Frontline treatment of sonrotoclax (BGB-11417) and zanubrutinib for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) demonstrates high undetectable minimal residual disease (uMRD) rates with favorable tolerability: Updated data from BGB-11417-101, an ongoing phase 1/1b study

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Introduction: Frontline CLL/SLL treatments with venetoclax and a Bruton tyrosine kinase (BTK) inhibitor have emerged as important therapy options with limited undetectable MRD rates. 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. Zanubrutinib, a next-generation BTK inhibitor, is highly effective in CLL, including in patients with high-risk disease features, and showed superior progression-free survival (PFS) with fewer cardiac adverse events (AEs) vs ibrutinib in a randomized study in patients with CLL/SLL. BGB-11417-101 (NCT04277637) is an ongoing phase 1/1b, dose-escalation/expansion study in patients with B-cell malignancies. Updated safety and efficacy data are shown for patients with treatment-naive (TN) CLL/SLL who received sonrotoclax + zanubrutinib at a median follow-up of 27.2 months (range, 3.1-42.1 months).

Methods: Zanubrutinib (320 mg once daily [QD] or 160 mg twice daily) was dosed for 8-12 weeks, and sonrotoclax (160 or 320 mg QD) was added with a ramp-up to target

dose. Patients were treated until progression, unacceptable toxicity, or protocol-defined elective discontinuation after 96 weeks of combination study treatment at target dose (24 cycles). Tumor lysis syndrome (TLS) was assessed per Howard 2011 criteria. Primary endpoints included safety per NCI-CTCAE v5.0, secondary endpoints included overall response rate (ORR) per iwCLL criteria, and exploratory endpoints included uMRD in peripheral blood (uMRD4: <1 CLL cell per 10,000 leukocytes [<0.01%]) per modified ERIC flow cytometry assay every 24 weeks after reaching sonrotoclax target dose.

Results: As of May 16, 2025, 137 patients with TN CLL/SLL were enrolled in the sonrotoclax 160- (n=51) and 320-mg (n=86) cohorts; at the cutoff date, 80 patients (58%) remained on treatment. Overall, median age was 62 years, 72% were male, and 91% were White. At baseline, 29% (39/133) of tested patients had high TLS risk, 61% (80/132) had unmutated IGHV, and 14% (18/128) had *TP53* mutation or del(17p). As of the data cutoff date, 60 patients have discontinued study treatment, the majority due to protocol-defined elective discontinuation (78%; n=47). Nine patients discontinued combination treatment due to TEAE (acute myeloid leukemia, chronic myelomonocytic leukemia, meningitis, and sinusitis; n=4), PD (n=1), patient withdrawal (n=2), and investigator decision (n=2). Five patients discontinued sonrotoclax or zanubrutinib only due to TEAE. The most common any-grade treatment-emergent AEs (TEAEs) were neutropenia (42%), COVID-19 (39%), contusion (39%), and diarrhea (30%). Neutropenia was the most common grade ≥3 TEAE (27%). No clinical or laboratory TLS occurred, and no TEAEs led to death.

In 135 efficacy-evaluable patients, the ORR was 100%, with complete response (CR)/CR with incomplete marrow recovery (CRi) in 47% and 50% of the 160- and 320-mg cohorts, respectively. Across cohorts, median time to response was 2.6 months (range, 1.5-10.8 months) and median time to CR/CRi was 9.1 months (range, 3.9-34.5 months). At the time of data cutoff, the best uMRD4 rate across both dose levels was 94% (127/135) and no patient with uMRD4 reverted to MRD4+. By week 96 of combination treatment, 83 of 88 patients (94%) had uMRD4 and 47 of 88 (53%) electively discontinued treatment (median time off treatment, 4.9 months [range, 0.1-14.9 months]). In the 320-mg cohort, median time to uMRD was 2.8 months (range, 2.3-21.9 months) of combination treatment at the target dose and the best uMRD4 rates by week 24, 48 and 96 were 81%, 92% and 98%, respectively. To date, only 1 patient (160 mg) has experienced disease progression (Richter transformation).

Conclusions: Sonrotoclax (160 and 320 mg) + zanubrutinib was well tolerated in patients with TN CLL/SLL, with low rates of treatment discontinuation due to TEAE and no TLS. Efficacy was substantial, with a 100% ORR in assessed patients and a best uMRD4 rate of 94%. High blood uMRD4 rates occurred early and deepened over time, including in patients with high-risk disease factors, such as unmutated IGHV, *TP53* mutation, and del(17p). With a median follow-up of 27.2 months, no PFS events occurred in the 320-mg cohort. A registrational phase 3 study (CELESTIAL-TNCLL, BGB-11417-301) of this combination with sonrotoclax 320 mg is ongoing.