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REVIEW

Real-life diagnostic and therapeutic approach to CLL/SLL in tuscany: the 2025 consensus

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Abstract

Management of chronic lymphocytic leukemia/ small lymphocytic lymphoma. (CLL/SLL) has undergone a significant paradigm shift, with chemo immunotherapy being virtually abandoned in favor of targeted agents. A panel of CLL/SLL experts from Tuscany proposes an updated real-life diagnostic and therapeutic approach that integrates genomic and somatic prognostic factors into routine risk stratification and treatment decisions. While the safety and efficacy of new agents are well-established in both clinical trials and real-world series, the rapid introduction of second-generation BTK inhibitors and BCL-2 antagonists necessitates a uniform and shared approach for daily clinical practice. This updated consensus reinforces the essential role of FISH for 17p deletion and TP53 mutational status before every treatment line, while IGHV mutation status should be performed for initial risk assessment. Reflecting current evidence, the proposal emphasizes a comprehensive pretreatment workup, with a particular focus on cardio-oncological screening and monitoring according to recent ESC guidelines to mitigate risks associated with BTKIs. The consensus reaffirms abdominal and superficial lymph node ultrasound as the gold standard radiological investigation for both diagnosis and response evaluation in CLL, offering a practical and radiation-free tool for longitudinal monitoring. Treatment selection is tailored based on age, genetic risk, and comorbidities, prioritizing zanubrutinib, acalabrutinib, and venetoclax-based regimens to prevent unnecessary toxicities. Furthermore, the consensus addresses the management of high-risk scenarios, including Richter transformation and the emerging role of pirtobrutinib and BTK degraders. By combining the latest clinical evidence with extensive daily experience, this updated Tuscany consensus provides a practical framework for optimized, personalized management of CLL/SLL patients in the modern therapeutic era.

Keywords Chronic Lymphocytic Leukemia · Small Lymphocytic Lymphoma · Targeted Therapies · BTK · BCL-2 · Venetoclax · Ibrutinib · Acalabrutinib · Zanubrutinib · Pirtobrutinib

Introduction

Chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL) is the result of clonal proliferation and progressive accumulation of mature, clonal and monomorphic B cells within blood, bone marrow, lymph nodes, and spleen [1].

CLL/SLL has an age-adjusted incidence of 4.6 per 100,000 inhabitants per year [2] and this is the most frequent type of leukemia in the Western world.

The median age at diagnosis is 70 years [2] and CLL/SLL is about twice as frequent in men as in women [2] and less than 10% of CLL/SLL patients at the diagnosis are younger than 45 years [3].

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While the incidence of CLL/SLL has been stable over the last two decades, the mortality is continuously declining, and the 5-year overall survival is now estimated to reach 88.5% [2]. In 2015, an epidemiological study involving 68% of Italian hematology departments was conducted; this study estimated that over 17,000 individuals affected by this disease are living throughout the country, with a prevalence of 28 cases per 100,000 inhabitants [4]. It should be acknowledged that epidemiological estimates of CLL/SLL may be underestimated, particularly in studies not systematically including flow cytometry, which may fail to identify early-stage CLL or cases with low-level lymphocytosis, such as monoclonal B-cell lymphocytosis [3]. The precision of CLL prevalence data is strictly dependent on the application of standardized immunophenotyping, which is essential to confirm the diagnosis and distinguish CLL from other B-cell malignancies; without the integration of such standardized flow cytometry protocols, a significant proportion of asymptomatic or early-stage cases may remain undetected in population-based studies [5].

Considering a population of 3,600,000 individuals, we can estimate that approximately 1,000 individuals affected by CLL/SLL live in Tuscany. Considering the inhabitants divided into age groups with different incidence rates (5 cases per 10,000 from 50 to 70 years of age, and 20 cases per 100,000 from 70 to 90 years of age), we can estimate approximately 250 new cases per year in the region.

A limited number of risk factors have been identified, which include exposure to herbicides, such as "Agent Orange", and pesticides, sun exposure, atopic health conditions, and radiation [6]. Nevertheless, there is also a familiar predisposition: indeed, 10% of patients have a familiar history of the same disease, with a 6-9-fold risk of developing CLL/SLL in first degree relatives. The risk of monoclonal B lymphocytosis (MBL) is also increased where there are 2 or more family members with CLL [7], even if there is no indication for performing genetic screening in these families.

Studies over the years have led to the understanding that CLL/SLL is initiated by a series of sequential genetic and chromosomal alterations that can also affect prognosis [8]. CLL/SLL is often initiated by the loss or addition of large chromosomal material (e.g., deletion 13q, deletion 11q, trisomy 12), followed later by additional mutations that render the leukemia increasingly aggressive [8].

Approximately 80% of CLL/SLL patients carry at least one of these common chromosomal aberrations: del(13q) - around in half of cases; trisomy 12 in up to one-fifth of patients; del(11q) in 10% of patients, and del(17p) in 5–8% of cases [8] del(17p) reflects the loss of the tumor suppressor gene *TP53* [9] mutations of *TP53* are associated with poorer overall (OS) and progression-free survival (PFS), and require specific therapeutic approaches [8].

Another important factor in the pathophysiology of CLL is represented by the mutation status of the immunoglobulin heavy chain variable region gene (IGHV). Approximately one-half of patients with CLL have an unmutated-IGHV status (< 2% deviation from the germline sequence). These patients typically have a shorter interval between diagnosis and disease progression, and poorer outcomes. In contrast, subjects carrying mutated-IGHV status (≥ 2% deviation) experience a more indolent clinical course ([10, 11]). The clinical course of CLL/SLL is highly variable, which is likely related to the individual profile of chromosomal and genetic aberrations [8]. International guidelines recognize the utility of the diagnostic and prognostic factors in the management of patients with CLL [8, 12, 13].

Most patients at diagnosis are asymptomatic, and will develop symptoms within a few years, while some individuals remain asymptomatic for decades [14]. A diagnosis of CLL is often an incidental finding of lymphocytosis (lymphocytes > 5×10^9/L), whereas in other cases [8], such as in SLL, the first clinical presentation is lymphadenopathy, while B symptoms or cytopenias are less frequent [8].

CLL/SLL is considered an indolent disease, and in its early stages it may remain asymptomatic. Some CLL/SLL patients may be under active surveillance (watch and wait approach), while others with CLL/SLL-derived symptoms may require treatment [15].

In 2019 and in 2022, our working group elaborated a consensus, suggesting a real-life diagnostic and therapeutic approach to CLL/SLL that would help clinicians in daily practice ([16, 17]). Considering recent therapeutic advances affecting the CLL/SLL management, herein we provide an update of the previous Tuscany consensus in CLL management.

This updated proposal was developed and validated by 18 hematologist experts in management of CLL/SLL patients in Tuscany. The approach outlined is derived from their experience in daily clinical practice and is supported by guidelines, clinical trials results, and drugs prescribing regulations in Italy. The produced document would be useful for the entire Italian scientific community because strictly compliant with Italian Medicines Agency (AIFA) rules. This document was not created for use outside the European Union, but it could be adapted in accordance with the marketing authorization rules of the drug regulatory agencies in the individual countries.

Diagnosis

Clear recommendations have been given for diagnosis of CLL/SLL [12, 15]. The process of diagnosing CLL usually begins with a routine and complete blood test, peripheral

blood smear, and flow cytometry to confirm clonality of B-lymphocytes, at least 5000 clonal B cells/mcL (5 x 10^9/L) in the peripheral blood. Compared to our previous suggestions [17] there are no relevant updates in the diagnostic phase.

Briefly, CLL must be differentiated from MBL and SLL [12, 15]. There are two types of MBL, high count MBL (defined as clonal B cell count of 0.5–4.9 × 10^9/L), and low count MBL (defined as clonal B cell count < 0.5 × 10^9/L). Recent studies have shown that the risk that high count MBL would progress to CLL requiring therapy is 1–2% per year; in contrast, the risk of low count MBL progression is lower ([18, 19]). The diagnosis of SLL requires the presence of lymphadenopathy and/or splenomegaly, with less than 5000 B lymphocytes/mcL (5 × 10^9/L) in the peripheral blood [13].

In addition, the clonality of B cells should be confirmed by flow cytometry in order to detect the characteristic CLL immunophenotype, namely clonal kappa or lambda light chain restriction, co-expression of the surface antigen CD5 and the B cell antigens CD19, and CD23, and low levels of CD20 and CD79b [12, 15]. High expression of CD200 is also a useful marker for CLL, but with low specificity (36%) [20].

CLL - at diagnosis

At diagnosis, a patient's careful medical history is necessary, particularly regarding cardiovascular comorbidities, prior or current malignancies, and concomitant medications. In our clinical practice, we perform a complete blood test, physical examination (abdomen and palpable lymph nodes) and imaging studies (ultrasound and X-ray of chest) (Table 1).

Molecular analysis to detect IGHV mutation status can provide useful prognostic information [12, 15], enabling physicians to provide more accurate patient counseling and better define the frequency of follow-up. Since IGHV mutational status is unchanged over time, it needs to be performed only once before starting treatment.

It is important to counsel patients about the increased risk of infection (due to impaired cellular and humoral immune function) with need for appropriate vaccinations and the need for undergoing timely screening procedures for other cancers [21]. Patients with CLL have a higher risk for recurrence of basal and squamous skin cell carcinoma compared with those without CLL [22], so, annual screening for skin cancers is recommended. About vaccinations, recombinant anti-herpes zoster, anti-SARS-CoV-2, anti-flu, anti-meningococcal, anti-pneumococcal, and anti-Haemophilus influenzae vaccinations are recommended for all patients with CLL, possibly already at diagnosis [23], according to the national indications.

CLL – watch & wait

During active observation, patients undergo serial monitoring, with collection of medical history, physical examination, and complete blood count assessment every 6–12 months [24]. In our clinical practice, we perform an abdominal ultrasound at least once a year (timing to be defined according to clinical needs).

CLL- before treatment

The Table 2 lists the criteria for starting treatment according to the iwCLL guidelines.

Before treatment, 13% of patients with CLL may present with autoimmune cytopenias. Resistance of these cytopenias to steroid treatment, rituximab, or other immunological therapies nevertheless represents one of the criteria for initiating therapy [25].

Moreover, for the choice of treatment, it is necessary to consider **several factors**, including:

1. Comorbidities and performance status

Before treatment, a comprehensive assessment of performance status, comorbidities and concomitant medications is fundamental for tailoring personalized treatment. Various general tools are available for assessing patient's comorbidities, such as the Cumulative Illness Rating Scale (CIRS) [26], and G8 score for elderly people [27].

2. Cardiovascular comorbidity

The pretreatment workup before therapy should include a targeted cardio-vascular examination, including electrocardiogram (ECG) and blood pressure measurement to identify possible risk factors, first of all atrial fibrillation (AF) and hypertension (HTN) [28]. Recently, cardio-oncological European guidelines have been published, offering specific recommendations for Bruton Kinase Inhibitors (BTKIs) candidates.

The principal class of side effects associated with BTKIs is related to the cardiovascular system, with atrial fibrillation (AF) and hypertension being particularly notable due to their frequency, and ventricular arrhythmias due to their severity. It is crucial to monitor blood pressure and pulse in these patients before starting BTKIs and during therapy (Table 3) [28].

2.1 Patient with history of atrial fibrillation (AF)

Patients with a history of AF and no additional risk factors should be treated with the typical standard of care for

Table 1 CLL/SLL diagnostic work-up

Category	Details / Tests	Notes
Medical History	Previous or concurrent malignancies Pulmonary infections (suspected or confirmed tuberculosis) History of arrhythmias Family history of sudden cardiac death Uncontrolled hypertension	
Physical Examination	Complete clinical evaluation	Focus on lymph nodes, spleen, liver, infection signs
Blood Tests	CBC Creatinine Uric acid LDH Transaminases Total and fractionated bilirubin Total proteins Serum protein electrophoresis IgG, IgA, IgM levels Serum β2-microglobulin	
Peripheral Blood Smear	Morphology evaluation	
Immunophenotyping	Lymphocyte immunophenotype on peripheral blood	Essential for diagnosis
IgHV Mutation Analysis	Sanger or NGS	IgHV mutations are stable over time Can be done at diagnosis or treatment initiation Cut-off: 98% homology
FISH (11q, 17p)	Not recommended at diagnosis	Perform at treatment initiation because abnormalities may change over time
Bone Marrow Aspiration	Performed only in specific cases	Indicated in cytopenias or suspected Richter transformation
Imaging	Total-body ultrasound: detailed lymph node size and characteristics; splenic area measurement Chest X-ray	
Additional Imaging (Selective Use)	CT or MRI (selected cases only; not routine) PET-CT	PET-CT recommended when Richter syndrome is suspected to guide biopsy

Table 2 Criteria for starting therapy

Progressive lymphocytosis with an increase of ≥50% over 2 months or LDT < 6 months (if lymphocytosis > 30×10^9/L, a longer observation period may be required in patients with lymphocytosis < 30×10^9/L).
Evidence of progressive marrow failure with development (or worsening) of anemia (Hb < 10 g/dL) and/or thrombocytopenia (platelet count < 100×10^9/L).
Massive splenomegaly (≥6 cm from the costal arch) or progressive or symptomatic splenomegaly.
Massive lymphadenopathy (nodes with longest diameter ≥ 10 cm) or progressive or symptomatic lymphadenopathy.
Autoimmune anemia and/or thrombocytopenia resistant to corticosteroids.
Symptomatic extra lymphatic involvement.
Disease-related systemic symptoms: • Weight loss ≥ 10% in the last 6 months • Significant asthenia/fatigue (ECOG ≥ 2) • Fever ≥ 38 °C for ≥ 15 days without evidence of infection • Night sweats for ≥ 1 month without evidence of infection

Table 3 Recommended cardiovascular assessment in patients with CLL/SLL

Assessment	Recommendation
Medical history	Comprehensive cardiovascular history
Blood pressure	Baseline blood pressure measurement
Electrocardiography	Baseline 12-lead electrocardiogram
Concomitant therapies	Review of concomitant medications
Cardiovascular risk factors	Assessment of diabetes, obesity, hypertension, dyslipidemia, and chronic kidney disease
Structural heart disease	History of valvular heart disease
Cardiac rhythm and function	History of arrhythmias, heart failure, or left ventricular dysfunction
Ischemic heart disease	History of coronary artery disease
High cardiovascular risk or established cardiovascular disease	Transthoracic echocardiography and baseline cardiac biomarkers

BTKIs therapy used in patients without a history of AF. The second-generation BTKIs are preferred over ibrutinib for this population because of their lower risk of AF, as well as evidence of less effect on platelet function than ibrutinib in pre-clinical work; however, the risk of bleeding remains similar [28]. The differential cardiovascular safety profile of BTKIs is supported by both pre-clinical and clinical evidence. Mechanistically, ibrutinib's off-target inhibition of cardiac kinases like CSK promotes an arrhythmogenic substrate [29]. Clinically, this translates into a higher AF burden compared to next-generation, more selective inhibitors; for instance, the **ALPINE** trial demonstrated a markedly lower AF incidence with zanubrutinib versus ibrutinib (7.1% vs. 17.0%) [30].

2.2 Patient with history of hypertension (HTN)

Patients with a history of HTN can be successfully treated with BTKIs therapy, but the recommended adjustments to standard care include clinical monitoring of blood pressure, including at least biweekly checks. If HTN is not controlled, it is necessary to initiate treatment according to current HTN treatment guidelines [28].

2.3 Patient with history congestive heart failure (CHF)

Before initiating treatment, patients with CHF should undergo an echocardiogram, ECG, and Holter monitoring to identify any arrhythmias at baseline. Repeat the ECG at 3 months and continue with ongoing cardiology reviews. However, it is strongly recommended to treat these patients in collaboration with a cardiologist or cardio-oncologist [28].

In general, BTKIs should be avoided in patients with active CHF [28], but this is a relative contraindication, not an absolute one. A B-Cell Lymphoma 2 (BCL-2) antagonist may be a better option because of the lower risk of cardiovascular events, although patients need to be able to tolerate high volume hydration to prevent possible tumor lysis syndrome. If BTKI therapy is pursued, a second/third generation BTKI should be preferred to minimize the risk of AF [28].

2.4 Patient with history of ventricular arrhythmias

The use of BTKIs, especially ibrutinib, should be avoided in patients with a history of ventricular arrhythmias and cardiac arrest. Indeed, ibrutinib has been shown to increase the incidence of ventricular arrhythmias and sudden cardiac death [28].

As shown in Table 4, the only contraindications to starting BTKI are: a history of ventricular arrhythmia, uncontrolled HTN, and severe or uncontrolled CHF [28].

2.5 The role of cardio-oncology

In our clinical practice, as recommended by the ESC guidelines, we perform a baseline cardiological assessment with ECG before starting therapy.

It may be useful to use the HFA-ICOS or SCORE2 or SCORE2-OP scoring systems to assess cardiovascular baseline risk (available at https://www.cancercalc.com/hfa-icos_cardio_oncology_risk_assessment.php; https://www.mdcalc.com/calc/10499/systematic-coronary-risk-evaluation-score2; https://www.mdcalc.com/calc/10503/score2-older-persons-score2-op).

For medium, high and very high-risk patients, it would be useful to refer them to cardio-oncologists to optimize risk factors and provide a personalized management plan. The consensus also proposes a template to be sent to cardiologists, indicating the patient's cardiovascular comorbidities and the type of treatment for which the patient is a candidate (Table 5).

Table 4 Cardiac considerations for Bruton tyrosine kinase inhibitor therapy

Clinical condition	Recommendations
Atrial fibrillation	Assess baseline risk (high vs. low). Low-risk patients may be treated with BTK inhibitors. Prefer second-generation BTK inhibitors (acalabrutinib or zanubrutinib) or alternative therapies. BTK inhibitor therapy may be continued after multidisciplinary discussion in patients with permanent or persistent atrial fibrillation, hypertension, or history of myocardial infarction. BTK inhibitors are not recommended in patients with a history of ventricular arrhythmias, family history of sudden cardiac death, severe or uncontrolled hypertension, severe or uncontrolled congestive heart failure (LVEF < 30%), or need for dual antiplatelet therapy or combined antiplatelet and anticoagulant therapy.
Hypertension	BTK inhibitor therapy may be used if hypertension is well controlled. Blood pressure should be monitored at least every 2 weeks during the first 3–6 months of therapy.
Congestive heart failure	Baseline echocardiographic assessment is recommended. Restrict sodium intake to <2 g/day. Monitor body weight daily and blood pressure twice weekly. Management should involve a multidisciplinary team or collaboration with a cardio-oncologist.
Ventricular arrhythmias	Ibrutinib should be avoided. The risk associated with second-generation BTK inhibitors (acalabrutinib or zanubrutinib) is currently unknown.

Table 5 Template for cardiac assessment

PATIENT REGISTRATION	First and Last Name: …… Gender: M □ F □ Date of Birth: ……
CARDIOVASCULAR RISK FACTORS	Age (>65 years for anthracyclines) □ Family history of CV events □ Smoking □ Hypertension □ Dyslipidemia □ Diabetes □ Obesity □ Previous heart disease □ (Specify……)
HEMATOLOGICAL HISTORY	Pathology: …… Planned or ongoing treatment:…… Thoracic radiotherapy □ (Dose and date)…… Anthracyclines □ (Dose……) Proteasome inhibitors □ (which ……) BTKI □ (which ……) TKI □ (which ……) Other therapies □ …… Risk of Secondary Hemochromatosis: Yes □ No □ Reason:……
EXPECTED TOXICITY	Ventricular dysfunction □ Arrhythmias □ Hypertension □ Other □ ……
REASON FOR REQUESTING CARDIOLOGICAL EVALUATION	Pre-Treatment □ Scheduled Checkup □ Cardiac Toxicity (suspected or proven) □ Follow-up □ Pre-stem cell apheresis evaluation □ Pre-lymphocyte apheresis □ Pre-autologous transplant evaluation □ Pre-allogeneic transplant □

3. Bleeding risk management

Another relevant side effect associated with all BTKIs is the bleeding risk that may increase in patients on antiplatelet or anticoagulant therapy for other reasons. Thus, concurrent treatment with BTKIs and vitamin K antagonist or dual antiplatelet therapy should be avoided [28]. Apixaban, rivaroxaban, and edoxaban represent potential options for anticoagulation, due to their minimal interactions with CYP3A4. Oral Xa inhibitors may be started at a reduced dose for the initial 7–10 days, followed by titration to maintenance doses based on patient's tolerance. Because dabigatran is a major substrate for P-glycoprotein, its use is discouraged [31].

4. Renal impairment

The main risk for patients with renal impairment is the possibility of experiencing tumor lysis syndrome when starting venetoclax, which could lead to worsening renal function.

The current guidelines involving dose escalation, hydration, the use of hypouricemic agents or a debulking phase with anti-CD20 antibodies or BTKIs can mitigate this risk [32]. Regarding TLS risk score, greater disease burden (lymph nodes ≥ 10 cm or ≥ 5 cm with lymphocytes ≥ 25×10^9/L), and presence of significant kidney dysfunction may increase TLS risk [33].

5. Disease burden

Bone marrow biopsy may be useful prior to starting therapy to exclude other causes of cytopenias, especially in CLL/SLL patients, who are often > 70 years old at time of treatment and may have other conditions (e.g., myelodysplastic syndrome).

Moreover, bone marrow may show signs of autoimmune phenomena in the absence of massive CLL infiltration, in contrast to other possible features of cell-mediated cytotoxicity. Therefore, a bone marrow biopsy might be needed in the context of suspected autoimmune cytopenias to better assess diagnosis and aid in choice of treatment [15]. The consensus establishes to evaluate the bone marrow biopsy in case of SLL.

Computed tomography (CT) should not be considered as an initial diagnostic tool, except for specific cases based on clinical suspicion [15].

Richter transformation should be considered in patients with B-symptoms, rapid progression, asymmetric progression, or significantly elevated lactate dehydrogenase without an alternative cause [32]. If Richter's syndrome is suspected, the experts agreed that a PET-guided lymph node biopsy is recommended [15].

6. Infection disease status

Before starting therapy with anti-CD20 antibodies, screening for HBV, HIV, HCV, mycobacterium (quantiFERON) is mandatory [34].

For HBV, patients positive for HBsAg should receive antiviral prophylaxis with lamivudine, entecavir or tenofovir. Patients who test negative for the HBsAg, but have either anti-HBc or anti-HBs, should undergo serial HBV DNA measurements and, if the HBV DNA is detected in the serum, preemptive therapy should be started. Patients on anti-HBV prophylaxis or preemptive therapy should be monitored with monthly HBV DNA serum levels [34].

It is important to remember that in our clinical practice we recommend immunoglobulin supplementation for patients with hypogammaglobulinemia (typically IgG < 400 mg/dL) and recurrent severe infections.

7. Molecular testing

Next generation sequencing techniques (NGS) to determine IGHV mutation status are now available, even if traditional determination of IGHV by Sanger sequencing remains the methodology most commonly used in clinical practice and is still acceptable [21].

In a recent study, approximately 40% of all CLL patients had stereotyped B cell receptors distributed among 29 major subsets, and the incidence of the stereotypy was higher in IGHV unmutated form [35]. In our routine clinical practice, we consider that the kind of stereotype is not useful for treatment choice.

On the contrary, prior to first line and each line of therapy it is fundamental the assessment of *TP53* mutations, by NGS or Sanger sequencing [33]. Notwithstanding the clinical impact of the low-burden *TP53* mutations (VAF < 10%) is still a matter of debate, our group suggests to consider as poor prognostic factor all *TP53* mutation VAF values [8, 33].

Prior to first line and each line of therapy it is also useful performing FISH for 17p and 11q deletions, as presence of these chromosomal aberrations can influence treatment selection [33]. Del17p/TP53 mutation should not be used as an indication for initiating treatment. Karyotyping is not mandatory, but 5 or more found abnormalities can be considered to define patient as at high genomic risk [15, 36].

8. Preservation of fertility

There are currently no published studies on pregnancy during treatment with BTKIs or BCL2 inhibitors. Therefore, individuals of both sexes of childbearing age who intend to have children should be advised to preserve their gametes. Each center already has the necessary procedures in place with the respective centers of reference for assisted reproduction.

9. Patient preferences

Patients should be engaged in treatment discussions about pros and cons of different therapeutic strategies. Socioeconomic/logistical factors and pharmaco-economic evaluations are also relevant.

Table 6 summarizes the examinations recommended to confirm the diagnosis, for follow-up, and before treatment of CLL/SLL [12, 15].

Table 6 Diagnostic work-up and follow-up assessment CLL/SLL

Clinical setting	Recommended assessments
At diagnosis	Comprehensive medical history with particular attention to prior or current malignancies, cardiovascular comorbidities, and concomitant medications. Laboratory tests including complete blood count, LDH, creatinine, total protein levels, serum protein electrophoresis, liver function tests, β2-microglobulin, and immunoglobulin levels (IgG, IgA, IgM). Peripheral blood smear examination. Immunophenotyping by flow cytometry. Physical examination including abdominal assessment and evaluation of palpable lymph nodes. Imaging with total body ultrasound and chest X-ray. Assessment of infectious history and recommended vaccinations. Annual screening for skin cancers.
Follow-up (asymptomatic patients)	Laboratory tests as at diagnosis. Physical examination, including abdominal and lymph node assessment. Total body ultrasound at least once every 12 months, according to clinical need.
Before treatment	Assessment of comorbidities and performance status, including comorbidity index. Laboratory and infectious disease assessment as at diagnosis, including screening for HBV, HCV, HIV, and latent tuberculosis. Clinical evaluation of disease burden. Molecular testing, including FISH, karyotype and molecular analyses. Assessment of fertility preservation and pregnancy testing - when appropriate. Consideration of patient's preferences, social and logistical factors, and pharmaco-economic evaluation.

Table 7 Rai and Binet staging systems for CLL

Staging system	Stage	Definition
Rai	0 (low risk)	Lymphocytosis in peripheral blood and/or bone marrow
Rai	I–II (intermediate risk)	Lymphocytosis with enlarged lymph nodes, splenomegaly, and/or hepatomegaly
Rai	III–IV (high risk)	Lymphocytosis with anemia (hemoglobin < 11 g/dL) or thrombocytopenia (platelet count < 100×10^9/L)
Binet	A	Hemoglobin ≥ 10 g/dL, platelet count ≥ 100×10^9/L, and fewer than three involved lymph node areas
Binet	B	Hemoglobin ≥ 10 g/dL, platelet count ≥ 100×10^9/L, and three or more involved lymph node areas
Binet	C	Hemoglobin < 10 g/dL and/or platelet count < 100×10^9/L

Prognosis

Several systems can be used for risk stratification and staging. Binet's and Rai's clinical staging systems are still in use today, regardless of recent biological advances (Table 7). Both are based on physical examination (lymph node involvement, hepatomegaly, and/or splenomegaly) and blood test results (presence of anemia or thrombocytopenia), and define three prognostic groups with different disease burden. However, regardless of their widespread use, these classifications have some limitations in identifying patients who will have a more aggressive disease course and predicting response to treatment [36].

The prognostic assessment

The CLL-IPI (CLL International Prognostic Index), that incorporates the biological factors of the leukemia (*TP53* and *IGHV* mutation status) along with tumor burden (clinical stage and beta-2-microglobulin levels) and age, has demonstrated effectiveness in predicting time to first treatment (TTFT) and overall survival with conventional chemotherapy. However, its usefulness in predicting OS with new treatments is limited [32]. Thus, we do not advice CLL-IPI calculation as useful in the clinical practice. Analogously, we don't advise to use the IPS-E (International Prognostic Score for Early-Stage CLL), for predicting TTFT or setting the follow-up timing. Currently, there are no prognostic markers whose routine use in clinical practice significantly alters management outside of clinical trials.In conclusion, we have no prognostic efficacious markers to be used in the clinical practice

Geriatric assessment

Despite the barriers to implementing geriatric assessment (GA) in clinical practice, particularly when there is limited time to evaluate patients, the mounting clinical evidence strongly supports its effectiveness [32]. The preferred screening tools endorsed by the ASCO and SIOG are the G8 and VES-13 [32]. GA has demonstrated to predict survival outcomes, facilitate the detection of treatment-related toxicities, and support decision-making processes, but no conclusive data had been produced in CLL/SLL.

Treatment

Treatment decisions

Prior to treatment, active observation policy should be used according to iwCLL guidelines [12, 15]. In practical terms, this means that patients with asymptomatic early-stage disease (Rai 0, Binet A) should be observed without therapy until symptomatic disease or evidence of disease progression is observed because treatment of these patients does not confer any survival benefit [37]. The presence of del(17p), *TP53* mutation, other markers associated with poor prognosis, absolute lymphocyte count, lymph node size, should not be used as an indication to start treatment.

Choice of optimal therapy should take into consideration both patient-related and disease-related factors, such as previous treatments and toxicities [38]. These factors are listed in the Table 8.

To optimize treatment outcomes, the selection of frontline therapy must be tailored to individual patient profiles. For fit, younger patients, time-limited regimens (e.g., venetoclax plus obinutuzumab) are often preferred to achieve deep remissions and treatment-free periods [15]. Conversely, for patients with high-risk genetic features such as del(17p) or TP53 mutations, continuous treatment with second-generation BTKIs (acalabrutinib or zanubrutinib) remains the cornerstone of management due to their sustained efficacy. In the presence of cardiovascular comorbidities, the superior selectivity of newer BTKIs or venetoclax-based approaches is prioritized to minimize arrhythmic risks [15]. Finally, for frail patients or those with significant renal impairment, treatment choice is guided by the safety profile and the feasibility of tumor lysis syndrome (TLS) monitoring [15].

It is also important to consider the drug–drug interactions to choose the best therapy (Table 9**).** Pharmacokinetic simulations showed that nirmatrelvir/ritonavir markedly increased BTK inhibitor exposure (53.88-fold for ibrutinib, 3.18-fold for zanubrutinib and 6.54-fold for acalabrutinib, supporting dose-adjustment strategies of ibrutinib 25 mg every 48 h, zanubrutinib 80 mg twice daily, and acalabrutinib 25 mg twice daily during co-administration [39]. No data about venetoclax dose-adjustment during Corona-virus infections been reported in literature.

First-line therapy

With reference to the treatment regimens suggested by the new NCCN guidelines for CLL/SLL [13], the experts propose an update of simplified scheme that represents the first-line therapeutic approach typically used in Tuscany **(**Fig. 1**).**

Indeed, continuous treatment with BTKI zanubrutinib, acalabrutinib, or ibrutinib is recommended for patients with del(17p) and/or TP53 dysfunction. The preference for continuous therapy in this subgroup is driven by several critical factors. Patients with *TP53* aberrations have highly unstable clones. While fixed-duration (FD) regimens (like venetoclax-based combos) can obtain deep remissions, data from CLL17 showed important differences in high-risk patients: the 3-year PFS for *TP53*-mutated patients was only 62.0% with venetoclax-obinutuzumab (VO) compared to 79.4% with continuous ibrutinib [40]. Continuous BTK inhibition provides constant suppressive pressure on the B-cell receptor (BCR) signaling pathway. In *TP53*-aberration cells, where DNA repair and apoptosis (targeted by venetoclax) are compromised, the persistent inhibition of proliferation via BTK appears more effective at preventing the "rapid rebound" seen after stopping FD therapy [41]. Moreover, long-term follow-up from the ELEVATE-TN and SEQUOIA trials reinforces that second-generation BTKIs (acalabrutinib/zanubrutinib) maintain high PFS rates in *TP53*-mutated cohorts over 4–5 years, whereas FD cohorts often show a "drop-off" in PFS shortly after treatment cessation [42, 43].

In the phase 3 ALPINE trial, zanubrutinib was directly compared with ibrutinib in CLL/SLL. Zanubrutinib showed significantly superior PFS (HR 0.65; 95% CI: 0.49–0.86; $p = 0.002$), higher ORR (85.6% vs. 75.4%), and a better safety profile with a lower incidence of atrial fibrillation (7.1% vs. 17.0%) and no cardiac-related deaths versus six in the ibrutinib arm. Patient-reported outcomes, including quality of life and symptom burden, also favored zanubrutinib [30].

Acalabrutinib, with or without obinutuzumab, versus chlorambucil and obinutuzumab was assessed in the ELEVATE-TN trial [43] After a median of 28,3 months, median PFS was greater with acalabrutinib-obinutuzumab and acalabrutinib monotherapy, compared with obinutuzumab-chlorambucil. With a median follow-up of 46.9 months, estimated 48-month PFS rates overall were 87.0% for

Table 8 Criteria guiding therapeutic decision-making in CLL/SLL

Domain	Considerations
Patient-related factors	Comorbidities, performance status, creatinine clearance, patient preferences, socioeconomic and logistical factors
Disease-related factors	Disease burden, presence of bulky disease, molecular and cytogenetic risk features
Treatment-related factors	Concomitant therapies and potential drug–drug interactions, prior treatment history and response, time to progression
Multidisciplinary evaluation	Cardiologic, geriatric, infectious disease, and other specialist assessments when appropriate
Health system factors	Pharmaco-economic considerations and regulatory prescription constraints

Table 9 Drug-drug interactions

DRUGS	VENETOCLAX	ZANUBRUTINIB	ACALABRUTINIB	IBRUTINIB
Apixaban				
Dabigatran				
Edoxaban				
Rivaroxaban				
Clopidogrel				
Warfarin				
Bisoprolol				
Metoprolol, Atenolol, Nebivolol, Propranolol				
Metformin				
Olmesartan				
Ramipril				
Amlodipine				
Pitavastatin, Pravastatin				
Simvastatin				
Rosuvastatin				
Atorvastatina				
Fluvastatin				
Lovastatina				
Valsartan				
Ezetimibe				
Furosemide				
Pantoprazole, Esomeprazole, Omeprazole			cp gastro-resistant	
Acetylsalicylic acid (Aspirin)				
NSAIDs				
Amiodarone				
Azithromycin				
Amoxicillin				
Cephalosporins				
Levofloxacin				
Ciprofloxacin				
Clarithromycin				
Meropenem				
Vancomycin				
Trimethoprim/Sulfamethoxazole				
Pregabalin				
Paracetamol				
Fluconazole				
Azoles				
Alfuzosin				
Nirmatrelvir/Ritonavir				
Tamsulosin				
Allopurinol				
Dexamethasone				

LEGEND

Major interaction
Potential moderate interaction
Week interaction
No interaction

acalabrutinib-obinutuzumab, 77.9% for acalabrutinib, and 25.1% for obinutuzumab-chlorambucil [43].

Ibrutinib as first-line therapy was studied in the RESONATE-2 trial. OS at 7 years was 78% with ibrutinib, and PFS was 59% for ibrutinib versus 9% for chlorambucil [44].

In the CLL14 trial, 432 patients were randomly assigned to receive either venetoclax plus obinutuzumab or chlorambucil plus obinutuzumab as first-line treatment; with a median follow-up of 39.6 months, patients given venetoclax plus obinutuzumab had a significantly longer PFS than those receiving chlorambucil plus obinutuzumab (HR 0.31, $p < 0.0001$) [39]. Median PFS was not reached in the venetoclax plus obinutuzumab group vs. 35.6 months in the chlorambucil plus obinutuzumab group. Three months after treatment completion, 40% of patients in the venetoclax–obinutuzumab arm had undetectable MRD levels $< 10^{-6}$ by

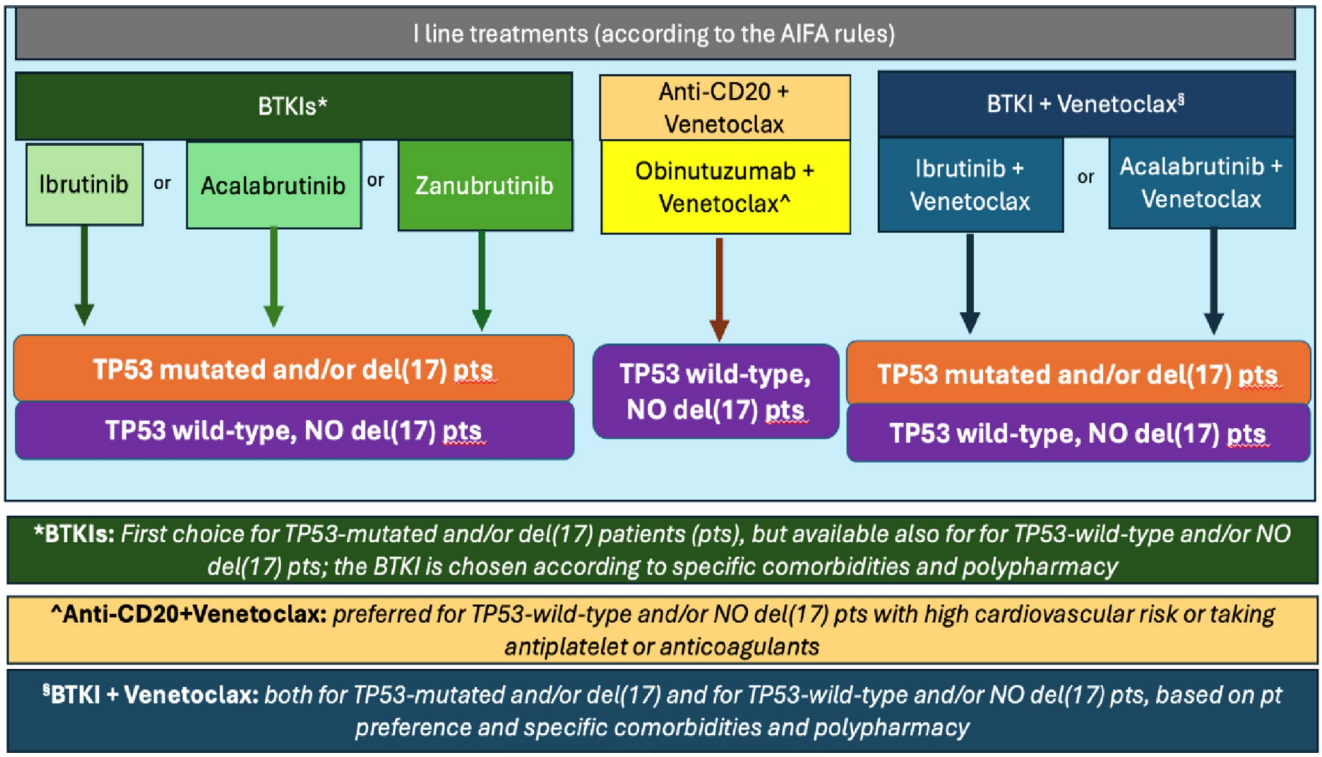

Fig. 1 First-line therapeutic approach for CLL/SLL, according to AIFA rules

next-generation sequencing vs. 7% in the chlorambucil–obinutuzumab arm [45, 46]. Thus, obinutuzumab plus venetoclax might represent a valid option for first-line treatment, especially in patients who do not accept continuous treatment and for those with comorbidities that could increase the risk of adverse events with BTKIs.

An important recent development in first-line CLL therapy is the FD combination of ibrutinib plus venetoclax, which aims to provide deep remissions while limiting treatment exposure. This regimen was investigated in the phase 2 CAPTIVATE study, enrolling treatment-naïve patients with CLL. The study consisted of two cohorts: the FD cohort, where patients received a 3-month lead-in with ibrutinib followed by 12 cycles of combined ibrutinib and venetoclax; and a MRD-guided cohort, where therapy was adapted based on MRD status. In the FD cohort, at a median follow-up of 38.7 months, the progression-free survival (PFS) rate was 88%, with an overall response rate (ORR) of 96%, and undetectable minimal residual disease (uMRD) in 75% of patients at the end of therapy. The safety profile was consistent with known toxicities of the individual agents, with manageable adverse events [47].

The phase 3 GLOW trial further confirmed the efficacy of ibrutinib-venetoclax in an older or unfit population. In this randomized study, 211 patients were assigned to receive 12 cycles of ibrutinib plus venetoclax or chlorambucil plus obinutuzumab. After a median follow-up of 31.5 months, the median PFS was not reached in the ibrutinib-venetoclax arm versus 19.0 months in the chlorambucil-obinutuzumab group (HR 0.214; 95% CI, 0.124 to 0.370; $p < 0.0001$). Furthermore, rates of uMRD in peripheral blood were significantly higher with ibrutinib-venetoclax (62.8% vs. 27.1%), confirming the deep and durable remissions achieved with the FD regimen [48].

The recent CLL17 trial compared FD VO and FD venetoclax-ibrutinib (VI) against continuous ibrutinib (I). At 3 years, the PFS rates were 81.1% (VO), 79.4% (VI), and 81.0% (I), demonstrating the non-inferiority of FD doublets compared to continuous monotherapy; notably, the rate of uMRD ($< 10^{-4}$) in peripheral blood was 73.3% for VO compared to 0% for continuous I [40].

Venetoclax administration carries a significant risk of tumor lysis syndrome (TLS), necessitating a standardized weekly dose ramp-up (20–400 mg) based on tumor burden and patient comorbidities [49]. Notably, renal impairment (creatinine clearance < 80 mL/min) is an independent risk factor that compromises the clearance of metabolic waste during rapid cytoreduction. Management in this population requires intensified prophylaxis with uric acid–lowering agents, adequate hydration (oral and/or intravenous), and close laboratory monitoring of electrolytes, uric acid, and renal function before and after each dose escalation [49] For high-risk patients with renal dysfunction, dose escalation should occur in a clinical setting to allow for immediate

intervention or treatment delay at the first sign of biochemical TLS. Adherence to these mitigation strategies ensures the safety of venetoclax therapy, even in patients with compromised renal function [49].

The CLL-FRAIL trial evaluated acalabrutinib monotherapy specifically in patients > 80 years old or those clinically frail. The trial met its primary endpoint with an Overall Response Rate (ORR) of 88%. This confirms that acalabrutinib is highly effective even without the addition of anti-CD20 antibodies or chemotherapy in vulnerable populations. The 24-month PFS rate was 82% [50].

Second and later lines of therapy

Relapse without symptoms is not an indication to restart therapy [15]. Treatment sequencing depends on first-line regimen, response duration, genetic/molecular profile, comorbidities, toxicities and mechanisms of resistance. About the possibility of assessing the mutations of BTK, PLCG or BCL2 as responsible for resistance, the Italian National Health System does not reimburse these tests; consequently, we don't suggest their routinely use. Nevertheless, in case of the C481S we suggest the use of venetoclax or no-covalent BTKIs [51].

Patients previously treated with chemoimmunotherapy may receive BTKIs or rituximab–venetoclax [52].

The MURANO trial demonstrated higher PFS (57.3% vs. 4.6%; HR 0.19) and OS (85.3% vs. 66.8%; HR 0.41) for venetoclax–rituximab compared with bendamustine–rituximab [53].

Among patients progressing on ibrutinib, venetoclax-based therapy improved OS and treatment-free survival (TFS) vs. other approved treatments [54], with an ORR of 79% [43]. BTKIs remain effective post-venetoclax: in 23 relapsed patients, median PFS and OS were 34 and 42 months, respectively; prolonged prior remission and uMRD predicted longer benefit, and activity persisted even with BCL2 Gly101Val mutation (2-year PFS 69%) [55].

Retreatment after fixed-duration ibrutinib–venetoclax is also feasible: indeed, half of relapsed patients respond to retreatment with either venetoclax or ibrutinib. Venetoclax retreatment is preferred when relapse occurs > 12 months after initial therapy, showing durable responses [47]. Ibrutinib retreatment is used when relapse occurs during/soon after venetoclax or when prior discontinuation was due to toxicity, achieving ORR ≈ 50% and median PFS > 12 months in responders [47].

Additional agents remain suitable options: idelalisib, duvelisib [56], and the non-covalent BTKI pirtobrutinib (after a covalent BTKI according to AIFA rules), which showed strong efficacy and tolerability, including ORR 69% in refractory to both covalent BTKIs and BCL2 inhibitors, that is usually preferred for the better tolerance [57]. The currently indicated and reimbursed therapeutic sequencing is reported in Fig. 2.

Allogeneic stem cell transplantation as a therapeutic option may be considered as a later-line treatment option in patients under 70 years of age with refractory disease (i.e. relapsed within 6 months of the end of treatment if therapy is at term or during the first 6 months of continuous therapies) or "high-risk" disease. The panel considers "high-risk" CLL to be disease that is refractory or relapsed within 2 years of previous treatment or characterized by acquired genetic abnormalities, such as del [17] or *TP53* mutations. The indication for allogeneic hematopoietic stem cell transplantation requires the failure of at least one BTKI and venetoclax. Finally, patients with CLL-related Richter's transformation also have an indication for allotransplantation preceded by chemoimmunotherapy. The timing of allotransplant could be established according to the deep of response. Consider refer each patient to a transplant center.

Response assessment

Assessment of response should always include physical examination and evaluation of the complete blood count. Marrow aspirate and biopsy can be performed in the presence of cytopenias of uncertain cause [15]. Ultrasound of the abdomen and assessment of superficial lymph nodes should always be carried out [58], while assessment of MRD and routine use of total-body CT are not indicated in general clinical practice [15]. On the other hand, ultrasound has been demonstrated to be a useful and radiation-free tool in daily practice to assess response to therapy [58]: indeed, lymph nodes assessment of response with ultrasound is related to the echo structure of superficial lymph nodes rather than the dimensions [58]. The panel recommends the response assessment by ultrasound of inguinal, axillary, cervical, supraclavicular, and infraclavicular regions. For each anatomical region, the parameters to be assessed are the number of pathological lymph nodes and their dimensions (in mm), reporting the longest longitudinal diameter. The echostructure of superficial lymph nodes must also to be described in CLL [58]. The spleen must be assessed reporting the longitudinal diameter in mm and the cross-sectional area cm^2. A summary of ultrasound assessment of CLL is provided in Table 10. During treatment with a BTKI, the first ultrasound should be performed after 3–6 months.

Response assessment should usually be carried out at least 2 months following completion of fixed duration therapies. Response categories are defined as complete remission (CR), partial remission (PR), stable disease (SD), progressive disease (PD), and refractory disease, as defined in Table 11. For continuous therapies, the response assessment

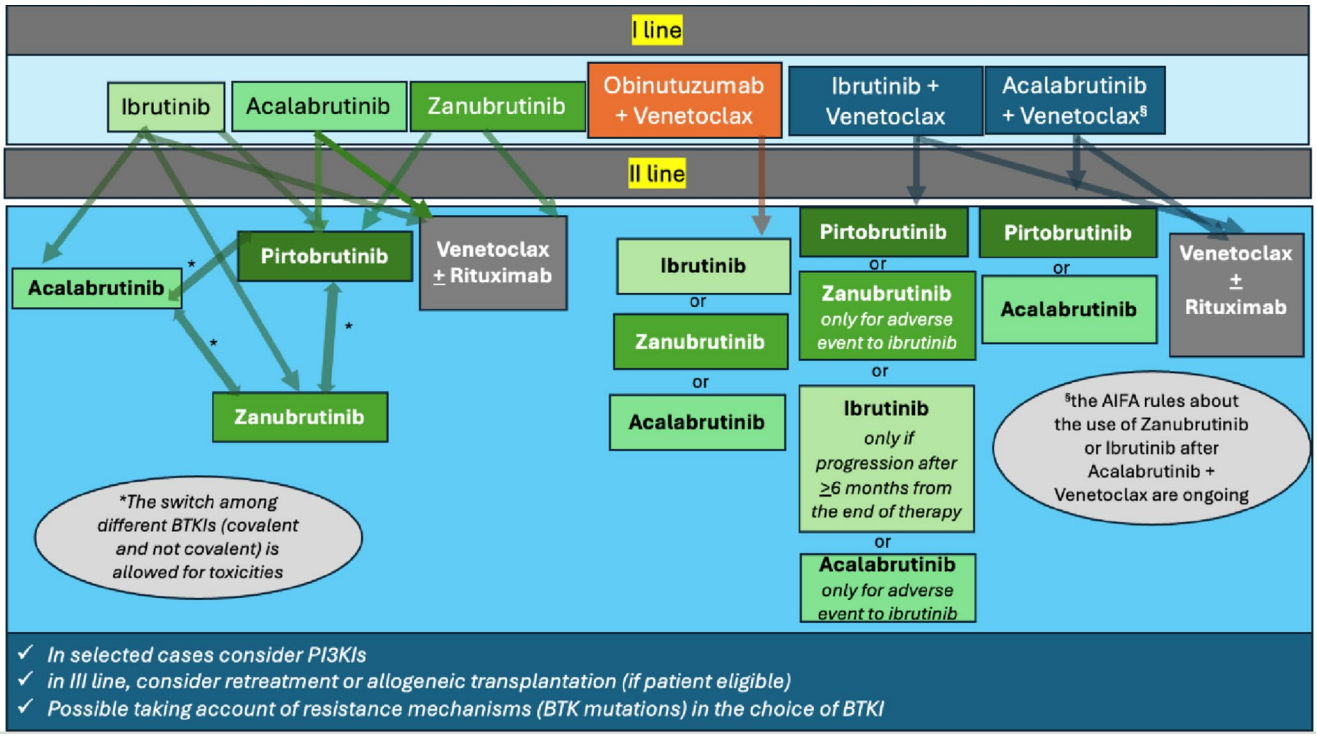

Fig. 2 Therapeutic sequencing of CLL/SLL, according to AIFA rules

Table 10 Ultrasound assessment in CLL

Ultrasound examination	Reporting recommendations
Thyroid	Describe abnormalities, if present
Liver	Describe abnormalities, if present
Gallbladder	Describe abnormalities, if present
Biliary tract	Describe abnormalities, if present
Pancreas	Describe abnormalities, if present
Kidneys	Describe abnormalities, if present
Abdominal aorta	Describe abnormalities, if present
Spleen	Report bipolar diameter and area (including reference values); describe the presence of hypoechoic areas or a homogeneous/inhomogeneous echotexture
Urinary bladder	Describe abnormalities and bladder filling at the time of examination
Lymph nodes (superficial and abdominal)	Report anatomical location; ultrasound characteristics (reactive vs. pathological); maximum diameter (mm); presence of colliquation/necrosis areas or sclerotic evolution

should be done after 3 and 6 months, and then every 6 months.

Future perspectives

In recent years, improved knowledge of the pathological mechanisms at the basis of CLL/SLL has led to the development and introduction of several targeted therapeutic agents. In addition to the conventional BTKIs, several new agents are being studied [57] such as pirtobrutinib (soon available) and nemtabrutinib, that appear to be more active and better tolerated than the previous BTKIs generation [59, 60]. Other BTKIs are being investigated, including the non-covalent inhibitor vecabrutinib [61–63] and rocbrutinib (LP-168), a dual binding BTKI [64].

Several combination therapies are also being studied. In the AMPLIFY trial, was evaluated fixed-duration therapy as first line acalabrutinib plus venetoclax (AV) ± obinutuzumab (AVO) versus chemoimmunotherapy (CIT); interim results showed that both AV and AVO significantly improved PFS (HR 0.65 and 0.42, respectively). The 36-month PFS rate was 83.1% for AVO and 76.5% for AV vs. 66.5% for CIT. Those combinations will be soon available [65, 66]. High-risk patients (del17p/TP53) traditionally experience shorter remissions with time-limited treatments compared to continuous BTKI therapy. However, the AMPLIFY trial investigates whether combining acalabrutinib with venetoclax

Table 11 Response criteria

Group	Parameter	CR	PR	PD	SD
A	Lymph nodes	None ≥ 1.5 cm	Decrease ≥ 50% (from baseline)*	Increase ≥ 50% from baseline or from response	Change of -49% to +49%
	Liver and/or spleen size†	Spleen size < 13 cm; liver size normal	Decrease ≥ 50% (from baseline)	Increase ≥ 50% from baseline or from response	Change of -49% to +49%
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease ≥ 50% (from baseline)	Increase ≥ 50% (from baseline)	Change of -49% to +49%
B	Platelet count	$\geq 100 \times 10^9$/L	$\geq 100 \times 10^9$/L or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL	Change of -49% to +49%
	Hemoglobin	≥ 11.0 g/dL (not transfused and without erythropoietin)	≥ 11 g/dL or increase ≥ 50% over baseline	Decrease of ≥ 2 g/dL from baseline secondary to CLL	Increase < 11.0 g/dL or < 50% over baseline, or decrease < 2 g/dL
	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥ 50% on successive biopsies	No change in marrow infiltrate

CR complete remission (all of the criteria have to be met); *PD* progressive disease (at least 1 of the criteria of group A or group B has to be met); *PR* partial remission (for a PR, at least 2 of the parameters of group A and 1 parameter of group B need to improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve); *SD* stable disease (all of the criteria have to be met; constitutional symptoms alone do not define PD)

*Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination in clinical trials or by physical examination in general practice)

†Spleen size is considered normal if, 13 cm. There is not firmly established international consensus of the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in clinical trials and be recorded according to the definition used in a study protocol

can induce deeper, undetectable MRD levels [65, 66] This approach aims to bridge the gap, potentially allowing high-risk patients to benefit from time-limited schedules with more durable outcomes.

Other novel therapeutic combinations were evaluated in the GAIA/CLL13 trial, where in fit patients without TP53 aberrations, fixed-duration triplet obinutuzumab-ibrutinib-venetoclax (OIV) and doublets VO proved superior to CIT. Long-term follow-up (4 years) showed PFS rates of 85.5% for OIV and 81.8% for VO vs. 62.0% for CIT [67].

Another promising treatment for CLL is chimeric antigen receptor (CAR) T-cell therapy. Regarding the target of CAR, most studies have used CD19 [68] CAR T-cell immunotherapy has been attempted in relatively small numbers of patients, but has been reported to induce durable remission in cases with relapsed/refractory CLL. The concomitant use of ibrutinib seems especially promising [69].

In this evolving therapeutic landscape, BTK degraders have emerged as a novel class of agents with the potential to overcome resistance to both covalent and noncovalent BTKIs [70]. These molecules exploit proteolysis-targeting chimeras (PROTACs) or similar technologies to selectively degrade BTK protein, rather than inhibit its activity. Preclinical studies have demonstrated potent antitumor activity of BTK degraders in CLL models, including those harboring resistance-conferring mutations, such as C481S. Early-phase clinical trials (e.g., NX-2127, NX-5948 and BGB-16673) are currently underway and have shown promising preliminary efficacy in relapsed/refractory CLL, including in patients previously treated with multiple lines of therapy and those with BTKIs-resistant disease [71–74].

Future challenges and conclusions

With the availability of new therapies for CLL, the optimal sequencing and combination strategies remain a question of debate. In the specific setting of ibrutinib or other BTKIs failure, venetoclax appears efficacious [75], while refractory to venetoclax showed best outcomes when consequently treated with ibrutinib or other BTKIs [70]. The use of some combinations of targeted agents also appears to be beneficial, although further studies will be needed to establish the optimal timing of these combinations and use in refractory/relapsing disease. Given the rapid progress in therapy being made in CLL, there is thus the need to frequently update recommendations for management. With this aim, we hope that the real-life diagnostic and therapeutic approach to CLL here proposed will be a useful guide for clinical practice.

Author contributions M.D., C.M.R., designed and drafted the consensus. All authors collected and analyzed clinical data and contributed to the cardiovascular safety sections. E.B. contributed to the diagnostic and ultrasound recommendations. All authors reviewed and approved the final manuscript.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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