Results from the phase 1 study of the novel BCL2 inhibitor sonrotoclax (BGB-11417) in combination with zanubrutinib for relapsed/refractory (R/R) CLL/SLL show deep and durable responses

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ABSTRACT

Aim: Sonrotoclax is a more selective and potent BCL2 inhibitor than venetoclax in biochemical assays. Zanubrutinib, a next-generation BTK inhibitor (BTKi), has improved PFS and tolerability vs ibrutinib in R/R CLL/SLL. Updated data for sonrotoclax + zanubrutinib in patients with R/R CLL/SLL in the ongoing BGB-11417-101 (NCT04277637) study are presented.

Method: Patients received zanubrutinib (320mg QD/160mg BID) 8-12 weeks before starting sonrotoclax with target dose (40/80/160/320/640mg QD) ramp-up. Endpoints included safety (CTCAE v5.0), ORR (iwCLL 2008 criteria), and minimal residual disease in blood (uMRD4).

Results: As of 31Oct2023, 45 patients were enrolled (40mg, n=4; 80mg, n=9; 160mg, n=6; 320mg, n=20; 640mg, n=6); four were in zanubrutinib lead-in, 41 started sonrotoclax. Of tested patients, 28% (11/40) had del(17p) and 72% (13/18) had unmutated IGHV. The median number of prior treatments was 1; seven patients had a BTK inhibitor (BTKi) as their last therapy. The median follow-up was 17 months (range, 0.5-32.6). No DLTs occurred; MTD was not reached up to 640mg. Dose expansion was completed with a recommended phase 2 dose of 320mg. Treatment-emergent AEs (TEAEs) in ≥20% were COVID-19 (27%), contusion (27%), neutropenia (27%), diarrhea (24%), nausea (24%), and fatigue (24%). Neutropenia was the most common grade ≥3 TEAE (20%). No tumor lysis syndrome or atrial fibrillation occurred. No TEAEs led to death, discontinuation, or dose reduction. Fourteen patients had sonrotoclax dose holds. For 32 response-evaluable patients, ORR was 97%. CR rate was 50%; median time to CR was 9.8 months. Of 4 patients with prior BTKi, 3 had PR or CR. All patients reaching week 48 achieved uMRD4 (Figure). Treatment is ongoing for all but 1 patient.

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