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

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ABSTRACT

Introduction: Sonro (BGB-11417) is a more selective and potent BCL2 inhibitor than venetoclax in biochemical assays. Zanu, a next-generation BTK inhibitor (BTKi), has improved PFS and tolerability, with fewer cardiac AEs, vs ibrutinib in patients (pts) with R/R CLL/SLL. Updated data for sonro + zanu in pts with R/R CLL/SLL in the ongoing BGB-11417-101 (NCT04277637) study are presented.

Methods: Pts received zanu (320 mg QD or 160 mg BID) 8-12 wk before ramp-up to the sonro target dose (40, 80, 160, 320, or 640 mg QD). The primary endpoint was safety (CTCAE v5.0); ORR (iwCLL 2008 criteria) and minimal residual disease in blood by ERIC flow every 24 wk (uMRD4) were secondary and exploratory endpoints, respectively.

Results: As of Oct 31, 2023, 45 pts 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 pts were still in zanu lead-in and 41 started sonro. Of tested pts, 28% (11/40) had del(17p) and 72% (13/18) had unmutated IGHV. Median number of prior treatments (tx) was 1 (range, 1-3); 7 pts had BTKi as last tx. Median follow-up was 17 mo (range, 0.5-32.6). With no DLTs, MTD was not reached up to 640 mg. Expansion was completed with a recommended phase 2 dose of 320 mg. 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 TLS or atrial fibrillation occurred. No TEAEs led to death, discontinuation, or dose reduction. Sonro dose holds occurred in 14 pts (median duration, 7 days). In 32 response-evaluable pts, ORR was 97% (31/32; 1 SD at 40 mg). CR rate was 50% (40 mg, 25%; 80 mg, 50%; 160 mg, 67%; 320 mg, 56%; 640 mg, 40%); median time to CR was 9.8 mo (range, 5.5-18.2). Of 4 pts with prior BTKi, 3 had PR (n=2) or CR (n=1). All pts

treated with sonro + zanu (160, 320, or 640 mg) reaching wk 48 had uMRD4 (**Figure**). Tx is ongoing in all but 1 pt (40 mg; discontinued due to progression).

Conclusions: Preliminary efficacy of sonro + zanu is encouraging, with a 97% ORR and deep responses, including uMRD, in R/R CLL/SLL. This combination has demonstrated a tolerable safety profile across all tested doses.