747-7
53. Langerbeins P, Robrecht S, Nieper P, et al. Ibrutinib in early-stage chronic lymphocytic leukemia: the randomized, placebo-controlled, double-blind, phase III CLL12 trial. *J Clin Oncol*. 2025;43(4):392-402. doi:10.1200/JCO.24.00975
54. International CLL IPI working group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. *Lancet Oncol*. 2016;17(6):779-790. doi:10.1016/S1470-2045(16)30029-8
55. Condoluci A, Terzi di Bergamo L, Langerbeins P, et al. International prognostic score for asymptomatic early-stage chronic lymphocytic leukemia. *Blood*. 2020;135(21):1859-1869. (In eng) doi:10.1182/blood.2019003453
56. Forconi F, Moss P. Perturbation of the normal immune system in patients with CLL. *Blood*. 2015;126(5):573-581. (In eng) doi:10.1182/blood-2015-03-567388
57. Mauro FR, Giannarelli D, Galluzzo CM, et al. Response to the conjugate pneumococcal vaccine (PCV13) in patients with chronic lymphocytic leukemia (CLL). *Leukemia*. 2021;35(3):737-746. doi:10.1038/s41375-020-0884-z
58. Roeker LE, Knorr DA, Pessin MS, et al. Anti-SARS-CoV-2 antibody response in patients with chronic lymphocytic leukemia. *Leukemia*. 2020;34(11):3047-3049. doi:10.1038/s41375-020-01030-2
59. Pleyer C, Ali MA, Cohen JI, et al. Effect of Bruton tyrosine kinase inhibitor on efficacy of adjuvanted recombinant hepatitis B and zoster vaccines. *Blood*. 2021;137(2):185-189. (In eng) doi:10.1182/blood.2020008758
60. Papi A, Ison MG, Langley JM, et al. Respiratory syncytial virus prefusion F protein vaccine in older adults. *New Engl J Med*. 2023;388(7):595-608. doi:10.1056/NEJMoa2209604
61. Sun C, Gao J, Couzens L, et al. Seasonal influenza vaccination in patients with chronic lymphocytic leukemia treated with ibrutinib. *JAMA Oncol*. 2016;2(12):1656-1657. (In eng) doi:10.1001/jamaoncol.2016.2437
62. Diamantopoulos PT, Kontandreopoulou CN, Stafylidis C, et al. Immunogenicity and safety of the recombinant adjuvanted herpes zoster vaccine in patients with chronic lymphocytic leukemia and multiple myeloma. *Vaccines*. 2024;12(11):1216. doi:10.3390/vaccines12111216
63. Gale RP, Chapel HM, Bunch C, et al. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. *New Engl J Med*. 1988;319(14):902-907. (In eng) doi:10.1056/nejm198810063191403
64. Shrestha P, Karmacharya P, Wang Z, Donato A, Joshi AY. Impact of IVIG vs. SCIG on IgG trough level and infection incidence in primary immunodeficiency diseases: a systematic review and meta-analysis of clinical studies. *World Allergy Organ J*. 2019;12(10):100068. doi:10.1016/j.waojou.2019.100068
65. Cowan J, Na IK, Gladiator A, Kamieniak M, Mustafa SS. Patient-reported outcomes with subcutaneous immunoglobulin in secondary immunodeficiency. *Front Immunol*. 2025;16:1528414. doi:10.3389/fimmu.2025.1528414
66. Gustafson R, Gardulf A, Hansen S, et al. Rapid subcutaneous immunoglobulin administration every second week results in high and stable serum immunoglobulin G levels in patients with primary antibody deficiencies. *Clin Exp Immunol*. 2008;152(2):274-279. doi:10.1111/j.1365-2249.2008.03620.x
67. da Cunha-Bang C, Rostgaard K, Andersen MA, et al. Risk of new malignancies among patients with CLL treated with chemotherapy: results of a Danish population-based study. *Br J Haematol*. 2021;193(2):339-345. doi:10.1111/bjh.17337
68. Lin WY, Fordham SE, Sunter N, et al. Genome-wide association study identifies risk loci for progressive chronic lymphocytic leukemia. *Nat Commun*. 2021;12(1):665. doi:10.1038/s41467-020-20822-9
69. Autore F, Pasquale R, Innocenti I, Fresa A, Laurenti F, Sora F, et al. Autoimmune hemolytic anemia in chronic lymphocytic leukemia: a comprehensive review. *Cancers (Basel)*. 2021;13(22):5804. doi:10.3390/cancers13225804
70. Go RS, Winters JL, Kay NE. How I treat autoimmune hemolytic anemia. *Blood*. 2017;129(22):2971-2979. doi:10.1182/blood-2016-11-693689
71. Dearden C, Wade R, Else M, et al. The prognostic significance of a positive direct antiglobulin test in chronic lymphocytic leukemia: a beneficial effect of the combination of fludarabine and cyclophosphamide on the incidence of hemolytic anemia. *Blood*. 2008;111(4):1820-1826 (In eng).
72. Birgens H, Frederiksen H, Hasselbalch HC, et al. A phase III randomized trial comparing glucocorticoid monotherapy versus glucocorticoid and rituximab in patients with autoimmune haemolytic anaemia. *Br J Haematol*. 2013;163(3):393-399. doi:10.1111/bjh.12541
73. Quinquenel A, Godet S, Dartigeas C, et al. Ibrutinib and idelalisib in the management of CLL-associated autoimmune cytopenias: a study from the FILO group. *Am J Hematol*. 2019;94(7):E183-E185. doi:10.1002/ajh.25480
74. Röth A, Bommer M, Hüttmann A, et al. Eculizumab in cold agglutinin disease (DECADE): an open-label, prospective, bicentric, nonrandomized phase 2 trial. *Blood Adv*. 2018;2(19):2543-2549. doi:10.1182/bloodadvances.2018024190

75. Hodgson K, Ferrer G, Montserrat E, Moreno C. Chronic lymphocytic leukemia and autoimmunity: a systematic review. *Haematologica*. 2011;96(5):752-761. doi:10.3324/haematol.2010.036152
76. Visco C, Ruggeri M, Laura Evangelista M, et al. Impact of immune thrombocytopenia on the clinical course of chronic lymphocytic leukemia. *Blood*. 2008;111(3):1110-1116. doi:10.1182/blood-2007-09-111492
77. Provan D, Butler T, Evangelista ML, Amadori S, Newland AC, Stasi R. Activity and safety profile of low-dose rituximab for the treatment of autoimmune cytopenias in adults. *Haematologica*. 2007;92(12):1695-1698. doi:10.3324/haematol.11709
78. Paul S, Jain N, Ferrajoli A, et al. A phase II trial of eltrombopag for patients with chronic lymphocytic leukaemia (CLL) and thrombocytopenia. *Br J Haematol*. 2019;185(3):606-608. doi:10.1111/bjh.15581
79. Ghazal H. Successful treatment of pure red cell aplasia with rituximab in patients with chronic lymphocytic leukemia. *Blood*. 2002;99(3):1092-1094. doi:10.1182/blood.v99.3.1092
80. Kyrou DSK, Koulierakis G, Vrontaras N, Stamatopoulos K, Karamanidou C. The looming cancer: a qualitative study on the experience of living with chronic lymphocytic leukemia (CLL) before the initiation of treatment. *Eur J Cancer Care*. 2024;2024:4034801. doi:10.1155/2024/4034801
81. Tadmor T, Melamed G, Alapi H, Gazit S, Patalon T, Rokach L. Vitamin D supplement for patients with early-stage chronic lymphocytic leukemia is associated with a longer time to first treatment. *Blood Adv*. 2024;8(14):3840-3846. doi:10.1182/bloodadvances.2023011458
82. Chen S, Zhang M, Gao Y, Zeng Y. Causal effects of vitamin D on leukemia risk: insights from two-sample Mendelian randomization analysis. *Nutr Hosp*. 2025;42(2):311-318. doi:10.20960/nh.05541
83. McCaughan D, Roman E, Smith A, Patmore R, Howell D. Treatment decision making (TDM): a qualitative study exploring the perspectives of patients with chronic haematological cancers. *BMJ Open*. 2022;12(3):e050816. doi:10.1136/bmjopen-2021-050816
84. Molica S. Defining treatment success in chronic lymphocytic leukemia: exploring surrogate markers, comorbidities, and patient-centered endpoints. *Expert Rev Hematol*. 2024;17(7):279-285. doi:10.1080/17474086.2024.2366534
85. 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;144(18):1924-1935. doi:10.1182/blood.2024024631
86. 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):744-759. doi:10.1016/S1470-2045(24)00196-7
87. Munir T, Girvan S, Cairns DA, et al. Measurable residual disease-guided therapy for chronic lymphocytic leukemia. *N Engl J Med*. 2025;393(12):1177-1190. doi:10.1056/NEJMoa2504341
88. Al-Sawaf O, Stumpf J, Zhang C, et al. Fixed-duration versus continuous treatment for chronic lymphocytic leukemia. *N Engl J Med*. 2025;394(11):1084-1096. doi:10.1056/NEJMoa2515458
89. 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):1423-1433. doi:10.1016/S1470-2045(23)00452-7
90. William W, Wierda PB, Allan J, et al. Final Analysis of Fixed-Duration Ibrutinib + Venetoclax for Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) in the Phase 2 CAPTIVATE Study. Abstract #S156. *HemaSphere*. 2025;9:e70151.
91. Shadman M, Munir T, Ma S, et al. Zanubrutinib and venetoclax for patients with treatment-naïve chronic lymphocytic leukemia/small lymphocytic lymphoma with and without Del(17p)/TP53 mutation: SEQUOIA arm D results. *J Clin Oncol*. 2025;43(21):2409-2417. doi:10.1200/JCO-25-00758
92. Levin M.D., Kersting S., Dubois J., et al. Improved efficacy with response- and mrd-guided ibrutinib-obinutuzumab (IO) intensification after ibrutinib-venetoclax (IV) in first line chronic lymphocytic leukemia (CLL) patients: primary analysis of the HOVON 158/next step phase 2 trial. *Blood*. 2024;144:1013. doi:10.1182/blood-2024-207452
93. Brown JR, Seymour JF, Jurczak W, et al. Fixed-duration acalabrutinib combinations in untreated chronic lymphocytic leukemia. *N Engl J Med*. 2025;392(8):748-762. doi:10.1056/NEJMoa2409804
94. 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;146:2168-2176. doi:10.1182/blood.2024028205
95. 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;39(31):3441-3452. doi:10.1200/JCO.21.01210
96. Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med*. 2023;388(4):319-332. doi:10.1056/NEJMoa2211582
97. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib-obinutuzumab improves survival vs chemoimmunotherapy in treatment-naive CLL in the 6-year follow-up of ELEVATE-TN. *Blood*. 2025;146(11):1276-1285. doi:10.1182/blood.2024024476
98. 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):780-787. doi:10.1200/JCO-24-02265
99. Seymour JF, Byrd JC, Ghia P, et al. Detailed safety profile of acalabrutinib vs ibrutinib in previously treated chronic lymphocytic leukemia in the ELEVATE-RR trial. *Blood*. 2023;142(8):687-699. (In eng) doi:10.1182/blood.2022018818
100. Simon F, Ligtvoet R, Bohn JP, et al. Acalabrutinib treatment for older (>/=80 years old) and/or frail patients with CLL: primary end point analysis of the CLL-Frail trial. *Blood*. 2025;26:3153-3162. doi:10.1182/blood.2025028550
101. Jurczak W, Kwiatek M, Czyz J, et al. BRUIN CLL-313: randomized phase III trial of pirtobrutinib versus bendamustine plus rituximab in untreated patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. *J Clin Oncol*. 2026;44(6):466-475. doi:10.1200/JCO-25-02380
102. Woyach JA, Qiu L, Grosicki S, et al. Pirtobrutinib versus ibrutinib in treatment-naive and relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. *J Clin Oncol*. 2025;44:476-485. doi:10.1200/JCO-25-02477
103. Byrd JC, Furman RR, Coutre SE, et al. Ibrutinib treatment for first-line and relapsed/refractory chronic lymphocytic leukemia: final analysis of the pivotal phase Ib/II PCYC-1102 study. *Clin Cancer Res*. 2020;26(15):3918-3927. doi:10.1158/1078-0432.CCR-19-2856
104. Tam CS, Anderson MA, Simkovic M, et al. Zanubrutinib in the treatment of patients with del(17p) and/or TP53 CLL/SLL: analysis across clinical studies. *Blood Adv*. 2025;10(3):694-706. doi:10.1182/bloodadvances.2025015986
105. Huber H, Tausch E, Schneider C, et al. Final analysis of the CLL2-GIVe trial: obinutuzumab, ibrutinib, and venetoclax for untreated CLL with del(17p)/TP53mut. *Blood*. 2023;142(11):961-972. doi:10.1182/blood.2023020013
106. Davids MS, Ryan CE, Lampson BL, et al. Phase II study of acalabrutinib, venetoclax, and obinutuzumab in a treatment-naïve chronic lymphocytic leukemia population enriched for high-risk disease. *J Clin Oncol*. 2025;43(7):788-799. doi:10.1200/JCO-24-02503

107. Kater AP, Harrup R, Kipps TJ, et al. The MURANO study: final analysis and retreatment/crossover substudy results of VenR for patients with relapsed/refractory CLL. *Blood*. 2025;145(23):2733-2745. doi:10.1182/blood.2024025525
108. Mato AR, Roeker LE, Allan JN, et al. Outcomes of front-line ibrutinib treated CLL patients excluded from landmark clinical trial. *Am J Hematol*. 2018;93(11):1394-1401. doi:10.1002/ajh.25261
109. Mato AR, Hill BT, Lamanna N, et al. Optimal sequencing of ibrutinib, idelalisib, and venetoclax in chronic lymphocytic leukemia: results from a multicenter study of 683 patients. *Ann Oncol*. 2017;28(5):1050-1056. doi:10.1093/annonc/mdx031
110. Sharman JP, Munir T, Grosicki S, et al. Phase III trial of pirtobrutinib versus idelalisib/rituximab or bendamustine/rituximab in covalent bruton tyrosine kinase inhibitor-pretreated chronic lymphocytic leukemia/small lymphocytic lymphoma (BRUIN CLL-321). *J Clin Oncol*. 2025;43(22):2538-2549. doi:10.1200/JCO-25-00166
111. Awan FT, Schuh A, Brown JR, et al. Acalabrutinib monotherapy in patients with chronic lymphocytic leukemia who are intolerant to ibrutinib. *Blood Adv*. 2019;3(9):1553-1562. doi:10.1182/bloodadvances.2018030007
112. Mato AR, Hess LM, Chen Y, et al. Outcomes for patients with chronic lymphocytic leukemia (CLL) previously treated with both a covalent BTK and BCL2 inhibitor in the United States: a real-world database study. *Clin Lymphoma Myeloma Leuk*. 2022;23:57-67. (In eng) doi:10.1016/j.clml.2022.09.007
113. Kater AP, Arslan Ö, Demirkan F, et al. Activity of venetoclax in patients with relapsed or refractory chronic lymphocytic leukaemia: analysis of the VENICE-1 multicentre, open-label, single-arm, phase 3b trial. *Lancet Oncol*. 2024;25(4):463-473. doi:10.1016/S1470-2045(24)00070-6
114. Thompson MC, Harrup RA, Coombs CC, et al. Venetoclax retreatment of patients with chronic lymphocytic leukemia after a previous venetoclax-based regimen. *Blood Adv*. 2022;6(15):4553-4557. doi:10.1182/bloodadvances.2022007812
115. 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. doi:10.1056/NEJMoa2300696
116. Simon F, Ligtvoet R, Fuerstenau M, et al. Redefining early vs late progressive disease (PD) in chronic lymphocytic leukemia: a pooled analysis of fixed-duration therapies. *Blood*. 2025;146(supplement 1):2107.
117. Lin VS, Lew TE, Handunnetti SM, et al. BTK inhibitor therapy is effective in patients with CLL resistant to venetoclax. *Blood*. 2020;135(25):2266-2270. doi:10.1182/blood.2020004782
118. 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):2808-2817. doi:10.1182/bloodadvances.2025016006
119. Niemann CU, Dubois J, Nasserinejad K, et al. Long-term follow-up of MRD-guided ibrutinib plus venetoclax in relapsed CLL: phase 2 VISION/HO141 trial. *Blood Adv*. 2025;9(15):3665-3675. doi:10.1182/bloodadvances.2024015180
120. Mato AR, Hess LM, Chen Y, et al. Outcomes for patients with chronic lymphocytic leukemia (CLL) previously treated with both a covalent BTK and BCL2 inhibitor in the United States: a real-world database study. *Clin Lymphoma Myeloma Leuk*. 2023;23(1):57-67. doi:10.1016/j.clml.2022.09.007
121. Sharman JP, Coutre SE, Furman RR, et al. Final results of a randomized, phase III study of rituximab with or without idelalisib followed by open-label idelalisib in patients with relapsed chronic lymphocytic leukemia. *J Clin Oncol*. 2019;37:1391-1402. doi:10.1200/JCO.18.01460
122. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *New Engl J Med*. 2014;370(11):997-1007. (In eng) doi:10.1056/NEJMoa1315226
123. Tournilhac O, van Gelder M, Eikema DJ, et al. The European landscape on allogeneic haematopoeietic cell transplantation in Chronic Lymphocytic Leukaemia between 2009 and 2019: a perspective from the Chronic Malignancies Working Party of the EBMT. *Bone Marrow Transplant*. 2023;58(6):621-624. doi:10.1038/s41409-023-01955-z
124. Schetelig J, Hoek J, Stilgenbauer S, et al. Allogeneic hematopoietic cell transplantation for patients with TP53 mutant or deleted chronic lymphocytic leukemia: results of a prospective observational study. *Bone Marrow Transplant*. 2021;56(3):692-695. doi:10.1038/s41409-020-01013-y
125. Barge L, Tran S, Kennedy G, et al. Outcomes of allogeneic haemopoietic transplant for chronic lymphocytic leukaemia in the modern era. *Intern Med J*. 2025;55(7):1105-1113. doi:10.1111/imj.70050
126. Montoya S, Bourcier J, Noviski M, et al. Kinase-impaired BTK mutations are susceptible to clinical-stage BTK and IKZF1/3 degrader NX-2127. *Science*. 2024;383(6682):eadi5798. doi:10.1126/science.adi5798
127. Mhibik M, Gaglione EM, Eik D, et al. Cytotoxicity of the CD3×CD20 bispecific antibody epcoritamab in CLL is increased by concurrent BTK or BCL-2 targeting. *Blood Adv*. 2023;7(15):4089-4101. doi:10.1182/bloodadvances.2022009517
128. 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):641-654. doi:10.1016/S0140-6736(23)01052-8
129. Soilleux EJ, Wotherspoon A, Eyre TA, Clifford R, Cabes M, Schuh AH. Diagnostic dilemmas of high-grade transformation (Richter's syndrome) of chronic lymphocytic leukaemia: results of the phase II National Cancer Research Institute CHOP-OR clinical trial specialist haemato-pathology central review. *Histopathology*. 2016;69(6):1066-1076. doi:10.1111/his.13024
130. Kittai AS, Marchetti M, Al-Sawaf O, et al. International consensus statement on diagnosis, evaluation, and research of Richter transformation: the ERIC recommendations. *Blood*. 2025;146(3):291-303. doi:10.1182/blood.2024028064
131. Mato AR, Wierda WG, Davids MS, et al. Utility of PET-CT in patients with chronic lymphocytic leukemia following B-cell receptor pathway inhibitor therapy. *Haematologica*. 2019;104(11). doi:10.3324/haematol.2018.207068
132. Barrett A, Harris C, Eyre TA. Clonal relatedness as a prognostic marker in Richter transformation of chronic lymphocytic leukemia: a systematic review. *Blood Adv*. 2025;9(11):2773-2780. doi:10.1182/bloodadvances.2024015594
133. Eyre TA, Schuh A, Wierda WG, et al. Acalabrutinib monotherapy for treatment of chronic lymphocytic leukaemia (ACE-CL-001): analysis of the Richter transformation cohort of an open-label, single-arm, phase 1-2 study. *Lancet Haematol*. 2021;8:e112-121. (In eng) doi:10.1016/s2352-3026(21)00305-7
134. Wierda WG, Shah NN, Cheah CY, et al. Pirtobrutinib, a highly selective, non-covalent (reversible) BTK inhibitor in patients with B-cell malignancies: analysis of the Richter transformation subgroup from the multicentre, open-label, phase 1/2 BRUIN study. *Lancet Haematol*. 2024;11(9):e682-e692. doi:10.1016/S2352-3026(24)00172-8
135. Cwynarski K, van Biezen A, de Wreede L, et al. Autologous and allogeneic stem-cell transplantation for transformed chronic lymphocytic leukemia (Richter's syndrome): a retrospective analysis from the chronic lymphocytic leukemia subcommittee of the chronic leukemia working party and lymphoma working party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol*. 2012;30(18):2211-2217. doi:10.1200/JCO.2011.37.4108

136. Guièze R, Eikema DJ, Koster L, et al. Allogeneic hematopoietic stem-cell transplantation for patients with Richter transformation: a retrospective study on behalf of the Chronic Malignancies Working Party of the EBMT. *Bone Marrow Transplant*. 2024;59(7):950-956. doi:10.1038/s41409-024-02256-9
137. Davids MS, Rogers KA, Tyekucheva S, et al. Venetoclax plus dose-adjusted R-EPOCH for Richter syndrome. *Blood*. 2022;139(5):686-689. doi:10.1182/blood.2021011386
138. Al-Sawaf O, Ligtvoet R, Robrecht S, et al. Tislelizumab plus zanubrutinib for Richter transformation: the phase 2 RT1 trial. *Nat Med*. 2024;30(1):240-248. doi:10.1038/s41591-023-02722-9
139. Tedeschi A, Frustaci AM, Condoluci A, et al. Atezolizumab, venetoclax, and obinutuzumab combination in Richter transformation diffuse large B-cell lymphoma (MOLTO): a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2024;25(10):1298-1309. doi:10.1016/S1470-2045(24)00396-6
140. Guièze R, Ysebaert L, Roos-Weil D, et al. Blinatumomab after R-CHOP bridging therapy for patients with Richter transformation: a phase 2 multicentre trial. *Nat Commun*. 2024;15(1):6822. doi:10.1038/s41467-024-51264-2
141. Kater AP, Janssens A, Eradat H, et al. Epcoritamab monotherapy for Richter transformation (EPCORE CLL-1): findings from a single-arm, multicentre, open-label, phase 1b/2 trial. *Lancet Haematol*. 2026;13(1):e8-e21. doi:10.1016/S2352-3026(25)00327-8
142. Kittai AS, Bond D, Huang Y, et al. Anti-CD19 chimeric antigen receptor T-cell therapy for Richter transformation: an international, multicenter, retrospective study. *J Clin Oncol*. 2024;42:2071-2079. doi:10.1200/JCO.24.00033
143. Beyar-Katz O, Benjamini O, Delgado J, et al. CD19 CAR T-cell therapy in Richter transformation: a multicentre retrospective analysis by the European Research Initiative on chronic lymphocytic leukaemia. *J Cell Mol Med*. 2025;29(20):e70841. doi:10.1111/jcmm.70841