CLL: EHA 2026 to Address Unmet Needs in Treatment Selection

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Managing chronic lymphocytic leukemia (CLL) presents a persistent clinical dilemma: how to optimise initial therapy and subsequent lines of treatment in a rapidly evolving landscape of targeted agents. The upcoming European Hematology Association (EHA) 2026 meeting will address these pressing questions, aiming to clarify optimal strategies for patient stratification and resistance management.

KEY TAKEAWAYS

- The Pivot: The focus is shifting from broad treatment approaches to highly individualised, risk-adapted strategies for CLL patients.
- The Data: Future research will likely present comparative effectiveness data for BTK inhibitors versus BCL-2 inhibitors in specific patient subgroups, particularly those with high-risk features.
- The Action: Clinicians should prepare for increasingly complex treatment algorithms that integrate genomic profiling and minimal residual disease (MRD) assessment to guide therapy decisions.

Chronic lymphocytic leukemia (CLL) is characterised by the accumulation of mature, monoclonal B lymphocytes in the blood, bone marrow, and lymphoid organs.1 While many patients experience an indolent course, a significant proportion requires treatment due to disease progression or symptoms.1 The advent of targeted therapies, specifically Bruton's tyrosine kinase (BTK) inhibitors and B-cell lymphoma-2 (BCL-2) inhibitors, has revolutionised CLL management, moving away from chemoimmunotherapy as a first-line approach.2 However, despite these advances, critical questions remain regarding optimal treatment sequencing, management of resistance, and strategies for patients with high-risk genetic features such as del(17p) or TP53 mutations.3 The EHA 2026 meeting is anticipated to provide further clarity on these areas, with a particular emphasis on data that informs treatment selection in specific patient populations.
CLL is the most common leukemia in adults in Western countries, with an incidence of approximately 4-5 cases per 100,000 individuals per year. The median age at diagnosis is typically in the late 60s to early 70s, and it is more prevalent in men than in women. The disease course is highly variable, ranging from stable disease requiring no immediate intervention to rapidly progressive forms. Initial diagnosis often occurs incidentally during routine blood tests, revealing persistent lymphocytosis. Further diagnostic workup includes immunophenotyping by flow cytometry to confirm the monoclonal B-cell population and distinguish CLL from other B-cell lymphoproliferative disorders. Prognostic factors such as IGHV mutational status, FISH analysis for chromosomal abnormalities (e.g., del(13q), del(11q), trisomy 12, del(17p)), and TP53 mutation status are crucial for risk stratification and treatment planning. Patients with unmutated IGHV, del(17p), or TP53 mutations are generally considered to have high-risk disease and often require more aggressive treatment strategies.1

Current guidelines recommend BTK inhibitors (e.g., ibrutinib, acalabrutinib, zanubrutinib) or BCL-2 inhibitors (e.g., venetoclax, often in combination with an anti-CD20 antibody) as front-line therapy for most patients requiring treatment.4 The choice between these classes is often influenced by patient comorbidities, potential side effect profiles, and physician preference.4 However, head-to-head comparisons in specific high-risk subgroups are still emerging. For instance, while BTK inhibitors have demonstrated superior progression-free survival (PFS) compared to chemoimmunotherapy in patients with del(17p)/TP53 mutations, the optimal sequencing or combination with BCL-2 inhibitors in this population remains an active area of investigation.5 Similarly, the role of minimal residual disease (MRD) negativity as a surrogate endpoint for long-term outcomes, particularly with fixed-duration venetoclax-based regimens, will be a key discussion point.6

Addressing Unmet Needs in CLL Management

The EHA 2026 agenda is expected to feature presentations and discussions addressing several unmet needs in CLL. One primary focus will be on refining prognostic markers beyond established genetic aberrations. Novel biomarkers, including those related to the tumour microenvironment or specific immune cell subsets, may offer additional insights into disease aggressiveness and response to targeted therapies.7 Furthermore, the management of patients who develop resistance or intolerance to initial targeted therapies represents a significant challenge. For example, patients progressing on a BTK inhibitor may be candidates for a BCL-2 inhibitor, and vice versa. However, data on the efficacy and safety of sequential therapy, particularly after multiple lines of targeted agents, are still accumulating.8

Another critical area of discussion will involve the role of allogeneic stem cell transplantation (allo-SCT) in the era of novel agents. While allo-SCT was historically considered for high-risk relapsed/refractory CLL, its position has diminished with the efficacy of BTK and BCL-2 inhibitors.9 However, for patients who fail multiple lines of targeted therapy, particularly those with complex karyotypes or Richter's transformation, allo-SCT may still offer a curative option.9 The EHA 2026 meeting is anticipated to present updated guidelines or consensus statements regarding patient selection for allo-SCT in the contemporary treatment landscape. Additionally, the development of novel agents, such as non-covalent BTK inhibitors, PI3K inhibitors, and CAR T-cell therapies, will be reviewed, with early-phase clinical trial data potentially highlighting their efficacy in heavily pretreated populations.10 The integration of these emerging therapies into existing treatment algorithms will be a central theme, aiming to provide clinicians with evidence-based guidance for managing complex CLL cases.

For a comprehensive overview of haematological conditions, including detailed insights into chronic lymphocytic leukaemia management, consult the Oxford Handbook of Clinical Haematology.

> **CLINICAL IMPLICATIONS**
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> The ongoing evolution of CLL treatment, particularly with the continued refinement of targeted therapies, demands that clinicians remain acutely aware of the nuances in patient selection and sequencing. The EHA 2026 focus on individualised approaches underscores a growing expectation for precision medicine in haematology. Simply prescribing a BTK inhibitor or a BCL-2 inhibitor is no longer sufficient; understanding the specific genetic profile of the patient, their comorbidities, and the potential for resistance mechanisms will be paramount. This necessitates a greater reliance on comprehensive genomic profiling at diagnosis and potentially at relapse, moving beyond basic FISH panels.

> For the pharmaceutical industry, the emphasis on comparative effectiveness and resistance management signals a shift towards more sophisticated trial designs. Head-to-head studies comparing different agents within the same class, or across classes, in specific high-risk populations, will be crucial for market differentiation. Companies developing novel agents, such as non-covalent BTK inhibitors or CAR T-cell therapies, must demonstrate clear advantages in terms of efficacy, safety, or overcoming resistance, particularly in patients who have exhausted established options. The bar for market entry is rising, requiring robust data in increasingly challenging patient cohorts.
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> Patients, in turn, stand to benefit from these more tailored approaches, potentially experiencing improved outcomes and reduced treatment-related toxicities. However, the increasing complexity of treatment decisions also places a greater burden on patient education and shared decision-making. Clinicians will need to effectively communicate the rationale for specific treatment choices, the implications of genomic findings, and the potential benefits and risks of sequential therapies. The promise of personalised medicine in CLL is significant, but its successful implementation hinges on clear evidence, accessible diagnostics, and effective communication between clinicians and patients.

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