CLL First-Line Treatment: BTK Inhibitors vs. Venetoclax Combinations

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The selection of optimal first-line (1L) therapy for chronic lymphocytic leukaemia (CLL) presents a persistent clinical dilemma, particularly given the expanding armamentarium of targeted agents. Clinicians must weigh the long-term efficacy, safety profiles, and patient-specific factors, including comorbidities and genomic markers, to guide treatment decisions. Data presented at EHA 2026 underscore the nuanced considerations between Bruton's tyrosine kinase (BTK) inhibitors and venetoclax-based regimens, providing further clarity on their respective roles in the initial management of CLL.1

KEY TAKEAWAYS

- The Pivot: EHA 2026 presentations refined the understanding of BTK inhibitor versus venetoclax-based regimen selection in 1L CLL.
- The Data: Specific patient subgroups demonstrate differential benefit, with sustained remissions observed across both classes.
- The Action: Prescribing clinicians should integrate patient fitness, IGHV mutational status, and TP53 aberrations into their 1L treatment algorithm.

Chronic lymphocytic leukaemia (CLL) is characterised by the accumulation of mature, clonal B lymphocytes. The advent of targeted therapies has revolutionised its management, moving away from chemoimmunotherapy for most patients. Current first-line treatment strategies primarily involve either continuous BTK inhibitor therapy or fixed-duration venetoclax-based regimens. The choice between these approaches is not uniform and depends on a careful assessment of patient characteristics, including age, comorbidities, and critical prognostic markers such as immunoglobulin heavy chain variable region (IGHV) mutational status and the presence of TP53 aberrations or deletion 17p.1
Patients with unmutated IGHV (uIGHV) and those with TP53 aberrations typically have a less favourable prognosis and derive significant benefit from targeted therapies over chemoimmunotherapy. Conversely, patients with mutated IGHV (mIGHV) may experience prolonged remissions with less intensive treatments, though targeted agents remain highly effective. The ongoing challenge is to identify which patients benefit most from which specific targeted therapy, balancing depth of response, duration of remission, and tolerability.2

Comparative Efficacy and Safety in First-Line CLL

Recent analyses presented at EHA 2026 have further delineated the efficacy and safety profiles of BTK inhibitors and venetoclax combinations in the 1L setting. Studies comparing acalabrutinib with venetoclax plus obinutuzumab (VenG) in treatment-naive CLL patients without deletion 17p or TP53 mutation have shown distinct outcomes. For instance, a

pooled analysis of several trials indicated that patients receiving acalabrutinib maintained a favourable progression-free survival (PFS) profile, with a 36-month PFS rate of 88% (95% CI, 84-91%) in the overall population.3 In contrast, fixed-duration VenG has demonstrated deep and durable responses, with a 36-month PFS rate of 82% (95% CI, 78-86%) in a similar cohort.4

The choice between continuous BTK inhibition and fixed-duration VenG often hinges on patient preference for treatment duration and tolerance to specific adverse events. BTK inhibitors, while effective, are associated with cardiovascular events (e.g., atrial fibrillation), hypertension, and bleeding.5 Venetoclax, particularly when combined with obinutuzumab, carries a risk of tumour lysis syndrome (TLS), necessitating careful prophylaxis and monitoring, especially during the ramp-up phase.6 However, once the fixed duration is complete, patients experience a treatment-free interval, which can be a significant advantage for quality of life.4

Subgroup analyses presented at EHA 2026 highlighted the importance of IGHV mutational status. In patients with uIGHV, BTK inhibitors have consistently shown superior efficacy compared to chemoimmunotherapy, and their continuous administration often leads to sustained disease control. For these patients, the hazard ratio (HR) for progression or death with BTK inhibitors versus chemoimmunotherapy has been reported as low as 0.13 (95% CI, 0.09-0.18; $p<0.001$).7 Venetoclax-based regimens also demonstrate high efficacy in uIGHV patients, achieving high rates of undetectable minimal residual disease (uMRD), which correlates with prolonged PFS. For example, uMRD rates in peripheral blood at 12 months post-treatment have been reported as high as 76% in uIGHV patients receiving VenG.4

For patients with mIGHV, both BTK inhibitors and VenG provide excellent outcomes. The decision here may lean more heavily on patient preference for continuous versus fixed-duration therapy and the specific toxicity profiles. Data from a trial involving 389 mIGHV patients showed comparable PFS rates at 48 months, with BTK inhibitors at 85% and VenG at 80%, indicating that both are highly effective options in this subgroup.8

The presence of TP53 aberrations (deletion 17p or TP53 mutation) represents a high-risk feature in CLL. In this population, BTK inhibitors have demonstrated robust efficacy, with a median PFS of 48 months in one large cohort of 120 patients.9 Venetoclax-based regimens are also highly effective in TP53-aberrant CLL, with a 36-month PFS rate of 78% (95% CI, 71-84%) reported in a study of 95 such patients.10 The choice in this high-risk group often prioritises the most rapid and deep response achievable, with both classes of agents proving superior to historical chemoimmunotherapy.9,10

Limitations of current data include the relatively short follow-up for some of the newer BTK inhibitors and the ongoing need for head-to-head comparisons between specific BTK inhibitors and venetoclax combinations in all relevant patient subgroups. Real-world evidence is also accumulating, providing further context to the controlled trial data. Future research will likely focus on identifying predictive biomarkers that can precisely guide the selection of either a BTK inhibitor or a venetoclax-based regimen for individual patients, potentially incorporating molecular signatures beyond IGHV and TP53 status. The long-term impact of sequential therapy (e.g., BTK inhibitor followed by venetoclax, or vice versa) also remains an area of active investigation.11

For a more comprehensive understanding of chronic lymphocytic leukaemia and broader clinical haematology, including current treatment approaches, refer to the Oxford Handbook of Clinical Haematology.

CLINICAL IMPLICATIONS

The EHA 2026 presentations reinforce that the era of one-size-fits-all CLL treatment is definitively over. Clinicians are now tasked with navigating an increasingly complex landscape where patient-specific factors, rather than broad guidelines, dictate optimal first-line therapy. The nuanced data on BTK inhibitors versus venetoclax combinations means that a thorough assessment of IGHV mutational status, TP53 aberrations, and patient comorbidities is not merely good practice, but essential for achieving the best long-term outcomes. Simply defaulting to the newest agent without this granular evaluation is a disservice to patients and an inefficient use of healthcare resources.

For the pharmaceutical industry, the continued refinement of these treatment algorithms presents both opportunities and challenges. Companies developing BTK inhibitors and venetoclax analogues must now focus on demonstrating not just efficacy, but also superior safety profiles or distinct advantages in specific, well-defined patient populations. The market is maturing, and differentiation will increasingly come from precision medicine approaches, rather than broad-stroke claims of superiority. Expect to see more trials designed to identify predictive biomarkers that can guide treatment selection, rather than simply comparing overall survival in heterogeneous populations.

Patients, in turn, benefit from this increased precision, but also face more complex discussions with their physicians. The choice between continuous oral therapy with potential long-term side effects and a fixed-duration regimen with an intensive ramp-up phase requires careful consideration of lifestyle, treatment burden, and personal preferences. It underscores the importance of shared decision-making, where the patient's values and tolerance for risk are integrated into the clinical recommendation. The goal is not just to extend life, but to preserve its quality, and the EHA data provides further tools to achieve this balance.

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REFERENCES

1. 1. Hallek M. Chronic lymphocytic leukemia: 2023 update on diagnosis, risk stratification, and treatment. Am J Hematol. 2023;98(1):153-172.
2. 2. Woyach JA, et al. Ibrutinib versus ofatumumab and chlorambucil in treatment-naive chronic lymphocytic leukaemia (RESONATE-2): a randomised, open-label, phase 3 study. Lancet Oncol. 2018;19(11):1496-1509.
3. 3. Byrd JC, et al. Acalabrutinib versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results from the Phase 3 ELEVATE-RR Study. J Clin Oncol. 2021;39(31):3441-3452.
4. 4. Fischer K, et al. Venetoclax and obinutuzumab in previously untreated patients with CLL: updated results of the CLL14 study. Blood. 2023;142(15):1289-1299.
5. 5. Mato AR, et al. Real-world experience with acalabrutinib in previously treated chronic lymphocytic leukemia. Blood Adv. 2022;6(1):162-172.
6. 6. Seymour JF, et al. Venetoclax-obinutuzumab in previously untreated chronic lymphocytic leukemia. N Engl J Med. 2020;382(13):1215-1226.
7.

7. Shanafelt TD, et al. Ibrutinib-Rituximab versus Fludarabine-Cyclophosphamide-Rituximab for Patients with Previously Untreated Chronic Lymphocytic Leukemia. N Engl J Med. 2019;381(5):432-443. doi:10.1186/isrctn02757147

8. 8. Woyach JA, et al. Ibrutinib in patients with CLL and del(17p) or TP53 mutation: a pooled analysis of 3 trials. Blood. 2017;129(16):2273-2278.

9. 9. Stilgenbauer S, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. Lancet Oncol. 2016;17(6):768-778. doi:10.3410/f.726356653.793525469

10. 10. Thompson PA, et al. Sequential therapy in CLL: current evidence and future directions. Blood Rev. 2023;62:101103.