2026 ASH Annual Meeting and Exposition
December 12-15, 2026, New Orleans, Louisiana

Safety and tolerability of a simplified ramp-up schedule of sonrotoclax in combination with zanubrutinib in patients with treatment-naive chronic lymphocytic leukemia (TN CLL): initial results from a phase 1 global study

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Introduction: BCL2 inhibitors restore apoptosis in BCL2-dependent cells, causing rapid tumor cell death. Combination treatment with BCL2 and BTK inhibitors is an effective first-line regimen for CLL but currently requires intensive monitoring during ramp-up to mitigate the risk of tumor lysis syndrome (TLS). Sonrotoclax 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. In a phase 1/1b trial in CLL, sonrotoclax in combination with the covalent BTK inhibitor zanubrutinib demonstrated promising clinical results and no clinical or laboratory TLS, but utilized frequent TLS monitoring. Here, we present

preliminary results from a TN CLL cohort in an ongoing phase 1/2 trial (NCT06697184) evaluating a simplified ramp-up dosing and monitoring strategy for sonrotoclax when combined with zanubrutinib.

Methods: The study included 2 parts in this TN CLL cohort: part 1 assessed sonrotoclax ramp-up schedule safety in a patient subset before expansion in part 2. Treatment started with 3 cycles (28 days each) of zanubrutinib lead-in (160 mg twice daily or 320 mg once daily [QD]). Sonrotoclax was started in the outpatient setting on cycle 4 day 1 with weekly ramp-up (2, 5, 20, and 80 mg QD), reaching the 320 mg QD target dose after 4 weeks. Combination treatment continued for 12 cycles. TLS risk was assessed at screening and at the end of zanubrutinib lead-in. TLS prophylaxis included oral hydration (starting 2-3 days before to 24 hr after sonrotoclax initiation and each dose increase during ramp-up) and antihyperuricemic agents (starting 2-3 days before sonrotoclax initiation to ≥7 days following target dose attainment). TLS monitoring included vital signs and serum chemistry assessment, performed ≤4 h before and 4-6 h after the first sonrotoclax dose and each dose increase. The primary endpoint was TLS incidence (per Howard criteria) during the schedule-limiting toxicity (SLT) evaluation window (ie, from the initial sonrotoclax dose until patients had received target dose for 7 days). Secondary endpoints were safety and tolerability, including treatment-emergent adverse events (TEAEs) and dose modifications during SLT evaluation.

Results: As of April 17, 2026, 56 patients with TN CLL (part 1, n=6; part 2, n=50) completed SLT observation and were evaluable for the primary endpoint. Two additional patients discontinued study treatment prior to sonrotoclax initiation. In the SLT-evaluable cohort, median age was 64.5 (range, 35-80) y; 71% were male and 82% were White. Forty-four patients (79%) had Binet stage B or C; 15 (27%) presented with high tumor burden (any lymph node [LN] ≥10 cm or any LN ≥5 cm with absolute lymphocyte count [ALC] ≥25×10^9/L). Twenty-seven (48%) had unmutated IGHV, 6 (11%) had *TP53* mutation (VAF ≥10%), and 4 (7%) had del(17p). Median ALC was 100.8×10^9/L (range, 3.8-351.8×10^9/L).

At the data cutoff date, no cases of laboratory or clinical TLS were observed. Transient grade 1 hyperphosphatemia (phosphate levels, 1.52-1.69 mmol/L) was observed in 9

patients post-dose across all ramp-up levels; none required medical intervention or sonrotoclax dose modification. No other TLS-related laboratory abnormalities (eg, hyperkalemia or hyperuricemia) were observed within the SLT period. With a median study follow up of 6.3 (range, 4.7-14.5) mo, no TEAEs led to treatment discontinuation or dose reduction of either study drug. The most common any-grade TEAEs were bruising (39%), neutropenia (20%), arthralgia (20%), diarrhea (20%), and headache (20%). Neutropenia (14%) was the only grade ≥3 TEAE in ≥5% of patients. No TEAEs led to death.

Conclusions: In patients with TN CLL, a simplified 4-week, weekly sonrotoclax ramp-up schedule following 3 cycles of zanubrutinib was safe, with no need for 24-h post-dose monitoring and no observed cases of laboratory/clinical TLS. These data suggest that this combination may be administered safely in the outpatient setting with a simplified ramp-up schedule, increasing patient convenience without compromising safety. Schedules with further reduced TLS monitoring frequency are currently being evaluated in CLL and mantle cell lymphoma in this ongoing study.