Zanubrutinib + obinutuzumab + sonrotoclax in patients with treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma (TN CLL/SLL): Initial results from an ongoing phase 1/1b study, BGB-11417-101

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Introduction: Combination therapy with zanubrutinib, obinutuzumab, and venetoclax has demonstrated efficacy in patients with TN CLL/SLL, including those with high-risk disease features. Sonrotoclax (BGB-11417), 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, first-in-human, phase 1/1b dose-escalation/expansion study in patients with various B-cell malignancies. Presented here are initial safety and efficacy data for zanubrutinib + obinutuzumab + sonrotoclax combination therapy in patients with treatment-naive (TN) CLL/SLL in BGB-11417-101.

Methods: On cycle 1, day 1, patients begin receiving oral zanubrutinib (160 mg twice daily or 320 mg once daily) and intravenous obinutuzumab (100 mg on day 1, 900 mg on day 2, 1,000 mg on days 8 and 15 of cycle 1, and then 1,000 mg on day 1 of cycles 2-6 of each 28-day cycle). Oral sonrotoclax treatment begins on cycle 2, day 1, using a ramp-up schedule to reach the recommended phase 2 dose of 320 mg. Patients can continue treatment until disease progression, unacceptable toxicity, or undetectable minimal residual disease (uMRD4; <1 CLL cell per 10,000 leukocytes [<.01%]) in peripheral blood by next-generation sequencing (NGS; ClonoSEQ) after 15 cycles of treatment. Study endpoints include safety per NCI-CTCAE v5.0, overall response rate (ORR) per iwCLL guidelines, and MRD status as assessed by ERIC-approved flow cytometry (FC) assay and NGS, depending on the timepoint. Tumor lysis syndrome (TLS) is assessed per Howard (2011) criteria.

Results: As of May 16, 2025, 15 patients with TN CLL/SLL were enrolled and received zanubrutinib + obinutuzumab + sonrotoclax 320 mg. As of the data cutoff date, 6 patients remain on treatment and 9 patients have discontinued sonrotoclax (due to uMRD4 per NGS as protocol-mandated [n=8] and PI decision with uMRD4 per FC [n=1]). For all patients, the median age was 62 years, 53% were male, and 67% were White. At baseline, 1 patient (7%) had high tumor burden, and 10 patients (67%) had unmutated IGHV. The median study follow-up time was 14.6 months (range, 5.0-18.8 months). Maximum tolerated dose was not reached. The most common TEAEs were neutropenia (80%), nausea (47%), infusion-related reaction (40%), thrombocytopenia (40%), fatigue (33%), headache (33%), and insomnia (33%). The most common grade ≥3 TEAE was neutropenia (73%). No deaths due to TEAEs were seen. One patient experienced laboratory TLS prior to starting sonrotoclax. No laboratory or clinical TLS was observed during sonrotoclax ramp-up. No TEAEs led to discontinuation of any study drug.
In 10 efficacy-evaluable patients, the ORR was 100%, with a complete response (CR) + CR with incomplete marrow recovery (CRi) rate of 60%. A total of 10 patients reached the cycle 15 MRD assessment. The best blood uMRD4 rate per FC by cycle 15 was 100%; per NGS, the best blood uMRD4 rate at cycle 15 was 80% (8/10; 2 missing). The median time from reaching sonrotoclax target dose to uMRD4 was 2.7 months (range, 1.4-4.4 months). No PFS events occurred.

Conclusions: Combination therapy with zanubrutinib + obinutuzumab + sonrotoclax 320 mg was well tolerated by patients with TN CLL/SLL. No deaths or discontinuations of any study drug due to TEAE were observed and no laboratory or clinical TLS occurred during sonrotoclax ramp-up. Substantial efficacy was observed, with a 100% ORR and 60% CR + CRi rate. All patients with an available cycle 15 MRD assessment by NGS or FC achieved uMRD4 and remain in remission. With a median study follow-up of approximately 14.6 months, no PFS events have occurred, indicating the potential for zanubrutinib + obinutuzumab + sonrotoclax as a treatment option for patients with TN CLL.