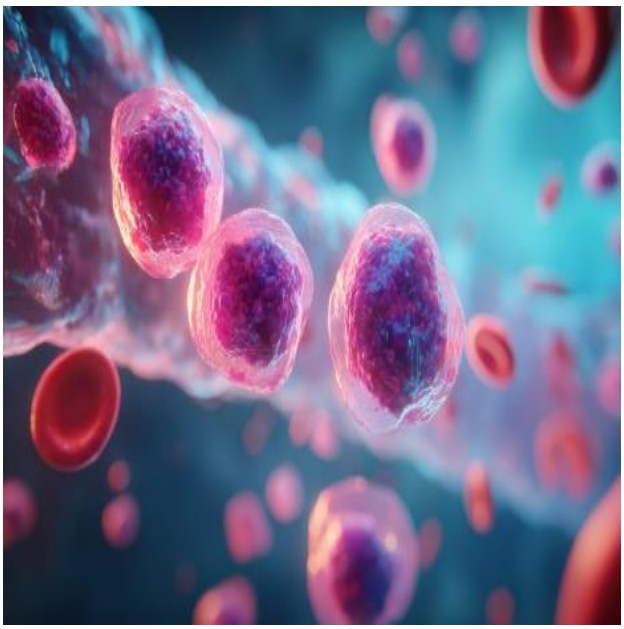
Sonrotoclax Plus Zanubrutinib Produces Deep MRD Responses in Treatment-Naive CLL

Key Takeaways

- A lead-in period of zanubrutinib (8–12 weeks) preceded sonrotoclax ramp-up to 320 mg daily, with elective protocol-defined discontinuation permitted after 96 weeks at target-dose combination therapy.
- Safety was characterized by neutropenia (38% any grade; 29% grade ≥3), contusion (38%), COVID-19 (33%), and URTI (30%), with no tumor lysis syndrome or treatment-related deaths.
- Efficacy outcomes included a 100% overall response rate, 55% complete response rate, median time to response of 2.6 months, and no progression in the 320-mg cohort at 30.9 months median follow-up.
- MRD kinetics showed deepening over time, with uMRD4 rates of 81% (week 24), 91% (week 48), and 98% (week 96), and no observed loss of MRD negativity once achieved.
- Next-generation sequencing demonstrated uMRD5 in 86% of evaluable patients, supporting phase 3 testing (NCT06073821, NCT07277231) to validate long-term clinical benefit.

EHA 2026 data show Sonrotoclax plus zanubrutinib drives rapid, durable uMRD in frontline CLL, even TP53/del17p.



Updated findings from a phase 1/1b study suggest that the investigational combination of sonrotoclax (Beqalzi; BeOne Medicines) and zanubrutinib (Brukinsa; BeiGene) may produce exceptionally deep responses in patients with previously untreated chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), including those with high-risk disease features. The data, presented at the 2026 European Hematology Association Congress, showed high rates of undetectable minimal residual disease (uMRD) and durable disease control with the all-oral regimen, supporting ongoing phase 3 evaluation of the combination.

Current frontline fixed-duration regimens that combine a Bruton tyrosine kinase inhibitor (BTKi) with a BCL2 inhibitor have demonstrated efficacy in CLL. However, investigators noted that rates of uMRD remain suboptimal, even with second-generation BTK inhibitors. Sonrotoclax, a

next-generation BCL2 inhibitor reported to have approximately 14-fold greater pharmacologic potency than venetoclax, is being evaluated as a strategy to deepen responses.

Investigating Sonrotoclax Plus Zanubrutinib

The study enrolled 86 patients who received 320 mg of zanubrutinib once daily for 8 to 12 weeks, followed by sonrotoclax with a ramp-up to the target only daily dose of 320 mg. Patients remained on treatment until disease progression, unacceptable toxicity, or protocol-defined elective discontinuation after 96 weeks of combination therapy at the target dose. At a median follow-up of 30.9 months, 45 patients (52%) remained on treatment, while 40 patients (47%) had discontinued sonrotoclax. Most discontinuations were due to protocol-defined elective treatment completion rather than toxicity.

The regimen demonstrated a manageable safety profile. The most common treatment-emergent adverse events (TEAEs) of any grade were neutropenia (38%), contusion (38%), COVID-19 infection (33%), and upper respiratory tract infection (30%). Grade 3 or higher neutropenia occurred in 29% of patients. Importantly, no cases of tumor lysis syndrome were reported, and no adverse events resulted in death.

Among 84 efficacy-evaluable patients, the overall response rate was 100%, with 55% achieving a complete response. Responses occurred rapidly, with a median time to response of 2.6 months. No patient in the 320-mg cohort experienced disease progression, resulting in an estimated 30-month progression-free survival rate of 100%.

Investigators Report Meaningful MRD Data

The most notable findings were observed in MRD analyses. The best uMRD4 rate, defined as fewer than 1 CLL cell per 10,000 leukocytes by flow cytometry, reached 99% overall. Among patients with TP53 mutations or del(17p), a subgroup historically associated with poorer outcomes, the uMRD4 rate was 100%.

Responses deepened over time. By weeks 24, 48, and 96, uMRD4 rates were 81%, 91%, and 98%, respectively. The median time from reaching the target sonrotoclax dose to achieving uMRD was 3 months. Notably, no patient who achieved uMRD4 subsequently lost MRD negativity during the follow-up period.

In next-generation sequencing analyses, 86% of evaluable patients achieved uMRD5, indicating even deeper levels of disease clearance below 1 malignant cell per 100,000 leukocytes.

Improving Outcomes in CLL

Investigators concluded that sonrotoclax plus zanubrutinib was well tolerated and produced uMRD rates exceeding 90%, including among patients with high-risk cytogenetic abnormalities. They noted that both the depth and speed of MRD responses suggest a differentiated profile compared with currently available frontline combination therapies.

The regimen is currently being further evaluated in 2 phase 3 clinical trials (NCT06073821, NCT07277231), which will help determine whether these promising early findings translate into improved long-term outcomes for patients with CLL.

REFERENCES

Cheah CY, Opat S, Lasica M, et al. (S145) first-line treatment of cll/sll with the all-oral combination of sonrotoclax and zanubrutinib achieves undetectable minimal residual disease rates of >90%, including in patients with del(17P)/TP53 Chan Y. Presented at: EHA 2026. June 11-14, 2026. Stockholm, Sweden. Abstract S145

News Source:

https://www.pharmacytimes.com/view/sonrotoclax-plus-zanubrutinib-produces-deep-mrd-responses-in-treatment-naive-cll