CLL: Aligning Patient Priorities with Targeted Therapy at EHA 2026

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> The management of chronic lymphocytic leukemia (CLL) has evolved significantly with the introduction of targeted therapies, yet a clinical dilemma persists in optimizing treatment initiation and sequencing to achieve sustained benefit while addressing individual patient priorities. At EHA 2026, discussions will focus on integrating patient-reported outcomes with established efficacy data to guide therapeutic decisions, emphasizing the need for a personalized approach beyond standard protocols.1

KEY TAKEAWAYS

- The Pivot: Treatment decisions in CLL are shifting towards explicit integration of patient priorities alongside clinical efficacy data.
- The Data: Long-term follow-up data for Bruton's tyrosine kinase (BTK) inhibitors and BCL-2 inhibitors demonstrate differential toxicity profiles and durations of response.
- The Action: Clinicians should incorporate structured patient preference assessments when discussing treatment initiation and sequencing, particularly regarding continuous versus fixed-duration regimens.

Chronic lymphocytic leukemia (CLL) remains a heterogeneous disease, with treatment paradigms increasingly reliant on targeted agents such as Bruton's tyrosine kinase (BTK) inhibitors and BCL-2 inhibitors. While these therapies have demonstrably improved progression-free survival (PFS) and overall survival (OS) compared to chemoimmunotherapy, the optimal timing for initiation and the sequence of these agents are not universally defined. Patient priorities, encompassing quality of life, treatment duration, and specific adverse event profiles, are critical considerations that often diverge from purely efficacy-driven decisions. The EHA 2026 session aims to synthesize current evidence on long-term treatment benefits with strategies for systematically incorporating patient values into clinical decision-making.1 Historically, treatment initiation in CLL was guided by International Workshop on CLL (iwCLL) criteria, focusing on disease progression or symptomatic burden. The advent of targeted therapies, however, has introduced options for earlier intervention in some high-risk settings, challenging the traditional 'watch and wait' approach. For instance, studies on BTK inhibitors like ibrutinib have shown sustained responses in treatment-naïve and relapsed/refractory CLL, with median PFS exceeding 5 years in some cohorts.2 However, these benefits are often associated with continuous therapy, leading to prolonged exposure to potential adverse events such as atrial fibrillation, hypertension, and arthralgia.3 In contrast, BCL-2 inhibitors such as venetoclax, particularly in combination with obinutuzumab, offer fixed-duration treatment regimens. The MURANO trial, for example, demonstrated a median PFS of 53.6 months for venetoclax-rituximab in relapsed/refractory CLL, with a defined treatment period of 24 months.4 This distinction between continuous and fixed-duration therapy presents a significant point of discussion regarding patient preference

and long-term tolerability.5

CLL is the most common leukemia in adults in Western countries, with an incidence of approximately 4.7 cases per 100,000 persons per year. The median age at diagnosis is typically in the late 60s or early 70s, meaning many patients present with comorbidities that influence treatment selection. The mechanisms of action for these targeted therapies differ significantly: BTK inhibitors block the B-cell receptor signaling pathway, crucial for CLL cell proliferation and survival, while BCL-2 inhibitors induce apoptosis by antagonizing the anti-apoptotic protein BCL-2. Understanding these distinct mechanisms and their associated toxicity profiles is essential for personalized treatment planning. The EHA 2026 session will also consider the evolving landscape of novel agents and combinations, including non-covalent BTK inhibitors and CAR T-cell therapies, and their potential integration into future treatment algorithms, particularly for patients with highly refractory disease or those intolerant to standard targeted agents.

Aligning Patient Priorities with Evidence

The EHA 2026 session will address the practical implementation of patient-centered care in CLL. This involves evaluating how patient-reported outcomes (PROs) can be integrated into clinical algorithms. For example, a patient's aversion to daily oral medication or a history of cardiovascular comorbidities might favor a fixed-duration regimen, even if a continuous therapy offers a marginally longer median PFS. Conversely, a patient prioritizing maximum disease control and willing to manage chronic side effects might opt for continuous treatment. The discussion will also cover the sequencing of these agents. For patients who progress on a BTK inhibitor, venetoclax-based regimens are a standard subsequent option, and vice versa. However, data on optimal sequencing in the frontline setting, particularly for high-risk patients with 17p deletion or TP53 mutation, are still evolving.6 The ELEVATE-TN trial demonstrated superior PFS with acalabrutinib plus obinutuzumab or acalabrutinib monotherapy compared to obinutuzumab plus chlorambucil in treatment-naïve CLL, with a hazard ratio (HR) for PFS of 0.26 (95% CI, 0.15-0.45; $p < 0.0001$) for acalabrutinib plus obinutuzumab versus obinutuzumab plus chlorambucil.7 These data underscore the efficacy of targeted agents but also highlight the need to balance efficacy with patient-specific factors, including potential financial toxicity and access to care.8

The session will also explore the role of minimal residual disease (MRD) assessment in guiding treatment decisions, particularly for fixed-duration regimens. Achieving undetectable MRD (uMRD) is a strong predictor of prolonged PFS in patients treated with venetoclax-based regimens.9 However, the clinical utility of MRD-guided treatment cessation or re-initiation in all settings, especially for continuous BTK inhibitor therapy, requires further investigation. The discussion will emphasize that while objective clinical endpoints remain paramount, the subjective experience of the patient must be systematically captured and weighed. This includes understanding patient preferences regarding routes of administration, frequency of clinic visits, and the impact of specific adverse events on daily life.10

> **CLINICAL IMPLICATIONS**
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> The EHA 2026 focus on aligning patient priorities with evidence in CLL is a timely and necessary evolution in oncology practice. For too long, treatment decisions, while evidence-based, have often overlooked the nuanced impact of therapy on a patient's daily life. The shift towards explicitly integrating patient preferences is not merely a 'nice to have' but a clinical imperative, particularly with the availability of multiple highly effective agents with distinct toxicity profiles and durations of therapy. Clinicians must move beyond simply presenting

efficacy data and instead engage in structured conversations that explore what 'long-term benefit' truly means for each individual patient, considering their lifestyle, comorbidities, and tolerance for specific side effects. The pharmaceutical industry, particularly companies like AbbVie and AstraZeneca, who market venetoclax and acalabrutinib respectively, should recognize that the future of market penetration for these highly effective drugs will increasingly depend on demonstrating not just superior PFS, but also superior patient-reported outcomes. This necessitates investment in PRO collection within clinical trials and the development of tools that facilitate shared decision-making. Simply stating a drug is 'well-tolerated' is insufficient; specific, quantifiable data on the impact of adverse events on quality of life, and how these compare across different regimens, will be crucial for guiding both patient and physician choices. The era of 'one-size-fits-all' in CLL, even among targeted therapies, is rapidly drawing to a close.

Ultimately, the challenge lies in translating these discussions into actionable clinical practice. Guideline bodies, such as the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO), will need to incorporate recommendations for patient preference assessment into their CLL management algorithms. This might involve standardized questionnaires or decision aids to help patients weigh the trade-offs between continuous BTK inhibitor therapy and fixed-duration BCL-2 inhibitor regimens. Without such integration, the risk remains that despite an abundance of effective treatments, patients may not receive the therapy that best aligns with their personal values and long-term quality of life goals, potentially leading to suboptimal adherence or premature discontinuation.

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