Sonrotoclax and zanubrutinib as frontline treatment for CLL demonstrates high MRD clearance rates with good tolerability: Data from an ongoing phase 1/1b study BGB-11417-101

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Introduction: The combination of venetoclax, a BCL2 inhibitor, with ibrutinib, a BTK inhibitor, is effective in CLL/SLL, but their clinical use can be limited by toxicity. Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, is a more selective and

more pharmacologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no drug accumulation. Zanubrutinib, a next-generation BTK inhibitor, is highly effective in CLL, including in patients with high-risk disease features and has shown superior progression-free survival (PFS) with fewer cardiac adverse events (AEs) vs ibrutinib in a randomized study in patients with CLL/SLL. BGB-11417-101 (NCT04277637) is an ongoing, first-in-human, phase 1/1b dose-escalation/expansion study in patients with various B-cell malignancies. Preliminary findings have shown that sonrotoclax, alone or in combination with zanubrutinib, is well tolerated at all doses tested up to 640 mg. Herein, we present updated safety and efficacy data of sonrotoclax + zanubrutinib in patients with treatment-naive (TN) CLL/SLL in BGB-11417-101.

Methods: Patients received zanubrutinib (320 mg once daily [QD] or 160 mg twice daily) for 8-12 weeks, then added sonrotoclax using a ramp-up schedule (weekly or daily) to the target doses (160 or 320 mg QD) to mitigate risk of tumor lysis syndrome (TLS). Patients were treated until progression, unacceptable toxicity, or could elect to stop after 96 weeks (24 cycles) of treatment. TLS was assessed per Howard (2011) criteria. Endpoints included safety per CTCAE v5.0 (primary), overall response rate (ORR) per iwCLL (secondary), and minimal residual disease assessed in blood per modified ERIC flow panel every 24 weeks after reaching sonrotoclax target dose (uMRD4; <1 CLL cell per 10,000 leukocytes [<0.01%]; exploratory).

Results: As of May 10, 2024, 112 patients with TN CLL/SLL were enrolled (sonrotoclax 160 mg QD, n=51; 320 mg QD, n=61). Median age was 62 y, 74% were male, and 92% were white. At baseline, 34% (38/112) of patients had high TLS risk, 51% (57/112) had unmutated IGHV, 20% (22/112) had *TP53* mutation, and 9% (10/112) had del(17p). Median follow-up was 18.3 mo (range, 4.4-29.9 mo) in all patients (160 mg, 16.0 mo [range, 9.1-29.9 mo]; 320 mg, 18.3 mo [range, 4.4-26.3 mo]). The most common TEAEs were neutropenia (41%), contusion (38%), COVID-19 (30%), and diarrhea (29%; 78% had grade 1 events). Neutropenia was the most common grade ≥3 TEAE (n=29, 26%); 2 patients had a dose reduction/drug hold, and none discontinued treatment. Two patients (both 160 mg) had grade 3 febrile neutropenia. No clinical or laboratory TLS occurred. No deaths occurred. Five patients (all 160 mg) discontinued combination treatment: 1 TEAE (cryptococcal meningitis), 1 PD, 1 patient withdrawal (had CR and

uMRD at time of withdrawal). Two patients in uMRD electively discontinued after 96 weeks of treatment. One patient (320 mg) discontinued zanubrutinib only due to intermittent diarrhea (grade 1).

The most common TEAE resulting in a dose hold was COVID-19 (n=19). In 108 response-evaluable patients, the ORR was 100% (complete response [CR]: 160 mg, 41%; 320 mg, 42%). Across both dose cohorts, the median time to response was 2.6 mo (range, 1.5-10.8 mo), and median time to CR was 8.4 mo (range, 3.9-17.1 mo). Week 24 best blood uMRD4 rates were 61% (31/51) with 160 mg and 77% (43/56) with 320 mg. Week 48 best blood uMRD4 rates were 79% (27/34) with 160 mg and 90% (43/48) with 320 mg. The median time to uMRD was 9.7 mo (range, 3.9-20.6 mo) and 8.5 mo (range, 5.4-19.9 mo) with 160 and 320 mg, respectively. No progression was seen in the 320 mg cohort.

Conclusions: Sonrotoclax (160 and 320 mg) in combination with zanubrutinib was safe and well tolerated in patients with TN CLL/SLL. Only one patient has discontinued combination treatment due to a TEAE. No cases of laboratory or clinical TLS were reported. Substantial efficacy was observed, with a 100% ORR in assessed patients and 90% best uMRD rate in patients in the 320-mg cohort who reached 48 weeks of therapy. High rates of blood uMRD4 occurred early and were sustained. With a median follow-up of 18.3 mo, only 1 PFS event occurred in the 160-mg cohort, and none occurred in the 320-mg cohort. A registrational phase 3 study (CELESTIAL-TNCLL, BGB-11417-301) assessing this combination with sonrotoclax 320 mg is recruiting.