Title: MRD-guided treatment with sonrotoclax + obinutuzumab induces deep and durable remissions in treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma (TN CLL/SLL): updated phase 1/1b study results

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Introduction: B-cell lymphoma 2 (BCL2) is an effective therapeutic target in CLL/SLL; however, therapies with improved safety and efficacy are needed. 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. Here, we present safety and efficacy results for S + obinutuzumab (O) in patients with TN CLL/SLL from a phase 1/1b study of S alone or in combination regimens for B-cell malignancies (NCT04277637).

Methods: O was administered intravenously on cycle 1 day 1 (C1D1; 100 mg), D2 (900 mg), D8 (1000 mg), and D15 (1000 mg), then on D1 of C2 through C6 (1000 mg); each cycle was 28 days. Beginning on C2D1, S was administered orally once daily with ramp-up to target doses of 160 or 320 mg. S + O was continued until progressive disease (PD), unacceptable toxicity, or undetectable measurable residual disease (uMRD4; <1 CLL cell per 10,000 leukocytes [<0.01%]) in peripheral blood (PB) by next-generation sequencing (NGS; ClonoSEQ) after 15 cycles. Endpoints included safety per NCI-CTCAE v5.0, overall response rate (ORR) per iwCLL guidelines, and MRD status per modified ERIC flow cytometry (FC) assay or NGS, depending on the time point. Tumor lysis syndrome (TLS) was assessed per Howard 2011 criteria.

Results: As of May 18, 2026, 55 patients with TN CLL/SLL were enrolled (S 160 mg, n=20; 320 mg, n=35). Overall, median age was 62 y, 65% of patients were male, and 89% were White. At baseline, 15% (8/54) had high tumor burden and 58% (31/53) had unmutated IGHV. Median follow-up was 20.9 months (range, 0.4-37.5 months) overall and 28.1 months (range, 2.9-37.5 months) in the S 320-mg cohort. As of the data cutoff date, 54 of 55 patients had discontinued treatment. Fifty-two patients (95%) discontinued treatment either after achieving uMRD4 following 15 treatment cycles (n=50; per protocol-mandated NGS [n=48] or per investigator based on uMRD4 by FC [n=2]) or due to PD (n=2). Four patients discontinued O only: two while remaining on S and achieving uMRD4 (S 320 mg; thrombocytopenia, n=2), and two prior to starting S (160 mg: investigator decision, n=1; prostate cancer, n=1). No patient discontinued S due to toxicity.

Across dose cohorts, the most common any-grade treatment-emergent adverse events (TEAEs) were thrombocytopenia (56%), infusion-related reaction (56%), and neutropenia (49%). Neutropenia was the most common grade ≥3 TEAE (40%). There were no deaths or S discontinuations due to TEAEs. No clinical or laboratory TLS occurred during S ramp-up; two patients had laboratory TLS after C1D1 of O prior to starting S ramp-up. No meaningful safety differences were observed among S dose cohorts.

Overall, the ORR was 94% (51/54), with a complete response (CR)/CR with incomplete marrow recovery (CRi) rate of 52% (28/54). In the S 320-mg cohort, ORR was 94% (33/35) and CR/CRi rate was 57% (20/35). For patients in the S 320-mg cohort reaching the C15 MRD assessment, the best C15 uMRD4 rate by FC was 89% (31/35; three not evaluable, one missing). Of patients who reached C15 with an NGS sample, 100% achieved uMRD5 (33/33) and 91% achieved uMRD6 (30/33; one indeterminate). In the S 320-mg cohort, median time to uMRD4 from the first O dose and the first S dose was 4.7 months (range, 4.6-7.6 months) and 3.7 months (range, 3.3-6.5 months), respectively. The 18-month

progression-free survival (PFS) rate was 94% (95% CI, 84%-98%). Four PFS events occurred: one death (S 160 mg; indeterminate cause; O alone discontinued after C1D9) and three PD events (all S 320 mg; 2 Richter transformations at C2 and C6 and one PD event 12 months after protocol-mandated discontinuation following uMRD4 achievement).

Conclusions: MRD-guided S + O treatment is highly active in TN CLL/SLL, resulting in deep and durable responses. Very high uMRD4 rates support a fixed-duration treatment paradigm with sonrotoclax combinations. Together with a favorable safety profile, these results support continued development of sonrotoclax-based combination therapies in CLL/SLL and across diverse hematologic malignancies. A registrational phase 3 study of sonrotoclax in combination with CD20-targeted agents is currently recruiting (CELESTIAL-RRCLL; NCT06943872).