Results from the phase 1 study of the novel BCL2 inhibitor sonrotoclax in combination with zanubrutinib for relapsed/refractory (R/R) CLL/SLL show deep and durable response

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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, has shown improved PFS and tolerability, including fewer cardiac AEs than ibrutinib in a randomized study of patients with R/R CLL/SLL and is approved for CLL. Updated safety and efficacy data for patients with R/R CLL/SLL treated with sonrotoclax + zanubrutinib in the ongoing BGB-11417-101 (NCT04277637) study are presented.

Material and Methods: Patients with R/R CLL/SLL received zanubrutinib (320 mg QD or 160 mg BID) 8-12 weeks before starting sonrotoclax (40, 80, 160, 320, or 640 mg QD) with ramp-up to the target dose to mitigate potential tumor lysis syndrome (TLS) risk. Prior BTK inhibitors were allowed if disease progression occurred on treatment. Patients were treated until disease progression or unacceptable toxicity. The primary endpoint was safety CTCAE v5.0. ORR iwCLL 2008 criteria and minimal residual disease assessed in blood by ERIC flow every 24 weeks (uMRD4) were secondary and exploratory endpoints, respectively.

Results: As of Oct 31, 2023, 45 patients with R/R CLL/SLL were enrolled (40 mg, n=4; 80 mg, n=9; 160 mg, n=6; 320 mg, n=20; 640 mg, n=6). Four patients were still in the zanubrutinib lead-in phase and 41 had started sonrotoclax. The median age was 65 years (range, 36-76); 28% of tested patients (11/40) had del(17p), and 72% (13/18) had unmutated IGHV. The median number of prior treatments was 1 (range, 1-3); 7 patients had a prior BTK inhibitor as their last therapy. Median follow-up was 17 months (range, 0.5-32.6). No DLTs occurred, and the MTD had not been reached up to 640 mg. Dose expansion was completed with a recommended phase 2 dose of 320 mg. Any-grade treatment-emergent AEs (TEAEs) in ≥20% of patients were COVID-19 (n=12; 27%), contusion (n=12; 27%), neutropenia (n=12; 27%), diarrhea (n=11; 24%), nausea (n=11; 24%) and fatigue (n=11; 24%). Neutropenia was the most common grade ≥3 TEAE (n=9; 20%). No TLS or atrial fibrillation occurred; no TEAEs led to death, discontinuation, or dose reduction. Sonrotoclax dose holds occurred in 14 patients for a median duration of 7 days, most commonly due to COVID-19 (n=7). For 32 response-evaluable patients, the ORR was 97% (31/32); 1 patient (40 mg) had SD. The complete response (CR) rate was 50% (40 mg, n=1 [25%]; 80 mg, n=4 [50%]; 160 mg, n=4 [67%]; 320 mg, n=5 [56%]; 640 mg, n=2 [40%]). Median time to CR was 9.8 months (range, 5.5-18.2). Of 4 response-evaluable patients with prior BTK inhibitor treatment, 3 achieved PR (n=2) or CR (n=1). All patients treated with sonrotoclax + zanubrutinib (160 mg, 320 mg, or 640 mg) who reached week 48 achieved uMRD4. Treatment is ongoing for all but 1 patient (40 mg) who discontinued due to disease progression.

Conclusions: Efficacy of sonrotoclax + zanubrutinib combination treatment is encouraging, with a 97% ORR and deep responses, including uMRD, in patients with R/R CLL/SLL. This combination has demonstrated a tolerable safety profile across all dose levels tested.