MRD-Guided therapy of sonrotoclax (BGB-11417) + obinutuzumab (O) in patients with treatment-naive CLL: Initial results from an ongoing phase 1/1b study, BGB-11417-101

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Introduction: The first-generation BCL2 inhibitor, venetoclax, is an effective treatment for CLL/SLL, but its usage may be limited by toxicity. Sonrotoclax, a next-generation BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no drug accumulation. BGB-11417-101 (NCT04277637) is an ongoing, phase 1/1b, dose-escalation/expansion study in patients with B-cell malignancies. Presented here are preliminary data for sonrotoclax + obinutuzumab in patients with treatment-naive (TN) CLL/SLL in BGB-11417-101.

Methods: Obinutuzumab is administered intravenously at 100 mg on day (D) 1, 900 mg on D2, 1,000 mg on D8 and D15 of cycle (C) 1, and then 1,000 mg on D1 of C2-6 of each 28-day cycle. Beginning on C2D1, sonrotoclax is administered orally once daily with ramp-up to the target doses, 160 or 320 mg. Patients can continue treatment until progressive disease (PD), unacceptable toxicity, or undetectable minimal residual disease (uMRD4; <1 CLL cell per 10,000 leukocytes [<0.01%]) in peripheral blood (PB) by next-generation sequencing (NGS; ClonoSEQ) after 15 treatment cycles. Study endpoints include safety per NCI-CTCAE v5.0, overall response rate (ORR) per iwCLL guidelines, and MRD status in PB per modified ERIC flow cytometry (FC) assay or NGS, depending on the timepoint. Tumor lysis syndrome (TLS) is assessed per Howard (2011) criteria.

Results: As of May 16, 2025, 55 patients with TN CLL/SLL were enrolled (160 mg, n=20; 320 mg, n=35), and 21 patients (all 320 mg) have discontinued sonrotoclax + obinutuzumab (due to uMRD4 per NGS as protocol-mandated [n=17], PI decision uMRD4 per FC [n=2], and PD [n=2]). Four patients discontinued obinutuzumab only per PI decision (160 mg, n=1), thrombocytopenia (320 mg, n=2), and prostate cancer prior to starting sonrotoclax (160 mg, n=1). For all patients, the median age was 62 y, 65% were male, and 89% were White. At baseline, 14% of patients (8/55) had high tumor burden and 58% (31/53) had unmutated IGHV. Median study follow-up was 8.9 months (range, 0.4-25.4 months) for all patients; 6.4 months (range, 0.4-9.0 months) for 160 mg; and 16.0 months (range, 2.9-25.4 months) for 320 mg. Maximum tolerated dose was not reached. The most common any-grade treatment-emergent AEs (TEAEs) were thrombocytopenia (56%), infusion-related reaction (56%), and neutropenia (49%). Neutropenia was the most common grade ≥3 TEAE (38%). No deaths due to TEAEs occurred, and no TEAEs led to sonrotoclax discontinuation. Two cases of laboratory TLS occurred after C1D1 of obinutuzumab prior to starting sonrotoclax; no clinical or laboratory TLS occurred during sonrotoclax ramp up. No meaningful safety differences were observed among sonrotoclax dose cohorts.
In 37 efficacy-evaluable patients (160 mg, n=7; 320 mg, n=30), the ORR was 89%; for the 320-mg cohort, ORR was 93% (28/30). Complete response (CR) rates (CR + CR with incomplete marrow recovery [CRi]) were 46% (all patients) and 43% (320 mg). For 23 patients in the 320 mg cohort who reached the C15 MRD assessment, the best C15 uMRD4 rate per FC was 87% (20/23; 2 not evaluable; 1 missing); per NGS, the uMRD4 rate at C15 was 78% (18/23; 5 missing). All patients with an available C15 MRD assessment achieved uMRD4 and remain in remission as of the data cutoff date. The median time from reaching sonrotoclax target dose to uMRD4 was 2.3 months (range, 1.4-5.6 months) in the 320-mg cohort. Three patients experienced PFS events: 1 died from an indeterminate cause (160 mg, discontinued treatment after C1D9 of obinutuzumab) and 2 had PD (320 mg; both Richter's transformation at C6 and C2).

Conclusions: Sonrotoclax + obinutuzumab was generally well tolerated in patients with TN CLL/SLL, with no sonrotoclax discontinuations or deaths due to TEAEs. No laboratory or clinical TLS events occurred during sonrotoclax ramp-up. Encouraging antitumor activity was observed with sonrotoclax 320 mg. High rates of blood uMRD4 occurred early and deepened over time. All patients with an available C15 MRD assessment by NGS or FC achieved uMRD4 and remain in remission. A registrational phase 3 study (CELESTIAL-RRCLL, BGB-11417-303) assessing this combination with sonrotoclax 320 mg is currently recruiting.