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Efficacy and safety of sonrotoclax in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL): a 2-year follow-up from a multicenter, open-label, phase 2 study

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Introduction: B-cell lymphoma 2 (BCL2) inhibition is an established treatment strategy for CLL/SLL. Sonrotoclax is a next-generation BCL2 inhibitor designed to have high selectivity and 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. In China, sonrotoclax is approved for adults with CLL/SLL who have had ≥1 prior systemic therapy, including a Bruton tyrosine kinase (BTK) inhibitor. In the primary analysis of a single-arm, multicenter, phase 2 study in patients with R/R CLL/SLL (NCT05479994), sonrotoclax demonstrated a favorable safety profile and induced high response rates, including deep responses and undetectable minimal residual disease (uMRD4; sensitivity, 10^{-4}) (Yi et al., ASH 2025). Here, we present updated efficacy and safety results.

Methods: Eligible patients had a confirmed diagnosis of R/R CLL/SLL, received prior chemoimmunotherapy (unless ineligible) and BTK inhibitor therapy, and had no prior BCL2 inhibitor. Patients received sonrotoclax 320 mg once daily following a 4-week twice-weekly or an 8-week weekly dose ramp-up schedule and continued treatment until progressive disease (PD) or unacceptable toxicity. The primary endpoint was independent review committee (IRC)–assessed overall response rate (ORR) per iwCLL 2018 criteria (CLL) or 2014 Lugano criteria (SLL). Secondary endpoints included duration of response (DOR), progression-free survival (PFS), time to response (TTR), overall survival (OS), and safety. Exploratory endpoints included the rate of uMRD4.

Results: One hundred patients with R/R CLL/SLL were enrolled. At baseline, 62.8% (54/86) had unmutated IGHV, 38.1% (37/97) had del(17p)/*TP53* mutations, 25.5% (25/98) had a *BTK* mutation, and 50.0% (50/100) were aged ≥65 yrs. As of May 7, 2026, the median study follow-up was 28.9 months (range, 0.2-42.4). Fifty-two patients (52.0%) continue receiving treatment. The most common reason for treatment discontinuation was PD (32.0%).

The IRC-assessed ORR was 77.0%, with the complete response rate increasing to 29.0% from the previous report (25.0%). IRC-assessed ORR was 75.9% (41/54) in patients with unmutated IGHV, 70.3% (26/37) in those with del(17p)/*TP53* mutations, 72.0% (18/25) in those with *BTK* mutations, and 78.0% (39/50) in those aged ≥65 yrs. Median TTR was 3.7 months (range, 1.3-11.1). The best uMRD4 rate in peripheral blood (PB) was 53% (53/100) in efficacy-evaluable patients and 77.9% (53/68) in MRD-evaluable patients. Median time from first sonrotoclax dose to PB uMRD4 was 6.4 months (range, 3-16). Patients who achieved PB uMRD4 at C12D1 were less likely to experience PD or death than those with detectable MRD4 (HR, 0.10; 95% CI, 0.02-0.41). Median PFS, DOR, and OS were not reached. The 2-year IRC-assessed PFS rate was 60.7% (95% CI, 49.7%-69.9%). The 2-year OS rate was 76.3% (95% CI, 66.2%-83.8%).

Median duration of sonrotoclax exposure was 21.9 months (range, 0.0-42.4). Most common all-grade/grade ≥3 treatment-emergent adverse events (TEAEs) were hematologic: neutropenia (60.0%/33.0%), thrombocytopenia (53.0%/13.0%), leukopenia (39.0%/12.0%), and anemia (39.0%/5.0%). Serious TEAEs occurred in 46.0% of patients. No additional TEAEs leading to dose reduction or treatment discontinuation have been observed since the primary analysis. No new grade 5 TEAEs were reported.

Conclusions: Sonrotoclax monotherapy demonstrates significant clinical activity in patients with heavily pretreated R/R CLL/SLL with a high rate of uMRD and durable responses. The sonrotoclax toxicity profile remains favorable with extended follow-up. These data add to the growing evidence that sonrotoclax can induce deep responses while maintaining a favorable safety profile across hematologic malignancies.