SONROTOCLAX MONOTHERAPY FOR TREATMENT OF PATIENTS WITH RELAPSED/REFRACTORY CLL: DATA FROM AN ONGOING PHASE 1/1B STUDY (BGB-11417-101)

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Background: B-cell lymphoma 2 (BCL2) inhibition is an established treatment strategy in CLL/SLL with the potential to induce deep responses. Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, is a more selective and potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no drug accumulation. BGB-11417-101 (NCT04277637) is an ongoing, first-in-human, phase 1/1b dose-escalation/expansion study in patients with various B-cell malignancies; previous interim analyses have indicated that sonrotoclax monotherapy is well tolerated at all doses tested, up to 640 mg once daily (QD).

Aims: Here, we report the safety, tolerability, and efficacy of sonrotoclax monotherapy in patients with relapsed/refractory (R/R) CLL/SLL without a history of prior venetoclax treatment.

Methods: Patients who had R/R CLL/SLL without a history of prior venetoclax, received sonrotoclax (planned doses: 80, 160, and 320 mg QD) with ramp-up to the target dose, and mandatory hydration and antihyperuricemic prophylaxis to mitigate potential risk of tumor lysis syndrome (TLS). All patients were treated until disease progression or unacceptable toxicity. The primary endpoint was safety per CTCAE v5.0. Secondary endpoints included establishing the maximum tolerated dose (MTD), recommended phase 2 dose, and overall response rate (ORR) per iwCLL 2018 criteria. Exploratory endpoints included the assessment of undetectable measurable residual disease (uMRD4) in blood by ERIC flow at week 12, then every 24 weeks thereafter.

Results: As of December 6, 2024, 18 patients with R/R CLL/SLL were enrolled (80 mg, n=4; 160 mg, n=7; 320 mg, n=7). The median age was 68 y (range, 55-84 y); 22.2% (4/18) had del(17p) and 66.7% (12/18) had unmutated IGHV genes. Ten patients (55.6%) had ≥3 prior lines of systemic cancer treatment; 17/18 (94.4%) had received a prior Bruton tyrosine kinase (BTK) inhibitor. Median study follow-up was 22.0 mo (range, 2.6-47.7 mo); 12 patients (66.7%) remain on treatment at data cutoff.

Dose escalation occurred per protocol at all defined doses. The MTD was not reached with a maximum assessed dose of 320 mg. Any-grade treatment-emergent adverse events (TEAEs) that occurred in ≥30% of patients were neutropenia (n=10; 55.6%); thrombocytopenia (n=9; 50.0%); upper respiratory tract infection (n=7; 38.9%); and cough, COVID-19, and diarrhea (n=6; 33.3% each). Neutropenia was the most common grade ≥3 TEAE (n=7; 38.9%). Two patients had laboratory TLS events during ramp-up; these events resolved within 24 h without sequela or dose modification and no clinical TLS was observed. No patients discontinued treatment due to TEAEs.

Across all dose levels, the ORR was 94.1% (16/17), and the complete response (CR) rate was 35.3% (6/17), in the efficacy evaluable set. In the 320-mg cohort, all patients achieved a response, and no disease progression was observed at data cutoff. The week 48 best blood uMRD4 rate was 50.0% (8/16; 80 mg, n=1; 160 mg, n=3; 320 mg, n=4). Median progression-free survival and duration of response were not reached in any cohort at the time of data cutoff.

Summary/Conclusion: Sonrotoclax monotherapy had a tolerable safety profile across all doses tested and had encouraging antitumor activity in patients with R/R CLL/SLL, most of whom received prior BTK inhibitors. No clinical TLS events were observed, indicating that TLS can be prevented with current measures. Based on this data, sonrotoclax is being tested with different regimens in pivotal studies.

Figure. Swimlane Plot of Treatment Duration With All Responses by Investigator Assessment