UPDATED RESULTS FROM THE PHASE 1 STUDY OF SONROTOCLAX (BGB-11417), A NOVEL BCL2 INHIBITOR, IN COMBINATION WITH ZANUBRUTINIB FOR RELAPSED/REFRACTORY CLL/SLL DEMONSTRATE DEEP AND DURABLE RESPONSES

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Background: Despite recent therapeutic advances, most treated patients (pts) with CLL/SLL experience disease relapse, necessitating further treatment (tx) with novel agents. BCL2 inhibition is an established CLL/SLL therapeutic strategy, and adding Bruton tyrosine kinase (BTK) inhibition may be synergistic. Sonrotoclax (BGB-11417), 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 (zanu), a next-generation BTK inhibitor, is highly effective in CLL, including in pts with high-risk disease features, and has shown superior progression-free survival (PFS) with fewer cardiac AEs vs ibrutinib in a randomized study in pts with R/R CLL/SLL.

Aims: To report updated safety and efficacy data for sonrotoclax + zanu in pts with R/R CLL/SLL in the ongoing BGB-11417-101 (NCT04277637) study.

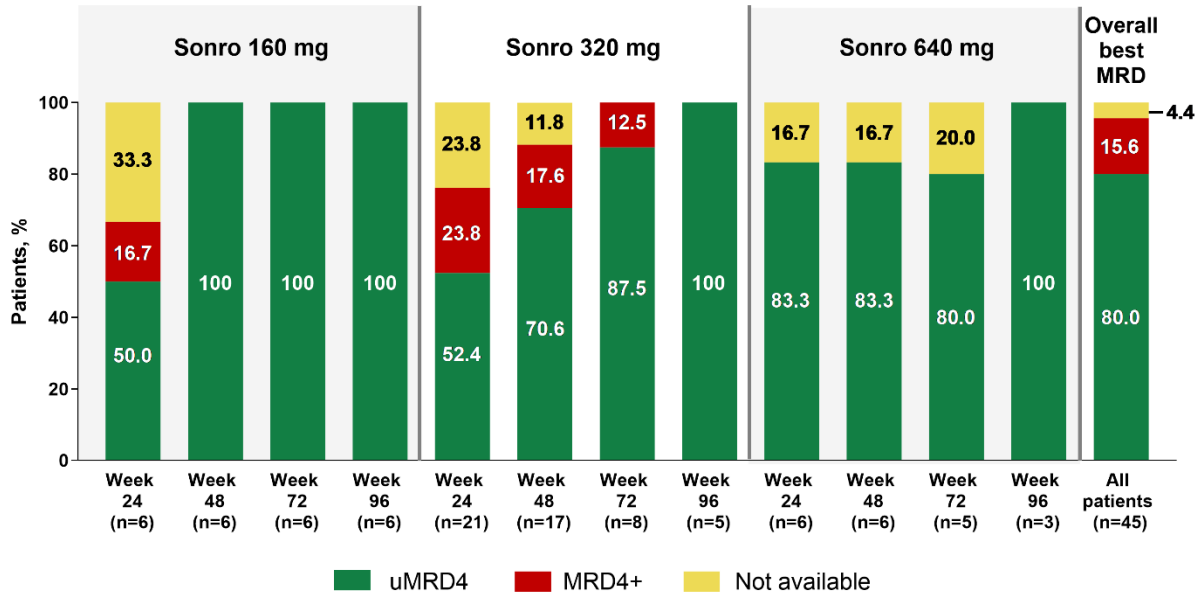
Methods: Pts with R/R CLL/SLL received zanu (320mg QD or 160mg BID) 8-12 wk before starting sonrotoclax (40, 80, 160, 320, or 640mg QD) with ramp-up to the target dose to prevent tumor lysis syndrome (TLS). Pts who previously progressed while on a BTK inhibitor were excluded from this cohort. Pts were treated until disease progression or unacceptable toxicity. The primary endpoint was safety per CTCAE v5.0; ORR per iwCLL 2018 criteria and undetectable measurable residual disease in blood by standardized ERIC flow cytometry every 24 wk (uMRD4) were secondary and exploratory endpoints, respectively.

Results: As of December 6, 2024, 47 pts with R/R CLL/SLL were enrolled and had received combination tx (sonrotoclax doses: 40mg, n=4; 80mg, n=9; 160mg, n=6; 320mg, n=22; 640mg,

n=6). Median age was 65 y (range, 36-76); 26.2% of tested pts (11/42) had del(17p) and 73.2% (30/41) had unmutated IGHV. Median number of prior txs was 1 (range, 1-3); 7 pts had a BTK inhibitor as their last prior therapy. Median follow-up was 29.4 mo (range, 10.2-45.8). No DLTs occurred; sonrotoclax MTD was not reached with doses up to 640mg. Dose expansion was completed with a recommended phase 2 dose of 320mg. The most common any-grade tx-emergent AE (TEAE) was COVID-19 (n=17; 36.2%). Neutropenia was the most common grade ≥3 TEAE (n=13; 27.7%; no febrile neutropenia). No cases of TLS occurred. Four pts (8.5%) discontinued tx due to TEAEs (myelodysplastic syndromes, meningococcal sepsis, plasma cell myeloma, and intracranial hemorrhage [discontinued zanu only]; n=1 each). No TEAEs led to death. In 46 response-evaluable pts, ORR was 95.7% (n=44; 2 pts [40 and 80mg] had SD); complete response (CR) rate was 50.0% (320mg, n=10 [47.6%]; 640mg, n=3 [50.0%]). Median time to CR was 10.2 mo (range, 5.3-42.4). Of 7 response-evaluable pts with prior BTK inhibitor tx, 6 achieved PR (n=5) or CR (n=1). Of 45 MRD-evaluable pts, 36 (80.0%) achieved uMRD4, with evidence of responses deepening over time. All pts treated with sonrotoclax 160, 320, or 640mg + zanu who reached wk 96 (n=14) achieved uMRD4 (**Figure**). One pt converted from uMRD to MRD4+ 6 mo after elective tx discontinuation and still remains in CR. With a median study follow-up of 29.4 mo, only 2 PFS events occurred (40mg, n=1; 320mg, n=1) and the 24-mo PFS rate was 94.5%.

Conclusion: Sonrotoclax + zanu combination tx demonstrated a tolerable safety profile across all dose levels tested. Antitumor activity of this combination is encouraging, with a 95.7% ORR, deep responses, and uMRD observed in pts with R/R CLL/SLL, including those previously treated with a BTK inhibitor.

Figure. Best overall MRD and MRD by weeks 24, 48, 72, and 96 of combination treatment[a]



[a] Percentages are based on number of patients who should have reached the specified week on target dose.