68th ASH Annual Meeting and Exposition
December 12-15, 2026
New Orleans, LA

Title: Sonrotoclax plus zanubrutinib produces durable responses and achieves uMRD4 in 99% of patients with treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma (TN CLL/SLL): ~40-month follow-up from a phase 1/1b trial

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Character count: 4458/4500 characters (including spaces)

Introduction: Oral, fixed-duration combinations of Bruton tyrosine kinase (BTK) and B-cell lymphoma 2 (BCL2) inhibitors are effective and generally well-tolerated first-line treatments for CLL/SLL. However, current regimens, including those using second-

generation BTK inhibitors, have suboptimal rates of undetectable measurable residual disease (uMRD) ranging from 29% to 47%. Sonrotoclax (S) is a next-generation BCL2 inhibitor designed to have high target selectivity, enhanced pharmacologic potency, and an optimized pharmacokinetic profile characterized by a shorter half-life and minimal drug accumulation. These properties may enable deeper target inhibition while mitigating toxicity. Zanubrutinib (Z) is a next-generation BTK inhibitor with demonstrated clinical superiority over standard-of-care treatment in both TN and relapsed/refractory CLL/SLL. In an ongoing phase 1/1b study evaluating S monotherapy or in combination with Z and/or obinutuzumab for B-cell malignancies (NCT04277637), S 320 mg + Z was established as the recommended phase 2 dose for TN CLL/SLL. Here, we report updated safety and efficacy results for S 320 mg + Z in TN CLL/SLL with a median follow-up of 39.5 months.

Methods: Patients received Z 320 mg once daily (QD) or 160 mg twice daily during an 8-12-week lead-in period, followed by S 320 mg QD + Z. The S target dose of 320 mg QD was reached using a dose ramp-up schedule. S + Z continued until disease progression, unacceptable toxicity, or protocol-defined elective discontinuation after 96 weeks of S + Z at the target dose. The primary endpoint was safety assessed per NCI-CTCAE v5.0. Secondary and exploratory endpoints included overall response rate (ORR) and uMRD at 10^{-4} sensitivity (uMRD4; <1 CLL cell per 10,000 leukocytes [<0.01%]) in peripheral blood (PB) by modified ERIC flow cytometry (FC) assay and next-generation sequencing (NGS; ClonoSEQ). Tumor lysis syndrome (TLS) was assessed by Howard 2011 criteria.

Results: As of May 18, 2026, 35 (41%) of 86 enrolled patients remained on treatment. Fifty-one patients discontinued treatment, the majority due to protocol-defined elective discontinuation (n=42). Seven patients discontinued combination treatment due to treatment-emergent adverse events (TEAEs; n=4: acute myeloid leukemia, chronic myelomonocytic leukemia, sinusitis, and well-differentiated liposarcoma), patient withdrawal (n=2), and investigator decision (n=1). Four patients discontinued S or Z only due to TEAEs or patient withdrawal. The median study follow-up was 39.5 months (range, 3.1-50.5 months). The most common (≥30%) any-grade TEAEs were

neutropenia (40%), contusion/bruising (38%), COVID-19 (34%), diarrhea (34%), and upper respiratory tract infection (31%). Neutropenia (31%) was the most common grade ≥3 TEAE. No clinical or laboratory TLS or grade 5 TEAEs occurred.

In 84 efficacy-evaluable patients (two of 86 did not have a postbaseline response assessment), the ORR was 100%, with 61% achieving a complete response. Median time from first Z dose to response was 2.6 months (range, 1.5-9.1 months). The best uMRD4 rate by FC was 99% (83/84), including 100% (10/10) in patients with del(17p)/*TP53* mutation. The best uMRD4 rates by weeks 24, 48, and 96 on target dose were 81% (69/85), 92% (78/85), and 98% (60/61), respectively. Median time to uMRD4 from first Z dose and first S dose was 7.2 months (range, 5.3-31.3 months) and 4.5 months (range, 3.3-28.4 months), respectively. In the NGS-evaluable set (n=80), the best uMRD5 rate was 89%. The 3-year progression-free survival rate was 100%. Only one disease progression event was observed in the S 320-mg cohort; after 43 months on study, a patient with unmutated IGHV had PD 15 months after elective discontinuation. No mutations in *BCL2*, *BTK*, or *PLCG2* were detected at progression, and the patient restarted S + Z combination treatment.

Conclusions: S + Z combination therapy continued to demonstrate favorable safety and achieved the highest uMRD4 and uMRD5 rates reported to date for oral doublet combinations in patients with TN CLL, including those with high-risk features. Responses continued to be rapid, deep, and durable, including in patients who electively discontinued therapy. These findings are consistent with the safety and efficacy profile observed with S-based regimens across hematologic malignancies. S + Z is currently being evaluated in two phase 3 TN CLL clinical trials (NCT06073821, NCT07277231).