Combination treatment with sonrotoclax (BGB-11417), a second-generation BCL2 inhibitor, and zanubrutinib, a Bruton tyrosine kinase (BTK) inhibitor, is well tolerated and achieves deep responses in patients with treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma (TN-CLL/SLL): data from an ongoing phase 1/2 study

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Background: Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, is a more selective and potent inhibitor of BCL2 than venetoclax in biochemical assays. Zanubrutinib, a next-generation BTK inhibitor, improved PFS with fewer cardiac AEs than ibrutinib in patients with CLL/SLL. BGB-11417-101 (NCT04277637) is an ongoing, first-in-human, phase 1/1b dose-escalation/expansion study of patients with B-cell malignancies. Presented here are data from patients with TN CLL/SLL treated with sonrotoclax + zanubrutinib.

Material and Methods: Patients received zanubrutinib (320 mg QD or 160 mg BID) 8 to 12 weeks before starting sonrotoclax with a ramp-up schedule to target doses of 160 or 320 mg QD to mitigate risk of tumor lysis syndrome (TLS). Patients were treated until progression or unacceptable toxicity. TLS was assessed per Howard 2011 criteria. The primary endpoint was safety per CTCAE v5.0; a secondary endpoint was ORR per iwCLL 2008 criteria, and minimal residual disease (uMRD4; <1 CLL cell per 10,000 leukocytes, or <0.01%) in blood by ERIC flow every 24 weeks was an exploratory endpoint.

Results: As of May 21, 2023, 94 patients with TN CLL/SLL were enrolled; 15 patients were still in zanubrutinib lead-in and 79 had started sonrotoclax (160 mg, n=32; 320 mg, n=47). Median follow-up

was 8.5 months (range, 0.6-18.2) for all patients, 12.1 months (range, 0.6-18.2) for 160 mg, and 7.0 months (range, 1.1-14.6) for 320 mg. No deaths occurred, and all patients remain on study. Treatment-emergent AEs (TEAEs) in ≥20% of patients who received sonrotoclax + zanubrutinib were contusion (35%), neutropenia (35%), COVID-19 (23%), and diarrhea (23%; grade ≥3 in 1 patient). Neutropenia was the most common grade ≥3 TEAE (17%). No clinical or laboratory TLS occurred. No patients experienced atrial fibrillation. One TEAE (cryptococcal meningitis at 11 weeks) led to treatment discontinuation. Sonrotoclax dose holds occurred in 17 patients (22%; median duration, 11 days [range, 3-37]); 3 patients (4%) had dose reduction. In 56 response-evaluable patients, ORR was 100% (CR: 160 mg, 36% [n=9]; 320 mg, 19% [n=6]). CR rate increased with time; the median time to CR was 10.1 months (range, 5.4-17.1). No progression events were reported in either cohort. Week 24 blood uMRD4 rates were 50% (12/24) for 160 mg and 65% (13/20) for 320 mg. Week 48 blood uMRD4 rates were 73% for 160 mg (11/15) and 100% (1/1) for 320 mg.

Conclusions: Sonrotoclax (160 and 320 mg) + zanubrutinib was well tolerated in patients with TN CLL/SLL. Only 1 patient discontinued treatment and 3 had dose reductions. No TLS was seen. Efficacy is encouraging, with 100% ORR in assessed patients, no PFS events, and high rates of blood uMRD4 occurring early. A phase 3 study assessing this combination is planned.