Sonrotoclax (BGB-11417) + zanubrutinib in patients with treatment-naive CLL/SLL: an ongoing phase 1/2 study

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ABSTRACT

Introduction: Sonrotoclax (BGB-11417) inhibits BCL2 with potency >10x that of venetoclax in biochemical assays. BGB-11417-101 (NCT04277637) is an ongoing, first-in-human, phase 1/2, dose-escalation/expansion in patients with B-cell malignancies treated with sonrotoclax±zanubrutinib, a next-generation Bruton tyrosine kinase inhibitor. Data are presented for the treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma (TN-CLL/SLL) cohort.

Methods: Patients received zanubrutinib (320mg QD or 160mg BID) 8-12 weeks before starting sonrotoclax using a ramp-up schedule starting from 1mg to the target dosage (160mg or 320mg QD). Tumor lysis syndrome (TLS) was assessed per Howard 2011 criteria. The primary endpoint was safety; secondary and exploratory endpoints were ORR (per iwCLL 2008 criteria), PFS, and minimal residual disease in blood per ERIC flow every 24 weeks (uMRD4; <0.01%).

Results: As of 21May2023, 94 patients with TN-CLL/SLL were enrolled; fifteen were receiving zanubrutinib monotherapy and 79 started sonrotoclax (160mg, n=32; 320mg, n=47). Median follow-up was 8.5 months (all patients; range: 0.6-18.2), 12.1 months (160mg; range: 0.6-18.2), and 7.0 months (320mg; range: 1.1-14.6). No deaths occurred; all patients continued on therapy. Treatment-emergent AE (TEAE) frequencies were similar between sonrotoclax dose groups. Most common TEAEs: contusion and neutropenia (35% each); neutropenia was the most common grade ≥3 TEAE (17%). No events of clinical or laboratory TLS or atrial fibrillation occurred. One TEAE (cryptococcal meningitis) led to treatment discontinuation. Sonrotoclax holds occurred in 22% (n=17) with a median duration of 11 days (range: 3-37); the most common TEAEs resulting in sonrotoclax holds were COVID-19 (11%; n=9) and diarrhea (4%; n=3). Dose reductions occurred in 4% (n=3). In 56 efficacy-evaluable patients, the ORR was 100% (CR: 160mg, 36%; 320mg, 19%). Across all doses, CR rates increased with time (median time to CR, 10.1 months [range: 5.4-17.1]). No progression was reported in either group. Week 24 blood uMRD4 rates were 50% (12/24; 160mg) and 65% (13/20; 320mg). Week 48 blood uMRD4 rates were 73% (11/15; 160mg) and 100% (1/1; 320mg); no patient has lost uMRD4.

Conclusion: Sonrotoclax (160mg and 320mg) plus zanubrutinib was well tolerated in patients with TN-CLL/SLL. Only 1 patient discontinued treatment, and 3 had dose

reductions. No TLS or cardiac toxicity were observed. With median follow-up of 8.5 months, efficacy was promising, with 100% ORR in assessed patients and no PFS events. High blood uMRD4 rates occurred early with deepening response by week 48. Based on these data, sonrotoclax 320mg was selected for the phase 3 study with zanubrutinib in TN-CLL.